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Original Article

A Single Center Retrospective Analysis of Patients With Recurrent Papillary Thyroid Carcinoma Undergoing Radiofrequency Ablation

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ABSTRACT

Background Radiofrequency ablation (RFA) is used in selected patients with recurrent or metastatic thyroid cancer who have high surgical risk or do not accept surgical treatment. However, long-term follow-up data are limited. Here, we present our single-center experience with the use of RFA in the treatment of recurrent or metastatic papillary thyroid carcinoma (PTC).

Material and Methods Patients who underwent RFA for recurrent or metastatic PTC at Bursa Uludag University Faculty of Medicine between September 2014 and January 2021 were included. The data in the endocrinology outpatient clinic follow-ups of the patients were analyzed retrospectively.

Results A total of 10 patients, 11 RFA procedures, and 13 residual or metastatic sites were evaluated. The mean age was 44.50±14.04 years. The mean largest diameter of the tumor in which RFA was applied was 11.85±5.95 mm. Patients developed no major complications. Two patients experienced minor complications. The mean follow-up duration was of 51.20±19.86 months. During the follow-up period, 12 (92.30%) of 13 RFA sites completely disappeared. In one patient (7.69%) residual tumor tissue was detected after RFA. There was no recurrence at the procedure site. A significant decrease was found in the largest diameter of the treated regions after RFA (p=0.002). Thyroglobulin and anti-thyroglobulin levels were not significantly different before and after RFA (p=0.44 and p=1.00, respectively).

Conclusions RFA is highly effective and safe for locally recurrent PTC. It shows promise as an alternative to surgery to control locoregional recurrence of PTC.

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Introduction

Thyroid cancer is the most common endocrinological malignancy, ranking in ninth place among all cancers worldwide. It has been reported that 5-year relative survival of thyroid cancer in Europe is around 80-90%.[1] The incidence of differentiated thyroid cancers has been increasing in recent years.[2,3] The most common subtype of thyroid cancer is papillary thyroid carcinoma (PTC). Most patients can be successfully treated with initial surgery and, if necessary, radioactive iodine therapy. However, local recurrence or distant metastasis occurs in the follow-up of some patients. Recurrent disease in operated patients mostly detected in the surgical bed or lymph nodes in the neck.[4] When recurrent thyroid cancers are detected, the standard treatment is reoperation followed by radioactive iodine therapy.[5,6] However, repeated neck operations present a higher risk of complications and can negatively affect the patient's quality of life.[6,7] In addition, some patients may be at high risk for surgery due to comorbidities. So, there is a need for alternative treatment options in recurrent or metastatic thyroid cancer.

Radiofrequency ablation (RFA) is a minimally invasive technique that provides coagulation necrosis in tissue. It has been used in the treatment of various solid tumors. In thyroid disease, RFA particularly has been tried in benign thyroid nodules.[5] However, there have not been enough studies on its use in thyroid cancer, and long-term follow-up data are limited.[5,8,9] RFA is mostly applied in selected patients with recurrent or metastatic thyroid cancer who have high surgical risk or do not accept surgical treatment.[8,10] Here, we present our single-center experience with the use of RFA in the treatment of recurrent or metastatic PTC. The aim of this retrospective analysis is to evaluate the efficacy and safety of RFA at long-term follow-up.

Material and Methods

Patients

A Patients who underwent RFA for metastatic or recurrent PTC at Bursa Uludag University Faculty of Medicine between September 2014 and January 2021 were included in the study. The exclusion criterias were age <18 years, follow-up period of <12 months, incomplete follow-up data. Finally, we enrolled 10 patients, 11 RFA procedures, and 13 residual/metastatic sites (nine metastatic neck lymph nodes, four thyroid lodges) in this retrospective analysis. Recurrence or lymph node metastasis was confirmed by ultrasonography (US)-guided fine-needle aspiration biopsy in all patients. The data in the endocrinology outpatient clinic follow-ups of the patients were analyzed retrospectively.

The data collected included age, gender, type and number of surgery, radioactive iodine therapy, presence of distant metastases before and after RFA, the time between diagnosis and RFA, RFA location and size, anesthesia, complications, follow-up time after RFA, sonographic and other imaging modalities (if available) findings, histopathological findings, recurrence in RFA region, thyroglobulin and anti-thyroglobulin levels (before and after RFA, and the last measured).

This study was approved by our institutional review board.

Ablation Procedures

All US-guided RFA procedures were performed by experienced radiologists in our center. A radiofrequency generator (STARmed) and a 17- or 18-gauge internally cooled electrode with 5-, 7- or 10-mm active tips were used based on the volume of the target tumor. The RFA power was 15-60 W. RFA procedure was performed using the moving-shot and hydrodissection technique. The ablation procedure was terminated when the tumor was entirely covered with hyperechoic zone.

Statistical Analysis

Analysis of the data was performed with SPSS (version 22.0) statistical software. Continous data were presented as mean±SD (range). The changes in serum thyroglobulin and anti-thyroglobulin levels and the largest diameter of the lesions before and after RFA were compared using Wilcoxon signed-rank tests. A p value <0.05 was considered as statistically significant.

Results

Although twelve patients underwent RFA for the treatment of metastatic or recurrent PTC in our hospital between September 2014 and January 2021, two patients were excluded from the study due to insufficient follow-up data. Ten patients with thyroid papillary carcinoma (eight females, two males) were included in the study. The main clinical features of patients before RFA are summarized in Table 1. A total of 11 RFA procedures and 13 residual/metastatic sites (nine neck lymph nodes, one isthmus, one right thyroid lodge, two left thyroid lodges) were evaluated. The mean age of the patients was 44.50±14.04 years (age range: 24-63). One patient underwent 2 RFA procedures from different regions (right zone 5 and right zone 2A, respectively). All patients had undergone surgery before RFA. The mean number of surgeries before RFA was 2 (range 1-3). Total thyroidectomy was performed in 5 patients, right lobectomy in 1 patient, total thyroidectomy and neck lymph node dissection in 3 patients, and pulmonary wedge resection in addition to total thyroidectomy and neck lymph node dissection in 1 patient. All patients received radioactive iodine therapy. Two patients (20%) had distant metastases before RFA (one mediastinal lymph node, one lung).

The mean time between the diagnosis of papillary carcinoma and the RFA procedure was 58.82±53.34 (range 7-156) months. Of the 11 RFA procedures, one was performed under general anesthesia and ten under local anesthesia. In two of the RFA procedures, ablation was applied to two regions simultaneously. The mean largest diameter of the lesion in which RFA applied was 11.85±5.95 mm (range 7-30 mm).

There were no patients who developed serious complications after RFA. Minor complications occurred in two patients (18.18%). One patient had swelling in the neck lasting for one week, and one patient had mild hoarseness lasting two weeks. No delayed complication was found during the follow-up period. The mean follow-up data of 51.20±19.86 (range 26-88) months after RFA were analyzed (*Table 2*). After the RFA procedure, all patients had US evaluation, thyroglobulin, and anti-thyroglobulin results. In the follow-up of the patients, 12 (92.30%) of 13 sites where RFA was applied, completely disappeared. Residual tumor tissue was detected in one patient (7.69%)

Table 1. Baseline patient characteristics before radiofrequency ablation.

Patient No.	Sex/age (years)	Type of surgery	Distant metastasis	Radiofrequency ablation location/level	Size (mm)
1	F/63	Total thyroidectomy	No	Left III Isthmus	7x7 30x30
2	F/46	Total thyroidectomy	No	Left VI	9x8
3	F/61	Total thyroidectomy	Mediastinal lymph node	Left thyroid bed	12x12
4	F/61	Total thyroidectomy	No	Right thyroid bed	15x10
5	F/43	Total thyroidectomy, neck dissection pulmonary wedge resection	Lung	Right IB Right IIB	10x10 10x10
6	M/47	Total thyroidectomy, neck dissection	No	Right V Right IIA	10x5 14x12
7	F/26	Total thyroidectomy, neck dissection	No	Left IIA	11x5
8	F/38	Right lobectomy	No	Right II-V junction	7x7
9	M/36	Total thyroidectomy	No	Right IB-III junction	11x10
10	F/24	Total thyroidectomy, neck dissection	No	Left thyroid bed	8x5

three months after RFA. It was in the left thyroid lodge and had a large diameter of 15 mm. This patient was treated with surgery and radioactive iodine therapy. No recurrence was observed at the procedure site in any of the patients who underwent RFA. A significant decrease was found in the largest diameter of the 13 treated regions after RFA compared to the pre-procedure (p=0.002). The mean serum thyroglobulin before RFA was 5.49±12.87 (range 0.2-43.8) mcg/L and after RFA 4.91±13.44 (range 0.14-45.3) mcg/L. There was no significant difference between the thyroglobulin levels before and after RFA (p=0.44). The mean final thyroglobulin level in the follow-ups of the patients was 7.46±16.16 (range 0.14-48.67). There was no significant difference between pre-RFA and the last thyroglobulin levels (p=0.07). No significant difference was found between the anti-thyroglobulin levels (IU/ml) of the patients before and after RFA (p=1.00). When the anti-thyroglobulin levels before RFA and the last measured anti-thyroglobulin levels were compared, no statistically significant difference was found (p=0.85). In the follow-up of four patients, metastases were detected outside the area where RFA was applied. All patients were alive at the time of study conducted.

Discussion

This single-center study showed the long-term effectiveness of RFA for controlling locally recurrent PTC. The complete disappearance rate after RFA was high (92.30%), and no recurrence was observed at the procedure site during long-term follow-up. However, there was no decrease in thyroglobulin and anti-thyroglobulin levels after RFA. Additionally, metastasis outside of the RFA area was detected in four patients. These results are consistent with the knowledge that RFA is only effective in locoregional control. Regarding complications, the safety of the RFA procedure was demonstrated. Minor complications occurred in two of 11 procedures in the study. None of the patients experienced any life-threatening or delayed complications.

Table 2. Long-term follow-up results of patients after radiofrequency ablation.

Patient No.	Follow-up time (month)	Complications after RFA	Residual tumor in RFA region	Tg (mcg/L)			Anti-Tg (IU/mL)		Metastasis after RFA
				Before RFA	After RFA	At last follow-up	Before RFA	After RFA	
1	88	No	No	0.20	0.56	48.67	148.1	145.9	Neck 2B, neck 5 sternoclavicular joint, lung
2	76	No	No	5.69	0.57	1.22	1.00	0.70	No
3	63	No	Left thyroid bed	43.8	45.3	29.20	0.80	3.40	Supraclavicular
4	51	Mild hoarseness	No	0.20	0.20	0.20	0.60	0.50	No
5	50	No	No	0.43	0.30	0.14	256.4	572.1	Lung, bone
6	47	Swelling in the neck	No	5.69	3.69	1.76	1.20	1.30	Neck 2A
7	46	No	No	0.47	0.20	0.14	24.2	5.30	No
8	38	No	No	1.31	0.30	0.17	2.20	1.00	No
9	27	No	No	0.20	0.14	0.14	9.90	12.7	No
10	26	No	No	0.30	0.30	0.22	1.00	1.30	No

RFA: radiofrequency ablation, Tg: thyroglobulin.

Surgery, followed by radioactive iodine therapy, is the established therapeutic approach for neck recurrences of PTC. Revision surgery for the recurrent disease has some challenges due to fibrosis caused by scar tissue formation and distortion of tissue planes. Thus, identification and preservation of the recurrent laryngeal nerve and parathyroid glands become difficult.[5,6,11] Furthermore, detecting small recurrent lesions may be difficult without US guidance.[12]

Recently, thermal ablative techniques (RFA, laser ablation, microwave ablation) and chemical ablative approaches (ethanol ablation) have been reported as an alternative to surgery for selected patients. Shin JE et al. compared RFA and ethanol ablation for the treatment of recurrent thyroid cancer. They found that the effectiveness of RFA was slightly higher. However, RFA was associated with higher voice complications.[9] There have been some reports regarding RFA for the treatment of thyroid carcinoma.[4,5,8-18] However, these studies have some limitations such as a small number of patients and short-term (mostly <5 years) follow-up duration.[11] Our study has a relatively long follow-up period compared to other reports. In recent years, Chung SR et al.[12] have reported longer-term outcome data of radiofrequency ablation for locally recurrent PTC. The mean follow-up duration was 80±17.3 months. Twenty-nine patients were reviewed and a mean tumor volume reduction of 99.5±2.9% was obtained. There were no delayed complications associated with RFA. In our study, although the volume could not be calculated due to insufficient size data, we showed a significant decrease in the largest diameter of tumor. Kim JH et al.[13] evaluated 73 patients with recurrent thyroid cancer. They demonstrated a high complete disappearance rate of 86.1% and low recurrence rate of 11.5% after three years of follow-up. They reported only one complication, transient vocal cord paralysis. A meta-analysis including 189 patients (mean six months of follow-up) demonstrated a significant decrease of tumor volume, the largest diameter of tumor, and thyroglobulin level after RFA. For malignant nodules, the overall complication rate was 10.98%, which is comparable with our results.[17] In our study, we also evaluated anti-thyroglobulin levels which may be associated with tumor burden.[19] We found a decrease in neither thyroglobulin nor anti-thyroglobulin levels with the treatment of RFA. It may be due to the small patient population or the presence of distant metastasis before RFA.

American Thyroid Association (ATA) suggests RFA in high-risk surgical patients or patients refusing additional surgery.[20] A recently published review article suggested RFA treatment for the early localized disease in patients who are poor operative candidates or have other reasons to avoid surgery.[5]

Limitations

Limitations of our study include the small number of patients and retrospective design. Further long-term follow-up or controlled prospective trials are needed.

Conclusions

RFA is highly effective and safe, when performed in experienced centers, for locally recurrent PTC and might be a promising treatment option to control locoregional recurrence of PTC.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: CA, EA; Study Design: EA; Supervision: CE, SC, OOG; Data Collection and/or Processing: EH, CA, FMS; Statistical Analysis and/or Data Interpretation: EA; Literature Review: EH, EA; Manuscript Preparation: EH; and Critical Review: CE, EE, FMS.

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Original Article

Comparison of Clinical Data and Treatment Responses of Patients With Essential Thrombocythemia Using Anagrelide by JAK2 Gene Mutation Status

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ABSTRACT

Background Essential Thrombocytemia (ET) is a clonal stem cell disease that manifests itself with proliferation in the megakaryocytic lineage in the bone marrow, with clinical presentations ranging from asymptomatic to bleeding and thrombosis spectrum. In medical treatment, aspirin and/or monitoring are recommended for low-risk patients, while cytoreductive therapy is recommended for high-risk patients. Cytoreductive therapy is often used in patients with a very high platelet count (>1,000,000/mm^3). The first choice in cytoreductive treatment is hydroxyurea, and anagrelid treatment is preferred in the young patient group and patients with hydroxyurea resistance/intolerance. This study aimed to evaluate the effects of the JAK2 mutation, which is associated with high risk, in the patient group receiving anagrelide therapy.

Material and Methods The files of patients diagnosed with ET according to 2016 WHO criteria and followed up under anagrelide therapy in our center between January 2002 and December 2021 were reviewed retrospectively. In addition to the demographic data of the patients, diagnostic tests, bone marrow evaluations, JAK2 mutation status, and laboratory data were noted. Patients were divided into two groups according to JAK2 mutation positivity and negativity. The obtained data were compared between the two groups.

Results Thirty-three patients (male/female: 20/13) treated with Anagrelide for the diagnosis of ET were included in the study. It was observed that 14 (42%) of the patients were positive for JAK2 mutation. There was no significant difference between the groups regarding age at diagnosis, gender, duration of anagrelide use, and bone marrow fibrosis degrees. When the laboratory tests were compared at the time of diagnosis, the WBC count was significantly higher in the JAK2 positive group; other series were similar. When the last control laboratory data of the patients were compared, leukocyte, neutrophil, and hemoglobin levels were observed to be significantly higher in JAK2 positive patients, while LDH levels were significantly lower.

Conclusions It was observed that JAK2 mutation positivity, which is associated with high risk in ET risk staging, did not negatively affect anagrelide treatment response. In ET patients, leukocytosis (>11.000/mm^3) has been identified as a risk factor for the whole lifespan. It was observed that the WBC counts of the patients who were positive for JAK2 were significantly higher at the time of diagnosis and during the treatment process. Since the LDH level after treatment is higher in patients with positive JAK2 mutation, it has been evaluated that JAK2 mutation may play a role in resistance to cytoreductive therapy.

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Introduction

Polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) are included in the BCR-ABL negative myeloproliferative neoplasms (MPN) group.[1] Clonal proliferation and cytokine hypersensitivity are essential in distinguishing them from reactive states.[2] Mutations that occur directly or indirectly in the Janus Kinase (JAK2) signal are essential in the pathogenesis of MPNs. The JAK2 mutation was positive in >95% of PV patients, while positive in 60% of ET and PMF patients. JAK2 is a non-receptor tyrosine kinase responsible for converting signals from class 1 cytokine receptors required for erythropoiesis, thrombocytopoiesis, myelopoiesis, and granulocyte-colony stimulating factor.[3] JAK2 is inactive, bound to clas1 cytokine receptors in the unstimulated state. The two most common mutations in JAK2 (V617F and exon 12 mutations) cause JAK2 activation without class 1 receptor stimulation.[1] In medical treatment, aspirin and/or monitoring are recommended for low-risk patients, while cytoreductive therapy is used for high-risk patients. Cytoreductive treatment is often recommended in patients with a very high platelet count (>1,000,000/mm^3). The first choice in cytoreductive treatment is hydroxyurea, and anagrelid treatment is preferred in the young patient group and patients with hydroxyurea resistance/intolerance. Our study aimed to evaluate the effects of JAK2 mutation on clinical and laboratory data before and after treatment with anagrelide.

Material and Methods

After obtaining approval from the local ethics committee approval, the files of patients diagnosed with ET according to 2016 WHO criteria[4] and followed up with anagrelide therapy between January 2002 and December 2021 in our center were retrospectively reviewed. Of the 122 patients whose files were evaluated, 33 patients whose JAK2 mutations were examined before treatment and who came to their regular follow-ups were included in the study. In addition to the demographic data of the patients, diagnostic and more recent laboratory values, bone marrow evaluations, and JAK2 mutation status were noted. Bone marrow fibrosis was scored between 0 and 4, with fibrosis four being the most severe. Patients were divided into two groups according to JAK2 mutation existence. The obtained data were compared between the two groups.

Statistical Analysis

The study's statistics were made in SPSS 26.0 (Chicago, IL) for Mac. Continuous variables are given with a mean, standard error, median, minimum and maximum values, while categorical variables are given numbers and percentages. The Shapiro Wilk test was used to determine the normal distribution. Independent-samples t-test was used to compare groups since it was observed to be suitable for normal distribution. Fisher's exact chi-square test was used for intergroup comparisons of categorical variables. $p<0.05$ was considered statistically significant in the study.

Results

Thirty-three patients (male/female: 20/13) who were treated with Anagrelide between 2002-2022 with ET diagnosis in our center were included in the study. The mean age of the patients was 48.96±11.94 years. It was observed that 14 (42%) of the patients were positive for JAK2 mutation. There was no significant difference between the groups regarding age at diagnosis, gender, duration of anagrelide use, and bone marrow fibrosis levels. When the laboratory tests at the time of diagnosis were compared, it was observed that the leukocyte count was significantly higher in the JAK2 positive group (11,940±3,524 vs. 9,313±2,737/mm^3, p=0.024). Although the platelet count was lower in JAK2 positive patients at the time of diagnosis, the difference could not reach statistical significance (879,285±272,731 vs. 1,030,021±424,448/mm^3, p=0.254). It was noted that other parameters were similar.

In the comparison of the data at the last control visit, it was determined that JAK2 positive patients' leukocyte (10,209±2,570 vs. 8,026±1,905/mm^3, p=0.010), neutrophils (6,626±1,977 vs. 5,248±1,356/mm^3, p=0.029) and hemoglobin (13.28±1.55 vs. 11.66±2.22 g/dL, p=0.027) levels were significantly higher, and LDH (216±28.55 vs. 281±95.22 U/L, p=0.049) levels were significantly lower. Although a lesser decrease was observed in the decrease in platelet count with

anagrelide treatment in the JAK2 positive group, the difference between the groups did not reach statistical significance. The number of patients whose bone marrow biopsy was available at diagnosis was 16 (48%). There was no significant difference between the groups regarding the degree of fibrosis (*Table 1*).

Table 1. Comparison of the data according to JAK2 mutation status.

	JAK2 negative (n=19)	JAK2 positive (n=14)	p value
Gender (male/female)	11/8	9/5	0.710
Age (year)	48.05±10.94	50.21±13.51	0.615
Age at onset (year)	38.58±11.12	41.07±11.97	0.542
Anagrelide duration (months)	99.79±69.07	105.21±67.55	0.823
Bone marrow fibrosis degree (n=16)	2.11±0.78	1.71±0.49	0.261
Laboratory values at the onset			
Anagrelide dose (mg)	1.48±0.6	1.23±0.34	0.208
Leukocyte (/mm^3)	9,313±2,737	11,940±3,524	0.024
Neutrophil (/mm^3)	6,388±2,851	8,115±3,699	0.299
Hemoglobin (g/dL)	12.66±2.01	13.83±2.26	0.128
Platelet (/mm^3)	1,030,021±424,448	879,285±272,731	0.254
MPV (fL)	11.96±17.16	8.4±1.64	0.464
BUN (mg/dL)	29.58±8.64	35.11±9.47	0.180
Creatinine (mg/dL)	0.79±0.16	0.82±0.16	0.662
AST (U/L)	23.92±13.09	20.33±8.26	0.481
ALT (U/L)	31.75±38.35	16.89±11.58	0.277
LDH (U/L)	265.57±103.98	247.75±59.17	0.763
Recent laboratory values			
Anagrelide dose (mg)	1.83±0.82	1.92±1.12	0.798
Leukocyte (/mm^3)	8,026±1,905	10,209±2,570	0.010
Neutrophil (/mm^3)	5,248±1,356	6.626±1,977	0.029
Hemoglobin (g/dL)	11.66±2.22	13.28±1.55	0.027
Platelet (/mm^3)	472,277±169,382	507,500±176,120	0.571
MPV (fL)	7.94±1.25	7.77±1.12	0.718
BUN (mg/dL)	35.73±15.16	38.83±28.88	0.722
Creatinine (mg/dL)	0.9±0.28	8.85±27.45	0.271
AST (U/L)	19.57±5.89	24.5±32.75	0.584
ALT (U/L)	20.4±9.88	18.75±22.42	0.800
LDH (U/L)	281±95.22	216±28.55	0.049
Amount of platelet reduction with anagrelide (ΔPLT)	536,577±417,074	371,785±253,847	0.203

MPV: mean platelet volume, BUN: blood urea nitrogen, AST: aspartate aminotransaminase, ALT: alanine aminotransaminase, LDH: lactate dehydrogenase.

Discussion

Our study observed that the JAK2 mutation did not cause a significant difference in terms of age, gender, age at diagnosis, and bone marrow fibrosis, and the effect on myeloid, erythroid, megakaryocytic series was similar at the time of diagnosis. After anagrelide treatment, patients with JAK2 mutation were found to have a significantly higher platelet count and lower LDH levels.

Although the frequency of JAK2 mutations in ET patients was found to be 60% in the literature, JAK2 mutation was found to be positive in 42% of the patients in our study.[5] Rumi et al.[6] reported that they observed a male/female ratio of 167/299 among 466 JAK2 patients and the median age at diagnosis of 50 (15-92). Our current study observed that the JAK2 positive male/female ratio was 9/5 in favor of the male gender, and the median age at diagnosis was 42 (20-59). This may be related to the relatively lower number of patients and the younger patients in the patient group who started on Anagrelide. Younger median age at diagnosis may also be associated with switching to Anagrelide rather than Hydroxyurea at more youthful generations for the concern of leukemogenic effects.

It has been reported that 10-15% of patients with ET and PV progressed to myelofibrosis within a median of 15 years.[7] In our study, no transformation into myelofibrosis was observed in accordance with laboratory data after approximately eight years of follow-up. Among the patients whose bone marrow biopsy was performed at the time of diagnosis, patients with positive JAK2 mutations had lower fibrosis scores, but it was determined that the difference could not reach statistical significance.

Since the JAK2 mutation is a mutation that provides a function (spontaneously active molecule), a significant increase can be expected in all three series.[8]

Conclusions

Our study observed that all three sequences were similar to those without JAK2 mutation in the diagnostic tests and hemogram parameters. After approximately eight years of anagrelide treatment, a more significant decrease in cell counts in the myeloid and erythroid series was observed with anagrelide treatment in those with negative JAK2 mutations. LDH levels typically increase with cellular destruction. Lower LDH levels with lower cellular count change after anagrelide treatment may suggest that JAK2 mutation should play a role in resistance to cytoreduction. Studies with more patients would be necessary to prove this hypothesis.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: FO, TGK; Study Design: TGK, FO; Supervision: FO, VO; Data Collection and/or Processing: TGK, TE, SE; Statistical Analysis and/or Data Interpretation: TGK, FO; Literature Review: TGK; Manuscript Preparation: TGK; and Critical Review: FO, VO, TE.

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Original Article

Comparison of Clinical Progress of COVID-19 Patients Followed in the Hospital by Vaccination Status

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ABSTRACT

Background Although COVID-19 vaccines cannot prevent infection with SARS-CoV-2, they do allow infected people to have a milder illness. In unvaccinated people, the disease progresses more severely and the disease can be fatal. Both inactivated (Sinovac) and mRNA (BioNTech-Pfizer) vaccines are used in Turkey. In this retrospective study, clinical course, radiological involvement and some laboratory parameters that are important for COVID-19 were compared in unvaccinated and vaccinated patients who were infected and followed up in the hospital.

Material and Methods Patients between the ages of 17-95 who were hospitalized in the COVID-19 isolation wards between June 2021 and November 2021 were included in the study. Various data of patients were scanned retrospectively from the hospital registry system.

Results While there was no difference in the mean age, highest fibrinogen, D-dimer, ferritin, creatinine, interleukin-6 (IL-6) values and COVID-19 PCR test negative times besides antibody levels, Group 2 (7.8 days) was found to be discharged significantly earlier than Group 1 (12.69 days) (p=0.046). There was a significant difference in low-dose thoracic computed tomography (CT) findings between the two groups (p=0.023).

Conclusions Our study results showed that regardless of the type of vaccine, vaccination against COVID-19 reduces hospitalization rates, length of stay and prevents serious involvement in the lungs.

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Introduction

Coronaviruses are important human and animal pathogens. At the end of 2019, it became a pandemic, starting with Wuhan in China's Hubei Province, it still continues today.[1] SARS-CoV-2 virus is a non-segmented, single-stranded, positive-sense RNA virus.[2] As of January 2022, COVID-19 infection had caused a total of 404,910,528 cases and 5,783,776 deaths worldwide.[3] In the majority of cases, the novel coronavirus SARS-CoV-2 causes respiratory illness that does not require special medical attention, but up to 20% of COVID-19 patients require hospitalization.[4] Severe COVID-19 infection triggers an unstable and uncontrolled cytokine response (termed cytokine storm), extreme endothelial inflammatory reactions, and vascular thrombosis. These, and possibly other yet unknown factors, may lead to the development of acute respiratory distress syndrome (ARDS), a major cause of death in COVID-19 patients.[5,6]

Although COVID-19 vaccines cannot prevent infection with SARS-CoV-2, they do allow infected people to have a milder illness. In unvaccinated people, the disease progresses more severely and the disease can be fatal. Messenger ribonucleic acid (mRNA)-based vaccines are the latest generation vaccines.[7] Current vaccines developed by companies Pfizer and Moderna use synthetic mRNA encoding the spike protein (S-protein) sequence of the coronavirus encapsulated in a lipid vesicle nanoparticle. In whole-pathogen-inactivated virus vaccines, which consist of killed/inactivated whole viruses or virus fragments, the genetic material of the pathogen is destroyed by heat, chemicals, or radiation so that they cannot reproduce, but their presence can still induce immunity. Sinopharm, SinoVac and Bharat Biotech's vaccines consist of inactivated virus.[7,8] Both inactivated (Sinovac) and mRNA (BioNTech-Pfizer) vaccines are used in Turkey. In this retrospective study, clinical course, radiological involvement and some laboratory parameters that are important for COVID-19 were compared in unvaccinated and vaccinated patients who were infected and followed up in the hospital..

Material and Methods

Patients between the ages of 17-95 who were hospitalized in the COVID-19 isolation wards between June 2021 and November 2021 were included in the study. Patients' symptoms, hematological and biochemical test results, radiological findings, clinical course, length of hospital stay, and negative time for COVID-19 polymerase chain reaction (PCR) were scanned retrospectively from the hospital registry system. Patients with missing data were excluded from the study. Single vaccinated and unvaccinated Group 1, double vaccinated or mixed vaccinated Group 2 was determined.

Statistical Analysis

Data obtained were analyzed using SPSS 24 software (IBM Corp, Armonk, NY). During the evaluation of study variables, descriptive statistical methods (mean, standard error, rate) were used. Data were analyzed using Student's t test, Mann-Whitney U test, Chi-square test and Fisher's exact test, as appropriate. A value of $p< 0.05$ was considered as statistically significant.

Results

The demographic characteristics, symptoms, clinical course and laboratory results of the patients are summarized in Table 1. 68 patients were included in the study. However, 14 patients with unknown vaccination status were excluded from the study. The female male ratio included in the study was 24/30. 55.6% of the patients were male, and the mean age of all patients was 50.76±16.82 years. The mean age was lower in male (47±18.39 years) patients than in female (55.46±13.58 years) patients, but no statistically significant difference was found ($p=0.06$).

When the vaccination status of the patients was evaluated, 26 (48.1%) patients were unvaccinated, 5 (9.3%) patients were single Sinovac, 3 (5.6%) patients were single BioNTech, 11 (20.4%) patients were double or more Sinovac and 7 (13%) patients had double BioNTech, 2 (3.7%) patients had mixed vaccine protocol. 2 (3.7%) patients were exitus. One of these patients was unvaccinated and the other had a mixed vaccine protocol. Group 1 (34 patients) was determined as single vaccinated and

Table 1. Comparison of patients according to their vaccination status.

Variables	Group 1 (n=34)					Group 2 (n=20)					p value
	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	
Age (year)	48.65	19.42	45.50	4	83	54.35	10.61	53.0	40	78	0.169
Fibrinogen (mg/dL)	624.44	152.55	596.50	301	892	579.21	147.04	574.0	339.0	879.0	0.299
D-dimer (mg/L)	3.93	6.98	1.31	0.20	35	3.24	7.88	0.82	0.24	35.0	0.185
Ferritin (ng/mL)	1071.44	1522.77	629.50	14	8827	942.21	1231.06	426.0	25.0	3898.0	0.266
CRP (mg/dL)	13.50	10.60	11.31	0.05	41.12	10.54	11.41	7.16	1.72	50.49	0.210
IL-6 (pg/mL)	48.87	77.01	18.30	4.17	417	31.13	40.77	9.12	2.0	133.0	0.197
Discharge time (day)	12.69	11.14	10.0	3.0	48.0	7.80	6.72	6.50	2.0	34.0	0.046
Negative time (day)	15.71	7.71	14.0	6.0	41.0	11.54	2.30	11.0	9.0	16.0	0.102
Antibody (U/mL)	94.68	67.0	107.05	14.6	150	305.86	312.64	150.0	22.30	750	0.245

SD: standard deviation, Min: minimum, Max: maximum.

unvaccinated, and Group 2 (20 patients) as double vaccinated or mixed vaccinated. While the rate of women in Group 1 was 44.1%, the rate of women in Group 2 was 45%, and there was no significant difference in gender distribution between the two groups (p=0.950).

While there was no difference in the mean age, highest fibrinogen, D-dimer, ferritin, creatinine, interleukin-6 (IL-6) values and COVID-19 PCR test negative times besides antibody levels, Group 2 (7.8 days) was found to be discharged significantly earlier than Group 1 (12.69 days) (p=0.046) (*Table 1*). There was a significant difference in low-dose thoracic computed tomography (CT) findings between the two groups (p=0.023) (*Table 2*). It was observed that the patient group without thorax CT involvement was in Group 2. While severe bilateral involvement was 58.8% in Group 1, it was 25% in Group 2.

When their comorbidities were evaluated, 17 (50%) patients in Group 1 and 9 (45%) patients in Group 2 had comorbidities. In Group 1, 7 (20.6%) patients had type 2 diabetes mellitus (T2DM), 3 (8.8%) patients had cancer, 9 (26.5%) patients had hypertension (HT), and in Group 2, 4 (20%) patients had T2DM, 2 (10%) patients had cancer, 3 (15%) patients had HT. Other comorbidities such as asthma, rheumatologic, neurologic, cardiac and thyroid diseases were seen at lower rates. When all comorbidities were compared, no significant difference was found between the two groups.

Discussion

In this study, in which COVID-19 positive cases, who were hospitalized in the same period, were fully vaccinated and the vaccine doses were insufficient or were not vaccinated, we found that the vaccine significantly shortened the hospitalization period. Although there was no difference in comorbidity, age and sex ratios between the two groups, we found that low-dose thoracic CT involvement was not significantly present or was less severe in the group with full vaccinations.

A placebo-controlled phase III study in more than 36,000 participants aged 16 years and over with a median follow-up of two months showed that the mRNA vaccine had 95 percent efficacy in preventing symptomatic COVID-19 infection after the second dose and 7 days after that (95% CI 90.3-97.6; 8 vs 162 subjects on placebo).[9] According to the interim results of a phase III study in Turkey

Table 2. Findings of thoracic computed tomography

Group 1 (n=34)		Group 2 (n=20)	
Finding	Frequency n (%)	Finding	Frequency n (%)
Bilateral severe	20 (58.8%)	Bilateral severe	5 (25%)
Bilateral intermediate	7 (20.6%)	Bilateral intermediate	6 (30%)
Bilateral mild	5 (14.7%)	Bilateral mild	4 (20%)
Unilateral severe	1 (2.9%)	Unilateral mild	1 (5%)
Unilateral mild	1 (2.9%)	No involvement	4 (20%)

which 10,000 participants participated, the vaccine effectiveness of the inactivated virus vaccine, which started 14 days after the full vaccination, was 83.5 percent.[10]

In our study, 28 patients who were hospitalized and followed-up because vaccines could not prevent symptomatic infection and 26 patients who had never been vaccinated were examined. Although the vaccine was insufficient to prevent symptomatic COVID-19 infection in some patients, it improved the clinical outcome and shortened the length of hospital stay.

Conclusions

Our study results showed that regardless of the type of vaccine, vaccination against COVID-19 reduces hospitalization rates, length of stay and prevents serious involvement in the lungs.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: SEY, IBG; Study Design: SEY, IBG; Supervision: SEY, IBG; Data Collection and/or Processing: IK, SEY; Statistical Analysis and/or Data Interpretation: IK, YO; Literature Review: IK, YO; Manuscript Preparation: IK, YO; and Critical Review: IK, YO.

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Original Article

Comparison of Ki-67 Index Values Between Patients With Operated Giant Prolactinomas and Macroprolactinomas

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ABSTRACT

Background Data on whether there is a histopathological difference in cellular features as determined with Ki-67 between giant prolactinomas and smaller macroprolactinomas are not fully clear. In this study, we aimed to compare Ki-67 value between patients followed-up with diagnosis of macroprolactinoma and giant prolactinoma and operated for different reasons.

Material and Methods Files of 15 patients with giant prolactinomas and 16 patients with macroprolactinomas who had been operated with various indications were retrospectively evaluated. Similar number of patients were included to carry out a reasonable analysis. Patients' demographics (age and gender), age at the time of diagnosis, tumor diameter during the diagnosis and at the last follow-up visit, initial and last PRL and Ki-67 values were compared between the groups. Ki-67 value was studied with MIB-1 monoclonal antibody method.

Results The mean age and gender were similar between the patients with macroprolactinomas and giant prolactinomas. The mean longest tumor diameter at diagnosis was measured as 18.13±9.42 mm in the macroprolactinoma and 47.07±9.70 mm in the giant prolactinoma group ($p<0.001$). The mean PRL level at diagnosis was found as 4534.93±12923.56 in the macroprolactinoma and 5513.08±7077.87 in the giant prolactinoma group ($p=0.008$). The mean Ki-67 value was found as 31.06±28.82 in the macroprolactinoma and 31.60±30.78 in the giant prolactinoma group. There was no significant difference between the groups in the Ki-67 values ($p=0.922$).

Conclusions Ki-67 value was similar between macroprolactinomas and giant prolactinomas, suggesting that mitotic activity as determined by Ki-67 value is not practical in indicating growth and proliferation characteristics of prolactinomas.

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Introduction

Prolactinomas are the most common hormone secreting adenomas of the pituitary, accounting for approximately 60% of all pituitary adenomas that cause clinical symptoms.[1] The prevalence of prolactinomas has been reported as 500 cases per million and the annual incidence as 27 cases per million.[2] Prolactinomas are classified based on their longest diameter measured on magnetic resonance imaging (MRI) as microprolactinomas (<10 mm), macroprolactinomas (>10 mm) and giant prolactinomas (> 40 mm).[3] Macroprolactinomas are more commonly encountered in women, leading to menorrhea, infertility and galactorrhea, are usually confined to sella turcica and do not cause compressive symptoms. Macroprolactinomas are more common in men and exhibit hyperprolactinemia, often leading to signs and symptoms of mass effect, including hypopituitarism, headaches and visual impairment due to compression of the optic chiasm and extracellular diffusion.[1,4,5]

Giant prolactinomas on the other hand are extremely rare, accounting for only 1-5% of all prolactinomas.[6] Giant prolactinomas are usually seen in men aged 20-50 years with a male-to-female ratio of ~9:1.[7] Giant prolactinomas are in general of benign nature, although these tumors are invasive and aggressive, extending into the suprasellar area and invading cavernous sinuses. The optic chiasm is often involved, causing visual defects and sometimes ophthalmoplegia. Patients with giant prolactinomas usually present with elevated prolactin (PRL) levels up to 100,000 ng/mL.[8] Male patients may complain of erectile dysfunction, hypogonadism, visual problems, headaches and weakness.

Treatment goals are similar between giant prolactinomas and macroprolactinomas, and include normalization of prolactin levels, tumor shrinkage with decompression of adjacent structures, especially the optic chiasm and cranial nerves, and normalization of testosterone levels.[8] Medical treatment of prolactinomas is mostly successful using dopamine agonists (DAs) as the first line therapy. However, several indications may require pituitary surgery as the second line treatment in a selected group of patients, including those who cannot tolerate or are resistant to medical treatment with DAs, patients that desire fertility, those with prolactinomas that impinge on the optic chiasm, psychiatric patients with contraindication to treatment with DAs and those and patients presenting with CSF leak or pituitary apoplexy.[1,9,10]

Ki-67 is one of the immunohistochemical markers of growth and proliferation used in the histological evaluation of different tumors. The utility of Ki-67 expression in the active cell cyle of prolactinomas is controversial.[11,12] In addition, data on whether there is a histopathological difference in cellular features as determined with Ki-67 between giant prolactinomas and smaller macroprolactinomas are not fully clear. In this study, we aimed to compare Ki-67 index between patients followed-up with the diagnosis of macroprolactinoma and giant prolactinoma and operated for different reasons.

Material and Methods

The files of 31 patients with 15 having giant prolactinomas and 16 macroprolactinomas, who had been operated with various indications and who had Ki-67 index studied through histochemical examinations in the Endocrinology and Metabolism clinic of our hospital between 2015 and 2019 were evaluated and included in this retrospective study. Similar number of patients were included to carry out a reasonable analysis. Tumor diameters were measured with gadolinium-enhanced pituitary MRIs performed at diagnosis and upon follow-up. The pituitary adenomas were evaluated in two groups, including those with a tumor diameter between 10-40 mm defined as macroprolactinomas and those >40 mm as giant prolactinomas.

Patients' demographics (age and gender), age at the time of diagnosis, tumor diameter during the diagnosis and at the last follow-up visit, initial and last PRL and Ki-67 values were recorded and compared between the groups. Data used in this study were obtained from the electronic information system and hospital archives.

Table 1. Demographic characteristics of the patients.

	Macroprolactinoma (n=16)	Giant prolactinoma (n=15)	Total (n=31)	p value
Age at diagnosis (year) (mean±SD)	34.06±7.92	39.13±10.84	36.52±9.63	0.188
Gender				0.01*
Male n (%)	5 (31.25)	12 (80)	17 (54.84)	
Female n (%)	11 (68.75)	3 (20)	14 (45.14)	

*Chi-square, p<0.05; SD: standard deviation.

Ki-67 Immunostaining

Ki-67 antigen was determined using MIB-1 monoclonal antibody. Surgical specimens were fixed in 10% buffered formalin and then embedded in paraffin blocks. Avidin-biotin-peroxidase method was used for Ki-67 Immunostaining.[13] Sections of 5 μm were cut and put onto glass slides, dried and were then incubated with MIB-1 antibody at 4 °C for 24 hours. The areas with highest concentrations of MIB-1 positive nuclei were analyzed at 400x magnification. The Ki-67 value was calculated in each slide as the rate of immunopositive nuclei based on 1,000. Hematogenous cells were excluded and only dark brown stained nuclei were considered positive.

Statistical Analysis

Data obtained in this study were statistically analyzed with SPSS v. 23 (SPSS, Statistical Package for Social Sciences, IBM Inc., Chicago, IL, USA) statistical software. Normality of the variables was tested with the Kolmogorov-Smirnov method. Since the variables were non-normally distributed, Mann-Whitney U method among the non-parametric tests was used in comparison of the continuous variables between the groups. Categorical parameters were compared using the Chi-square tests. Continuous variables are expressed as mean±standard deviation descriptive statistics and categorical variables as frequency (number, percentage). The statistical significance level was set at p<0.05.

Ethical Considerations

The study protocol was approved by the local ethics committee of the hospital. Patient consents were not needed as the study was retrospective in design, but the necessary permission was obtained from the hospital management for using archive files. The study was performed in accordance with the 1964 Declaration of Helsinki (DoH) and its later amendments.

Results

A total of 31 patients with prolactinomas were included in the study with 17 (54.84%) being male and 14 (45.14%) female. Sixteen (51.61%) of the patients had macroprolactinomas and 15 (48.39%) had giant prolactinomas. Five (31.25%) patients were male and 11 (68.75%) patients were female in the macroprolactinoma group, while 12 (80.00%) patients were male and 3 (20.00%) patients were female in the giant prolactinoma group. The male:female ratio was significantly higher in the giant prolactinoma group compared to the macroprolactinoma group (p=0.01).

The mean age at diagnosis was 36.52±9.63 year overall, 34.06±7.92 years in the macroprolactinoma group and 39.13±10.84 years in the giant prolactinoma group. No statistically significant difference was found between both groups in terms of the mean age (p=0.188). Demographic data of the patients are given in Table 1.

The mean tumor diameter was measured as 32.13±17.45 mm overall, 18.13±9.42 mm in

the macroprolactinoma group and 47.07±9.70 mm in the giant prolactinoma group (p<0.001). The mean tumor diameter at the end of follow-up was measured as 13.82±16.31 mm overall, 1.00±3.61 mm in the macroprolactinoma group and 24.93±14.72 mm in the giant prolactinoma group (p<0.001).

The mean PRL level at diagnosis was found as 5024.01±10249.95 ng/mL overall, 4534.93±12923.56 ng/mL in the macroprolactinoma group and 5513.08±7077.87 ng/mL in the giant prolactinoma group (p=0.008). The mean PRL level at the end of follow-up was found as 996.52±2463.35 ng/mL overall, 55.00±103.75 ng/mL in the macroprolactinoma group and 2155.32±3392.46 ng/mL in the giant prolactinoma group (p<0.001).

In the histopathological examinations; the mean Ki-67 value was found as 31.32±29.28 overall, 31.06±28.82 in the macroprolactinomas group and 31.60±30.78 in the giant prolactinoma group. There was no statistically significant difference between the groups in terms of the Ki-67 values (p=0.922) (*Figure 1*).

Discussion

Giant prolactinomas are distinguished from smaller macroprolactinomas with some clinical and biological characteristics. In the current literature, patients with a pituitary adenoma > 40 mm in diameter and a PLR level exceeding 1,000 ng/mL are considered to have giant prolactinomas, while macroprolactinomas are defined as adenomas with a diameter between 10-40 mm.[5,12] In the present study, we compared giant prolactinomas and macroprolactinomas in terms of clinical and histochemical characteristics.

Both macroprolactinomas and giant prolactinomas have a male predominance with a reported male to female ratio of 9:1 in giant prolactinomas.[6,14] Espinosa et al.[5] reported the rate of males as 47% in macroprolactinomas and 89% in giant prolactinomas. Artz et al.[15] reported the rate of male patients with macroprolactinomas as 56.7%. In our study, the rate of the males was 31.3% in the macroprolactinoma and 80% in the giant prolactinoma group. The difference between the studies in the rate of male patients might be resulted from the number of patients and inclusion criteria.

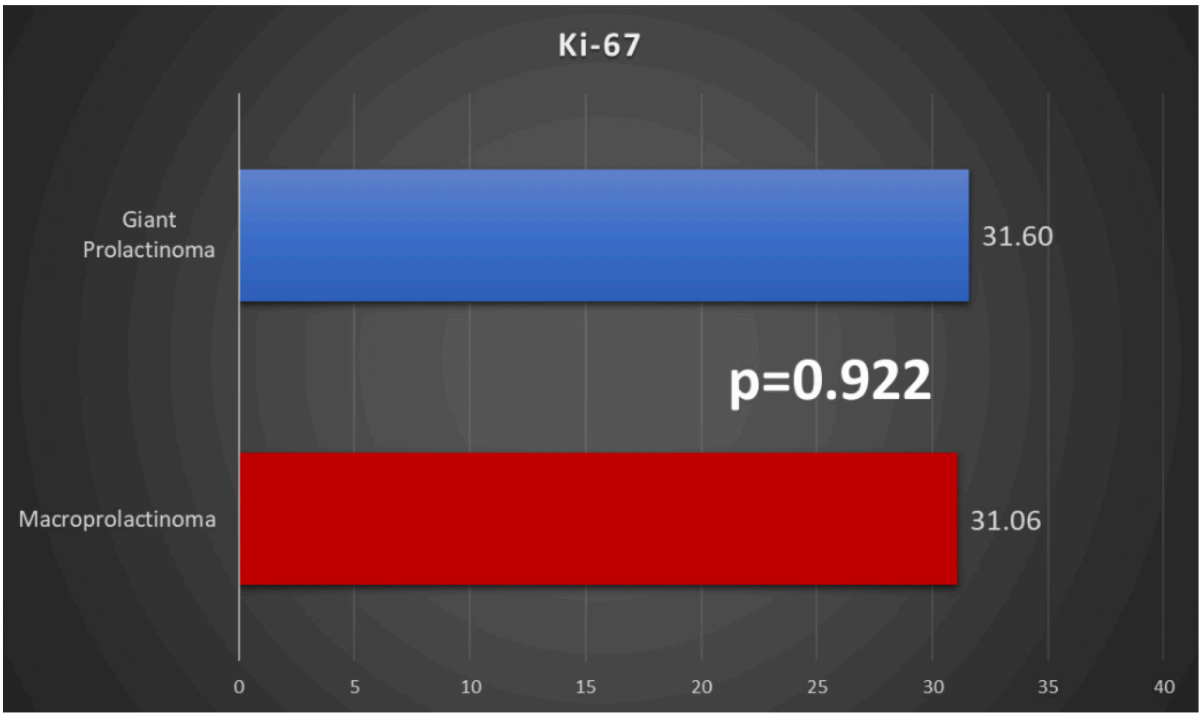

Figure 1. Ki-67 values of the patient groups with prolactinomas.

Approximately 60% of the adult males with macroprolactinomas are diagnosed before 40 years of age.[16] Although macroprolactinomas are most commonly seen in young men, they have also been reported in elderly males.[17] Whereas, giant prolactinomas are usually diagnosed in the 20-50 years age group.[8] Almalki et al.[18] reported the mean age at diagnosis as 38.1 years and Iglesias et al.[16] as 40 years. In our previous study, we found the mean age as 34.4 years.[12] In the present study, the mean age of all patients was found as 36.52 years and our finding was in the age range reported in the literature. There was no significant difference between the macroprolactinoma and giant prolactinoma groups in terms of the mean age (34.06 vs 39.13, p=0.188).

Normalization of PLR levels has been reported as 70-80% for macroprolactinomas and 60-68% for giant prolactinomas.[6,14] These rates are not surprising, because mitotic rate and proliferation of the giant tumors are only mildly increased in these adenomas compared to macroprolactinomas.[8] In our study, normalization of PLR levels was found as 100% in the macroprolactinoma and 80% in the giant prolactinoma group at the end of the follow-up.

Although most of the prolactinomas show a slow growth, some exhibit aggressive or invasive biological behavior.[19] However, there is no generally accepted marker available to identify invasiveness of pituitary adenomas. Recently, several cell cycle specific nuclear antigens have been used with various immunohistochemical methods to evaluate biological tumor characteristics. Among these antigens, Ki-67 is typically expressed at G1, S, G2 and M phases of the cell cycle during proliferation.[20] Ki-67 value can be readily obtained with monoclonal antibody MIB-1, which enables detection of the Ki-67 antigen in formalin-fixed, paraffin-embedded tissues.[19] Ki-67 has been reported to be useful in evaluating various brain tumors, providing information about cell proliferation and thus, prognosis.[21] However, it is still controversial whether Ki-67 is related to tumor aggressiveness or invasiveness in prolactinomas. Peak et al.[19] found no significant differences in the Ki-67 index in relation to age, gender and type of pituitary adenomas. In our previous study, we also did not observe a significant difference in Ki-67 values between invasive and non-invasive prolactinomas.[12] On the contrary, Pizarro et al.[22] argued that mitotic activity evaluated by the detection of Ki-67 antigen was significantly higher in invasive than in non-invasive pituitary adenomas and that Ki-67 could be used in therapeutic postoperative management since cut-off values associated with aggressive behavior of the tumor can be established. B□ lini□ teanu et al.[23] reported higher Ki-67 values in prolactinomas secreting PRL. However, in our study we compared Ki-values between macroprolactinomas and giant prolactinomas for the first time in the literature and could not find a statistically significant difference between the two types of pituitary adenomas (31.06 vs 31.60, p=0.922).

Study Limitations

This study has several limitations. The study was designed as retrospective and included a relatively small number of patients. In addition, correlations of Ki-67 with different parameters could not be analyzed due to sample size. Finally, we could not exactly compare our findings, because there is only one study comparing macroprolactinomas and giant prolactinomas, but it did not evaluate Ki-67 (Espinosa). Therefore, our study is the first to investigate the utility of Ki-67 value in indicating biological behavior of pituitary adenomas. We believe that our findings will raise a new debate in the utility of Ki-67 index in distinguishing pituitary adenomas in terms of invasiveness.

Conclusions

Ki-67 value, which is used as a marker of invasiveness and biological behavior of different tumors, was similar between macroprolactinomas and giant prolactinomas. This finding suggests that mitotic activity as determined by Ki-67 value is not effective on growth and proliferation characteristics of prolactinomas. However, our results should be supported with further comprehensive prospective studies with a larger series of patients.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: SC, OOG; Study Design: SC; Supervision: SC, OOG; Data Collection and/or Processing: SC, OOG; Statistical Analysis and/or Data Interpretation: SC; Literature Review: SC; Manuscript Preparation: SC; and Critical Review: OOG.

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Original Article

Evaluation of Insulinoma Cases Presented With Hyperinsulinemic Hypoglycemia: A Single-Centre Experience

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ABSTRACT

Background Insulinomas constituting the most common cause of endogenous hyperinsulinism-related hypoglycemia are neuroendocrine tumors originating from pancreatic beta cells. They are generally benign and solitary lesions. Although most cases are sporadic, multiple endocrine neoplasia (MEN) 1-related patients are also present.

Material and Methods Thirteen patients followed up in Bursa Uludag University Medical Faculty Endocrinology and Metabolic diseases clinic between the years 2012 and 2021 were retrospectively evaluated. Demographical, clinical, biochemical, radiological and histopathological data of the patients were assessed.

Results Eight of the patients were females, and five were males with an average age of 43±14.9 years. Ten of the patients had sporadic, and three had MEN1 syndrome-related insulinoma. During the prolonged fasting test, the patients had a mean lowest plasma glucose level of 36.4±6.2 mg/dL with a simultaneous mean insulin level of 11.3 (4.4-214.1) mIU/L and c-peptide level of 2.8 (0.46-12.8) mcg/L. In preoperative localization studies, a lesion was detected in 11 out of 13 (84.6%) patients with upper abdominal computed tomography and 6 out of 10 patients (60%) with magnetic resonance imaging. Six patients had grade 1, and 7 patients had grade 2 neuroendocrine tumor. The whole group's mean lesion diameter was 15 (11-48) mm. The mean patient follow-up duration was 30.5±23 months. Hypoglycemia recurred in none of the patients in the postoperative period, and only two patients (15.4%) developed postoperative diabetes mellitus.

Conclusions Preoperative localization rates in insulinomas increased due to non-invasive imaging methods and technological developments in recent years. This will probably cause earlier diagnosis and treatment, and pancreas preserving surgery option will be more available in most insulinoma cases.

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Introduction

Insulinomas are neuroendocrine tumors originating from pancreas beta cells. These tumors are known as the most common cause of endogenous hyperinsulinism-related hypoglycemia. The annual incidence of insulinomas is 0.4/100,000 individuals.[1] They are generally seen between the ages of 40 and 50 years. Insulinoma prevalence does not differ between the genders.[2] Benign and single lesions constitute 90% of the cases.[3] The presence of hypoglycemia, also known as the Whipple triad, is defined by the presence of sympathoadrenergic and/or neuroglycopenic symptoms of hypoglycemia and recovery of these symptoms through glucose intake define the main characteristic of insulinoma diagnosis.[2] Although hypoglycemia is mainly seen during fasting in insulinoma cases, it can also be seen following food intake.

Insulinoma can also be observed in 10-15% of patients diagnosed with multiple endocrine neoplasia type 1 (MEN1), although most insulinoma cases are sporadic.[4] Localizations of the lesions are tried to be detected through preoperative imaging studies in clinically and biochemically diagnosed insulinoma cases. Surgery is the primary curative option for lesions localizable through non-invasive and/or invasive methods. Different pharmacological treatment approaches can be applied in non-operable cases or required cases to control hypoglycemia until the surgery.[2] In this study, our objective was to discuss insulinoma diagnosis and treatment in light of the literature by presenting the demographical and clinicopathological characteristics of 13 insulinoma cases diagnosed and treated in our clinic.

Material and Methods

Study Population and Protocol

The study's consent was taken from Bursa Uludağ University Ethics Board. Thirteen patients hospitalized and examined in Bursa Uludağ University Endocrinology and Metabolism Diseases clinic due to hypoglycemia between January 1st 2012 and December 31st 2021 were included in the study. All patient data were attained retrospectively from the hospital record system. Patients who were clinically diagnosed with hyperinsulinism-related hypoglycemia had lesion localization provided through preoperative or intraoperative imaging and were histopathologically reported to have neuroendocrine tumors were included in the study. Patients whose diagnostic tests, surgical treatment and pathological evaluation were not performed in our centre were not included in the study.

If the measurement for diagnosis was impossible at the moment of spontaneous hypoglycemia, a 72-hour prolonged fasting test was started after the last meal and 1-2 hour routine capillary glucose measurements were made during the follow-ups. Plasma glucose, c peptide and insulin were measured in patients who developed hypoglycemia symptoms or were asymptomatic and had capillary glucose measurements detected below 70 mg/dL. Synchronous insulin level ≥3 mIU/L and c-peptide level ≥0.6 mcg/L with plasma glucose below 55 mg/dL were evaluated as the biochemical diagnosis for insulinoma. The test was ended with intramuscular or subcutaneous 1 mg glucagon injection in patients who were symptomatic and had plasma glucose value below 55 mg/dL or were asymptomatic with plasma glucose value below 45 mg/dL. Plasma glucose measurements were made in the 10th, 20th and 30th minutes following injection. Insulinoma was considered if plasma glucose had an increase over 25 mg/dL following glucagon application.

If required, a standard mixed meal test was performed following overnight fasting in patients with defined postprandial hypoglycemia symptoms. Samples were taken for glucose, insulin and c-peptide for five hours following 300 kcal (60% carbohydrate, 20% fat and 20% protein) food intake. Insulin and c-peptide values were evaluated during hypoglycemia.

Statistical Analysis

Sampling normality was evaluated through the Shapiro-Wilk test. Mean±standard deviation (SD) was used in normally distributed constant variables, and median (minimum-maximum values) was used for variables lacking normal distribution. Two independent variables were evaluated through student T or Mann-Whitney U tests. Kruskal-Wallis test was used in multiple variable conditions. $p<0.05$ was regarded as

statistically significant. SPSS (Statistical Package for the Social Sciences) 23 program was used for statistical analysis.

Results

Eight (61.5%) of the patients were female, and five (38.5%) were male. The average age of all patients was 43±14.9 years. The average age of females was significantly higher than males (51.7±9.9 years and 29.2±10.3 years respectively; p=0.002). Ten patients (7 female and 3 male) had sporadic, and three (1 female and 2 male) had familial insulinoma (MEN1). The average age was 30±12.3 years for patients with MEN1 syndrome and 47±13.8 years for sporadic patients. No significant difference was detected among them (p=0.06). Body mass index (BMI) was 36.9±7.7 kg/m^2 in females and 30.3 (26.7-40.6) kg/m^2 in males with no statistically significant difference among them (p=0.22).

Four females had hypertension, and 1 male had hypothyroidism as a comorbid disease. Nine patients had sympathoadrenergic symptoms or neuroglycopenic symptoms during the first admission. Four patients had no significant symptoms defined. Demographical and clinical characteristics of the patients during admission are shown in Table 1.

A 72-hour prolonged fasting test was made to investigate hypoglycemia etiology in eleven patients. Meantime between the start of the test and hypoglycemia detection was 7.09±7.66 hours in all patients and 9±8.79 hours in females and 2 (1-10) hours in males (p=0.25). Based on the prolonged fasting test, the plasma glucose of the patients was 36.4±6.2 mg/dl, insulin was 11.3 (4.4-214.1) mIU/L, and c-peptide was 2.8 (0.46-12.8) mcg/L (*Table 2*). Standard meal test was performed in two patients, including one male and one female, with postprandial hypoglycemia defined in anamnesis. Values for glucose and insulin were 19 and 28 mg/dL and 17.4 and 4 mIU/L, respectively.

In preoperative localization imaging, the pancreatic lesion was detected in 1 out of 6 patients whose ultrasonography (USG), in 11 out of 13 patients (84.6%) whose upper abdominal computed tomography (CT) and in 6 out of 10 patients (60%) whose upper abdominal magnetic resonance imaging (MRI) reports were available.

Table 1. Demographic and clinical patient characteristics.

	All patients	Female	Male	p value
Gender n (%)	13	8 (61.5%)	5 (38.5%)	
Age (years)	43±14.9	51.7±9.9	29.2±10.3	0.002
BMI (kg/m^2)	34.1±7.5	36.9±7.7	30.3 (26.7-40.6)	0.22
Symptoms				
Sympathoadrenergic (n)	9	7	2	
Neuroglycopenic (n)	9	5	4	
Comorbid diseases				
Hypertension (n)	4	4	-	
Hypothyroidism (n)	1	-	1	
MEN1 syndrome (n)	3	1	2	
SBP (mmHg)	137.1±16.8	134.5±11.7	140.8±23.3	0.55
DBP (mmHg)	86.4±11.7	86.8±11.3	85.8±13.5	0.88
Pulse (per min)	91.5±22.1	93.4±16.2	88.8±30.6	0.74

BMI: body mass index. SBP: Systolic blood pressure, DBP: diastolic blood pressure

Table 2. Prolonged fasting test evaluation.

	All patients	Female (n=7)	Male (n=4)	p value
Time to hypoglycemia (hours)	7.09±7.66	9±8.79	2 (1-10)	0.25
Plasma glucose (mg/dL)	36.4±6.2	31 (28-44)	38 (34-43)	0.44
Insulin (mIU/L)	11.3 (4.4 - 214.1)	7.3 (4.4-30.9)	15.6 (11.3-214.1)	0.08
C-peptide (mcg/L)	2.8 (0.46-12.8)	2.71 ± 2.15	3.35 (2.8-12.8)	0.18

Lesions detected in CT were in the head of the pancreas in five patients (45.5%), in the body of the pancreas in two patients (18.2%) and pancreatic tail in four (36.4%) patients. The number of patients with lesions detected at these locations in MRI was 3 (50%), 1 (16.7%) and 2 (33.3%), respectively. The maximum mean lesion diameter was 16.6±6.87 mm for all localizations, 20.6±7.23 mm for the head, 14.5 (13-16) mm for the body and 12.25 (7-20) mm for the tail in CT. Lesion dimensions were similar among all parts of the pancreas (p=0.25).

A calcium stimulation test was made in a total of three patients, including two patients with undetectable results in CT and one patient with suspicious localization in preoperative localization imaging. Patients were referred to surgery after determining the localization through this test.

All patients had surgery. Four patients (30.8%) had enucleation, three (23.1%) had partial distal pancreatectomy, five (38.5%) had Whipple procedure, and one (7.7%) had total pancreatectomy. Surgical reports showed that seven of the lesions were (53.8%) located in the pancreas head, one (7.7%) in the body, and four (30.8%) in the tail. No localization information was available in the surgical report of one patient.

Histopathologically, six of the patients had grade 1 neuroendocrine tumor (NET), and seven had grade 2 NET according to WHO 2017 classification. The mean diameter of the lesions was 15 (11-48) mm in the whole group and 16.25±4.74 mm in females, and 26.4±13.3 mm in males (p=0.07).

The mean patient follow-up duration was 30.5±23 months. Hypoglycemia recurred in none of the patients in the postoperative period, and diabetes mellitus was diagnosed only in two (15.4%) patients after surgery. None of the patients had recurrent lesions. One patient had liver metastasis during diagnosis and was cured through resection. It was observed that one patient used diazoxide and octreotide together, and one patient used only octreotide for hypoglycemia control in the preoperative period. None of the patients needed pharmacological treatment for hypoglycemia in the postoperative period.

Discussion

Demographical and clinicopathological characteristics of a total of 13 insulinoma cases, including 8 females and 5 males followed up in our clinic, were evaluated in our study. Diagnosis age was reported as 4-5th decades in the insulinoma cases in literature as in our patients.[5-7] Insulinoma can be seen earlier in familial MEN-1 cases. Younger diagnosis age in male patients in our study can be explained by the higher MEN-1 case rate in this group. Higher mean body mass index in our group compared to literature can be explained by the higher rate of female patients who have a more common rate of obesity, more prolonged hyperinsulinism exposure and ethical and/or cultural differences in our study group.[7] A significant difference was not detected when the patients' systolic and diastolic blood pressures were compared to literature.[8]

Based on 72-hour prolonged fasting tests made while investigating hypoglycemia etiology, nearly 2/3 of the patients became symptomatic or hypoglycemic in the first 24 hours of the test while most of the remaining patients became symptomatic or hypoglycemic in the first 48 hours.[2] All of our cases became symptomatic and

hypoglycemic in the first 24 hours. This situation can be related to the low number of our patients and their latter admission with the established clinical presentation to our hospital, a tertiary health centre.

In preoperative imaging studies performed after the clinical and biochemical provision of insulinoma diagnosis, localization success was provided at a rate of 84.6% through abdominal CT and 60% through MRI in our cohort. While lesion detection rates through MRI in literature were similar to our study, sensitivity through CT was detected lower.[6,9,10] Higher CT positivity rates in our study may be caused by the higher experience of our centre in CT evaluation or lesion diameters >1 cm during admission.

Other studies in the literature reported higher sensitivity rates for PET-CT compared to other conventional (such as CT, MRI) imaging methods. Our study could not provide a clear comparison on this subject as PET-CT result was available for only one patient.[6]

Insulinoma can be seen as a component of familial MEN-1. While a study detected the rate of patients diagnosed with MEN-1 as 6%, this rate was 23% in our patients.[11] This situation can be explained by the low number of our patients and the fact that our hospital is a tertiary centre.

Surgery is the curative treatment option for benign insulinomas.[2] Pancreas preserving surgery is recommended in these patients.[12] While the enucleation preference rate was approximately 60% in the surgical approach, the number of Whipple operations was relatively high in our cases.[13] This difference in the selection of surgical methods can be related to the admission of more severe cases as our hospital is a tertiary centre and the experience and approach of the surgeon.

An analysis in the literature reported that out of 25 patients with surgical and/or pathological reports available, 10 had tumors detected in the head of the pancreas, 4 in its body and 11 in its tail region.[14] While head and tail localization were similarly higher in our patients, body localization was interestingly lower. Although tumor sizes differed among the studies, they were similar to our study.[15]

Previous studies reported post-operative cure in nearly 90% of benign insulinomas in 10-20 year follow-up durations.[1] Hypoglycemia was not observed in any of the patients after surgery in an evaluation of 10 insulinoma cases published in our country.[14] Although the follow-up duration of our patients was shorter compared to the literature, cure rates were similarly relatively high. Diabetes mellitus formed in two of our patients (15.4%) in postoperative follow-ups, and this rate was somewhat higher than 2.2%, which was the rate in literature.[11] This high rate can be explained by Whipple and/or total pancreatectomy was made in a higher rate of our patients. Although recurrence rates of post-operative insulinoma were higher in MEN1 patients than the other patient group in the literature, recurrence has not yet been observed in our patients with MEN1 syndrome as the follow-up period was not long enough in our study.[1]

Conclusions

As a result, clinical and biochemical diagnosis approaches are essential in individuals with suspected insulinoma. Preoperative localization rates in insulinomas increase parallel to non-invasive imaging methods and technological developments in recent years. This will probably cause diagnosis and treatment to be provided earlier and the pancreas preserving surgery option to stand out more in most insulinoma cases. The low number of cases, short follow-up duration and lack of new imaging modalities in our centre were the weaknesses of our study. The strengths of our research are the application of all current approaches in our centre for all patients and the coordinated multidisciplinary approach of endocrinology, radiology, general surgery and pathology units.

Multi-centred studies with a high number of cases for a more detailed evaluation of the diagnoses, treatments and follow-ups of insulinomas will contribute significantly to literature in terms of medical and surgical approaches, diagnosis of these patients in a shorter period and application of effective imaging methods.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This study was approved by the ethics committee of Uludag University (approved number: 2022-2/9).

This chapter does not contain any studies with animals performed by any of the authors.

Authors' Contribution

Study Conception: EA, CE; Study Design: CA, EE; Supervision: EH, OOG; Data Collection and/or Processing: FMS, SC; Statistical Analysis and/or Data Interpretation: EA, CE; Literature Review: EA; Manuscript Preparation: EA; and Critical Review: CE.

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Original Article

Evaluation of Patients Performed With Saline Infusion Test With a Pre-diagnosis of Primary Hyperaldosteronism

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ABSTRACT

Background Primary hyperaldosteronism (PHA) is a primarily treatable cause of arterial hypertension characterized by low plasma renin and high aldosterone levels. The prevalence of secondary hypertension as a common endocrine cause is 5-13%. The plasma aldosterone/renin ratio (ARR) is the best available method for PHA screening. One or more confirmatory tests may be required to confirm or exclude patients' diagnoses. One frequently used confirmatory test is the saline infusion test (SIT). We aimed to screen the patients who underwent SIT with the preliminary diagnosis of PHA and to compare the results of the patients diagnosed with essential hypertension (EH) and PHA.

Material and Methods Seventy-seven patients with a history of drug-resistant hypertension or unexplained spontaneous or diuretic-induced hypokalemia or adrenal incidentaloma, or a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years) and undergoing saline infusion testing were included in the study.

Results Twenty-six (33.8%) of the patients were male, and 51 (66.2%) were female. The mean age of the patients was 54.5±13.7 years. EH was present in 39 (50.6%) patients, and PHA was present in 38 (49.4%) patients. Patients with PHA and EH were compared. There was no significant difference between mean systolic blood pressure, diastolic blood pressure, potassium, and aldosterone renin ratio (ARR) in the two groups ($p>0.05$). Basal plasma aldosterone ($p<0.05$), SIT 0^{th}, and 4^{th}-hour plasma aldosterone levels ($p<0.01$) was significantly higher in PHA than in EH. Aldosterone synthesizing adenoma (ASA) and idiopathic hyperaldosteronism (IHA) were compared. There were no significant differences between basal plasma aldosterone, SIT 0^{th}, and 4^{th}-hour plasma aldosterone levels, ARR, and potassium values ($p>0.05$). The mean sodium value was significantly higher than the IHA ($p <0.05$).

Conclusions Our study determined that the saline infusion test could be used to confirm the diagnosis of primary hyperaldosteronism. Its use alone was not sufficient in the differential diagnosis of aldosterone-synthesizing adenoma and idiopathic hyperaldosteronism.

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Introduction

Primary hyperaldosteronism (PHA) is a primarily treatable cause of arterial hypertension characterized by low plasma renin and high aldosterone levels.[1] Its prevalence is 5-13% as a common endocrine cause of secondary hypertension.[2] The two most common causes of PHA are bilateral idiopathic hyperaldosteronism (or idiopathic hyperplasia IHA, 60%) and unilateral aldosterone-secreting adenomas (ASA 30-40%).[3] Compared with patients with essential hypertension (EH), patients with PHA have a higher risk of cardiovascular and kidney disease.[4] Therefore, early diagnosis and treatment are essential. Treating PHA with either mineralocorticoid antagonists or unilateral adrenalectomy lowers blood pressure while correcting hypokalemia.It also improves impaired cardiac and renal function.[5]

The plasma aldosterone/renin ratio (ARR) is the best available method for PHA screening. Some drugs (diuretics, beta-blockers, etc.) and conditions (hypokalaemia, sodium restriction) may affect the test. If initial results are inconclusive or difficult to interpret, or if PHA is strongly suspected clinically, the ARR should be repeated.[6] It is recommended that patients with positive ARR undergo one or more confirmatory tests to confirm or exclude their diagnosis definitively. However, no further confirmatory testing is required in patients with hypokalemia with suppressed renin and plasma aldosterone level (PAL) >20 ng/dL.[6]

Clinical practice guidelines of the Endocrine Society recommend the following as confirmatory tests: saline infusion test (SIT), fludrocortisone suppression test, captopril challenge test , and oral sodium loading test. According to the 2008 Endocrine Society clinical practice guidelines, if the PAL measured at the 4th hour after SIT is below 5 ng/dL, PHA is excluded. If the PAL is above 10 ng/dL, PHA should be considered. The diagnosis is uncertain if the PAL is between 5-10 ng/dL.[7] On the other hand, Giacchetti et al.[8] suggested that a PAL above 7 ng/dL after SIT was sufficient to confirm the diagnosis of PHA. We aimed to screen the patients who underwent SIT with a prediagnosis of PHA and compare the results of the patients diagnosed with essential hypertension and PHA.

Material and Methods

This study was carried out in Bursa Uludag University Faculty of Medicine. The Uludag University Medical Board approved the study protocol. Seventy-seven patients with a history of drug-resistant hypertension, unexplained spontaneous or diuretic-induced hypokalemia or adrenal incidentaloma, or a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years) and undergoing saline infusion testing were included in the study.Seventy-seven patients whose β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers were discontinued at least two weeks before the test, and diuretics were discontinued at least four weeks before the test were included in the study.

In the SIT protocol, 500 mL/h 0.9% NaCl infusion was given intravenously for 4 hours between 08:00 and noon after the patient lay on his back for at least 2 hours. Plasma aldosterone and plasma renin levels were measured at 0 and 4 hours of the test. If the PAL measured at the 4th hour of SIT was below 5 ng/dL, PHA was excluded. If PAL was above 10 ng/dL, PHA was considered. If the PAL was between 5-10 ng/dL, the diagnosis was made according to the patient's clinical condition, laboratory, need for antihypertensive medication, and imaging.[6]

Multislice contrast-enhanced computed tomography (CT) or magnetic resonance imaging was used as an imaging technique in patients with suspected PHA. ASA was considered in patients with a unilateral solitary adrenal macroadenoma, a normal-appearing contralateral adrenal gland, and a positive laboratory test. IHA was considered in patients with bilateral micronodular hyperplasia or laboratory-positive patients with normal adrenal glands on CT.

Results

A total of 77 patients were included in the study. Of the patients, 26 (33.8%) were male, and 51 (66.2%) were female. The mean age of the patients was 54.5±13.7 years. EH was present in 39 (50.6%) patients, and PHA was current in 38

(49.4%) patients. Patients with PHA and EH were compared. There was no significant difference between the mean systolic blood pressure, diastolic blood pressure, potassium, and ARR in the two groups. There was a significant difference in basal plasma aldosterone ($p<0.05$) and plasma aldosterone ($p<0.01$) levels measured at the 0th and 4th hours of SIT test. Plasma aldosterone and SIT results of PHA and EH patients were given in Table 1. While the etiology was ASA in 24 (63.2%) patients diagnosed with PHA, it was IHA in 14 (36.8%) patients. Six (25%) of the patients diagnosed with ASA were operated on. Spironolactone was given to 25 (65.7%) patients diagnosed with PHA.

Two groups of patients with ASA and IHA were compared. The mean potassium value was 3.9±0.5 mEq/L in the group with ASA and 4.1±0.3 mEq/L in the group with IHA, and no significant difference was found between the two groups. The mean sodium value was 140.6±2.1 mEq/L in the group with ASA and 138.9±1.7 mEq/L in the group with IHA; a statistically significant difference was found ($p <0.05$). The basal plasma aldosterone and SIT results of ASA and IHA patients were showed in Table 2.

Discussion

The prevalence of PHA as the most common endocrine cause of secondary hypertension is 5-13%.[2] In addition, patients with PHA have a higher risk of cardiovascular and kidney disease than patients with EH.[4] Therefore, early diagnosis and treatment are essential. SIT is a frequently used test to confirm the diagnosis. We aimed to screen the patients who underwent SIT with a prediagnosis of PHA and compare the results of the patients diagnosed with EH or PHA.

In our patients with PHA, PAL (44.0±43.9 pg/ml) was significantly higher than in patients with EH (30.5±35.7 pg/ml). Seventy-seven patients participated in the study, and PHA (50.6%) was detected in 1 of 2 patients. In the study of Rossi et al.[9], PHA was found in 120 (37.9%) of 317 patients who underwent SIT. There was no statistical difference between the two groups in ARR. Ahmet et al.[10] suggested that the false positive ARR rate is particularly high in the female population compared to the male population and that different normal ranges should be developed for each gender. Twenty-six of our patients (33.8%) were male, 51 (66.2%) one of them was female.

Table 1. Comparison of PHA and EH laboratory results.

	PHA	EH	p value
Aldosterone (pg/mL)	44.0±43.9	30.5±35.7	<0.05
ARR	111.9±93.6	121.6±138.8	NS
SIT 0th hour aldosterone (pg/mL)	31.2±34.3	10.2±6.5	<0.01
SIT 4th hour aldosterone (pg/mL)	25.1±36.0	3.8±2.0	<0.01

NS: not significant, ARR: aldosterone renin ratio, SIT: saline infusion test.

Table 2. Comparison of ASA and IHA laboratory results.

	PHA	EH	p value
Aldosterone (pg/mL)	52.1±53.2	30.0±12.4	NS
ARR	117.1±102.9	102.8±77.9	NS
SIT 0th hour aldosterone (pg/mL)	35.7±42.2	24.4±15.9	NS
SIT 4th hour aldosterone (pg/mL)	31.1±45.0	15.7±7.1	NS

NS: not significant, ARR: aldosterone renin ratio, SIT: saline infusion test.

Female patients were more than males may have affected the result.

Studies also advocate that when calculating the ARR, the renin value should be fixed at a minimum (0.2 ng/mL/h or 2 mIU/ for PRA), and it is important, especially inpatient subgroups such as the elderly.[11] The mean age of our patients was 54.5±13.7 years. In addition, since patients with a prediagnosis of PHA and an ARR ratio of >20 were evaluated in this study, there is no data for patients with ARR <20 and a direct diagnosis of EH. These factors may have caused the ARR rates to be similar.

In the study of Alam et al.[12], patients diagnosed with PHA had HT for an average of 10.5 (3.5-18) years. Our patients had HT for an average of 13.0±8.2 years before PHA diagnosis. This indicates a significant delay between the onset of PHA and its diagnosis.

When the patients diagnosed with PHA and EH were compared, no difference was found between SBP and DBP. We can explain this by the fact that the population in which we perform SIT generally has severe hypertension, and 87% of our patients use antihypertensive drugs.

Although it did not reach statistical significance when comparing ASA and IHA, the mean PAL was 52.1±53.2 pg/mL in patients with ASA, while it was 30.0±12.4 pg/mL in IHA and was higher. While ARR was 117.1±102.9 in ASA, it was 102.8±77.9 in IHA, and there was no statistical difference. In addition, although the PAL measured at the 4th hour of SIT did not reach statistical significance, it was 31.1±45 pg/mL in ASA and 15.7±7.1 pg/mL in IHA. In the multicenter study by Rossi et al.[9], it was concluded that SIT was safe and specific to exclude PHA, but it had no place to differentiate between ASA and IHA. Arteriovenous sampling (AVS) was performed in 7 of our patients to differentiate ASA and IHA, but it was not successful because the right renal vein could not be catheterized. Therefore, the distinction between ASA and IHA could be made according to severe hypertension, spontaneous hypokalemia, high aldosterone levels, age and CT results. This is the limitation of our study and may have affected the results of IHA and ASA. This creates difficulties distinguishing between ASA and IHA for countries where AVS is difficult to reach.

When the two groups with ASA and IHA were compared, there was no statistical difference in potassium values when the two groups with PHA and EH were compared. The sodium value of the patients with ASA (140.6±2.1 mEq/L) was higher in the group with IHA (138.9±1.7 mEq/L), and it was statistically significant. Hypokalemia has been accepted as one of the distinguishing signs in PHA diagnosis. However, it was observed that less than 37% of patients with PHA presented with hypokalemia.[13] 87% of our patients were taking antihypertensive drugs at the time of admission. This may also have affected the results.

The limitations of our study can be listed as the retrospective nature of our study, the small number of patients, and the failure of our center in AVS.

Conclusions

In our study, it was determined that the saline infusion test can be used to confirm the diagnosis of primary hyperaldosteronism. In the differential diagnosis of aldosterone-synthesizing adenoma and idiopathic hyperaldosteronism, its use alone was not sufficient.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: CA; Study Design: CA; Supervision: CE, OOG; Data Collection and/or Processing: GA; Statistical Analysis and/or Data Interpretation: SC, OOG; Literature Review: SC, OOG; Manuscript Preparation: CA, OOG; and Critical Review: EA, FMS; Other: EE, EH.

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Original Article

Evaluation of Sitagliptin Therapy on the Levels of Fibroblast Growth Factor-19 (FGF19) In Patients With Type 2 Diabetes

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ABSTRACT

Background The specific association between sitagliptin and fibroblast growth factor-19 (FGF19) is yet to be clarified. In this study, we aimed to investigate the effect of sitagliptin therapy on the levels of FDF19 in patients with type 2 diabetes mellitus (T2DM).

Material and Methods A total of 35 patients newly diagnosed type 2 diabetes, and who had not received antidiabetic treatment before were included in this study. Sitagliptin therapy was administered as 100 mg/day. Patients' demographic, anthropometric features, glycaemic variables, lipid profiles and FGF19 values were evaluated at the baseline and at the 3rd month of the treatment and the obtained data were compared.

Results The mean age of the patients was 53.34±8.09 years. The mean weight, body mass index (BMI), hip circumference, postprandial blood glucose and glycosylated haemoglobin A1c (HbA1c) values were statistically significantly lower at the 3rd month of the treatment compared to the baseline values (for all, $p<0.05$). The mean FGF19 was found as 84.37±64.23 pg/mL at the baseline and 86.06±44.10 pg/mL at the 3rd month of the treatment and the difference was not statistically significant ($p=0.789$). A moderate negative correlation was found between FGF19, total cholesterol and low density lipoprotein cholesterol (LDL-c), and a moderate positive correlation between FGF19 and triglycerides.

Conclusions This study did not show a significant effect of sitagliptin therapy on FGF19. T2DM variables such as postprandial blood glucose and HbA1c were significantly improved. FGF19 was moderately correlated with total cholesterol and LDL-c in negative direction and with triglycerides in positive direction.

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Introduction

Type 2 diabetes mellitus (T2DM) is a serious chronic disease and important public health problem caused by increased blood glucose levels due to peripheral insulin resistance that can be accompanied by the development of beta-cell failure and insulin deficiency. The number of people with T2DM has increased 2-folds globally over the last few decades, positioning this disease as a rapidly expanding public health challenge.[1] According to the International Diabetes Federation (IDF) the number of diabetic people will rise to 700 million by 2045.[2]

In addition to the well-known risk factors such as body mass index, fat distribution, inactivity, family history and blood lipid levels, other biomarkers have emerged as important predictors of T2DM. Fibroblast growth factor 19 (FGF19) is a newly detected member of the endocrine subgroup of the FGF superfamily and has been the subject of recent attention.[3] Recent clinical studies have shown that FGF19 has an insulin-like regulatory function in metabolism and is inversely associated with the risk of developing T2DM.[4,5] On the other hand, FGF19 has been reported to also have an inverse correlation with cardiovascular disease (CVD) which is a common comorbidity in T2DM.

There are many treatment methods for T2DM, including drugs that improve glucose and metabolism, protect pancreatic cell function, and increase insulin sensitivity. Dipeptidyl peptidase-4 (DPP-4) inhibitors are a new type of antidiabetic drugs with cardiovascular protective effects, used widely in clinics. Sitagliptin is the first oral DPP-4 inhibitor approved by the US Food and Drug Administration (FDA) for the management of hyperglycaemia in patients with T2DM.[6] DPP-4 inhibitors are effective in glucose metabolism by preventing DPP-4 from deactivating glucagon-like peptide 1 (GLP-1) and glucose insulinotropic polypeptide (GIP) quickly.[7] However, the specific association between sitagliptin and FGF19 is yet to be clarified. In this study, we aimed to investigate the effect of sitagliptin therapy on the levels of FDF19 in patients with T2DM.

Material and Methods

The study protocol was approved by our Institutional Review Board and was conducted in accordance with the Declaration of Helsinki. A total of 35 patients aged 18 years and older, newly diagnosed type 2 diabetic and who had not received antidiabetic treatment before were included in this prospective observational study. Patients with clinically significant renal or hepatic disease, a history of heart disorder, severe hypertension and type 1 diabetes, pregnant women and those who refused participation were excluded from the study. All patients were educated on dietary and lifestyle changes.

Sitagliptin therapy was started at a dose of 100 mg/day. No other drugs were administered during the study period. Patients' demographics such as age, gender, anthropometric measurements, including weight, height, BMI, waist circumference, hip circumference, waist-to-hip ratio, fat percentage, systolic and diastolic blood pressure, pulse, biochemical parameters such as fasting and postprandial blood glucose, glycosylated haemoglobin A1c (HbA1c), ürea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), total cholesterol, triglycerides, albumin creatinine ratio (ARC), homeostatic model assessment (HOMA) index and FGF19 value were evaluated at the start (baseline) and at the end of the study (3 months). Blood sampling and laboratory investigations were performed according to routine standard methods. The human FGF-19 was measured in duplicate by sandwich enzyme-linked immunosorbent assay based on the recommendations of the manufacturer. Enzyme-linked immunosorbent assay (ELISA) was employed to test serum levels of FGF-19.

Statistical Analysis

Data obtained in this study were statistically analyzed using SPSS v.23 (SPSS, Statistical Package for Social Sciences, IBM Inc., Armonk, NY, USA) statistical software. Normality of the data was tested using the Kolmogorov-Smirnov method. Since the variables were skewed, among the parametric methods, paired t test was used to

compare the values between two groups, while categorical values were compared using Chi-square test. Continuous variables are expressed as mean+standard deviation and categorical variables as frequency (n, %). Correlations between the variables were evaluated with Pearson's correlation analysis. p<0.01 values were considered statistically significant.

Results

A total of 35 patients newly diagnosed with T2DM were included in this prospective study with 20 (57.1 %) being females and 15 (42.9 %) males. The mean age of the patients was 53.34±8.09 years. The mean weight (84.44±14.58 kg vs 86.10±15.26 kg), BMI (31.68±5.60 kg/m^2 vs 32.30±5.80 kg/m^2) and hip circumference (111.16±14.25 cm vs 113.44±13.08 cm) values were statistically significantly lower at the 3rd month of the treatment compared to the baseline values (for all, p<0.05). Anthropometric measurements of the patients at baseline and at the 3rd month of the treatment are given in Table 1.

There was no statistically significant difference between the baseline and 3rd month values in terms of systolic blood pressure, diastolic blood pressure and fasting blood glucose levels (for all, p>0.05). Postprandial blood glucose (PBG) and HbA1c level were statistically significantly lower at the 3rd month of the treatment compared to the baseline values (p<0.001). Clinical features of the patients are presented in Table 2.

When laboratory parameters were examined; HbA1c (6.51±1.19% vs 7.20±1.53%), AST (18.91±5.40 U/L vs 21.23±8.52 U/L) and ALT (21.11±6.81 U/L vs 23.83±10.15 U/L) were statistically lower at the 3rd month of the treatment compared to the baseline values (for all, p<0.01). No statistically significant difference was found between the baseline and the 3rd month values of the other biochemical parameters (for all, p>0.05).

The mean FGF19 was found as 84.37±64.23 pg/mL at the baseline and 86.06±44.10 pg/mL at the 3rd month of the treatment and the difference was not statistically significant (p=0.789). In Pearson's correlation analysis, there were moderate negative correlations between FGF19, total cholesterol and LDL-c, and a moderate positive correlation between FGF19 and triglycerides, while no significant correlation was found between FGF19 and the other studied parameters. Correlations of FGF19 and T2DM variables are presented in Table 3. None of the patients developed treatment-related side effects.

Discussion

FGF19, which is a recently discovered hormone secreted by the ileum, plays a critical role in the regulation of biliary acid, lipid and glucose metabolisms and modulation of insulin

Table 1. Changes in the anthropometric values and clinical features between the baseline and 3rd month values.

Parameter	Baseline mean±SD	3rd month mean±SD	p value
Weight (kg)	86.10±15.26	84.44±14.58	0.002*
BMI (kg/m^2)	32.30±5.80	31.68±5.60	0.002*
Waist circumference (cm)	106.53±13.97	104.87±13.52	0.067
Hip circumference (cm)	113.44±13.08	111.16±14.25	0.047*
Systolic blood pressure (mmHg)	124.12±9.57	125.88±8.57	0.157
Diastolic blood pressure (mmHg)	77.50±8.00	79.12±7.93	0.351

*Wilcoxon Single Ranks test; BMI: body mass index; SD: standard deviation.

Table 2. Prolonged fasting test evaluation.

Parameter	Baseline mean±SD	3rd month mean±SD	p value
Fasting blood glucose (mg/dL)	136.06±34.89	129.51±40.54	0.086
Postprandial blood glucose (mg/dL)	213.80±75.44	169.37±63.01	<0.001
HbA1c (%)	7.20±1.53	6.52±1.89	<0.001*
Creatinine (mg/dL)	0.88±0.18	0.86±0.19	0.275
AST (U/L)	21.23±8.52	18.91±5.40	0.02*
ALT (U/L)	23.83±10.15	21.11±6.81	0.014*
Total cholesterol (mg/dL)	203.71±34.83	195.91±40.95	0.159
HDL-c (mg/dL)	44.00±9.77	43.51±9.30	0.610
LDL-c (mg/dL)	126.71±32.93	128.80±37.41	0.731
Triglycerides (mg/dL)	163.89±62.63	156.57±77.59	0.334
HOMA index	5.31±3.76	5.04±4.21	0.561
FGF19 (pg/mL)	84.37±64.23	86.06±44.10	0.789

SD: standard deviation, HbA1c: glycosylated haemoglobin A1c, AST: aspartate aminotransferase, ALT: alanine aminotransferase, HDL-c: high density lipoprotein cholesterol, LDL-c: low density lipoprotein cholesterol, HOMA: homeostatic model assessment, FGF19: fibroblast growth factor-19.
*Wilcoxon Single Ranks test.

Table 3. Correlations between FGF19 and the variables of the patients.

Variable	r	p value
BMI (kg/m^2)	-0.133	0.453
Fasting glucose (mg/dL)	-0.273	0.113
Postprandial glucose (mg/dL)	-0.209	0.229
Total cholesterol* (mg/dL)	-0.346	0.042**
LDL-c* (mg/dL)	-0.495	0.002**
HDL-c (mg/dL)	-0.114	0.513
Triglycerides* (mg/dL)	0.424	0.011**
HbA1c (%)	-0.198	0.255

BMI: body mass index, LDL-c: low density lipoprotein cholesterol, HDL-c: high density lipoprotein cholesterol, HbA1c: glycosylated haemoglobin A1c.
*moderate correlation, **statistically significant.

sensitivity. Studies in the literature have shown a link between these metabolisms and chronic diseases including T2DM, suggesting that FGF19 is an independent factor for T2DM.[4,8] However, physiological functions of FGF19 in T2DM are yet to be fully clarified. Fu et al.[9] showed that FGF19 increased metabolic rate, decreased weight and reversed diabetes in high-fat-fed mice. FGF19 has been proposed to improve hyperinsulinemia, dyslipidemia, and insulin sensitivity and decrease body weight.[10] In the present study, we investigated the effect of sitagliptin therapy on the levels of fibroblast growth factor-19 in patients with T2DM and to our best knowledge there is still no publication on this issue, at least at the time of this study.

Sitagliptin is the first approved medication among the new class of oral antihyperglycemic agents, which improves the body's ability to lower blood glucose when it is elevated.[11] Sitagliptin is a selective inhibitor of the enzyme DPP-4, which metabolizes the naturally occurring incretin hormones GLP-1 and GIP. This process resulted in increased glucose-dependent insulin secretion from the pancreas and decreased hepatic glucose production.

In our study, HbA1c was significantly decreased with 3-month sitagliptin therapy compared to the baseline values ($p<0.001$). Similarly, Sakura et al.[12] reported significant improvement in HbA1c values in T2DM patients who were previously untreated with, or poorly responsive to, existing antihyperglycemics. However, some studies have reported different results. For instance, Shima et al.[13] studied sitagliptin alone or in combination with ursodeoxycholic acid and found that HbA1c did not change with sitagliptin alone, but significantly decreased with the addition of ursodeoxycholic acid to the treatment. This difference might be resulted from the fact that they include only 20 patients which all had liver disease in addition to T2DM, while we excluded patients with liver disease. Several studies have reported the effects of sitagliptin therapy on various DM related clinical parameters. Arnetz et al. studied the effects of sitagliptin therapy versus placebo in patients with glucose abnormalities. Waist circumference and BMI values were not affected by sitagliptin therapy, while creatinine was significantly increased.[14] In our study, waist circumference and creatinine did not change significantly, while BMI value was significantly decreased by sitagliptin. The difference was attributed to the different patient populations among the studies and number of the patients (10 patients in the mentioned study were assigned to sitagliptin group versus our 35 patients).

The inverse association between FGF19 and T2DM is well-known. FGF-19 has been shown to have insulin-like effects and to decrease glucose levels in rodents.[15] But the link of sitagliptin to this association remains unclear. In the present study, we found no significant effect of 3-month sitagliptin therapy on FGF19 levels. Acute DPP-4 inhibition with sitagliptin has been reported to reduce blood glucose and enhance the secretion of growth factors.[6] In an animal study, Xu et al.[16] stated that sitagliptin can protect liver tissue and modulate lipid metabolism in non-alcoholic fatty liver disease (NAFLD) mice via elevating FGF21 and FGF19, mediating expression levels of the key enzymes for lipid metabolism. In the same study, sitagliptin could facilitate lipid oxidation by facilitating secretion of FGF21 and FGF19. The different results might be attributed to different diseases involved in the studies. While the former study included women with polycystic ovarian syndrome, the latter included mice with NAFLD induced mice. We could not find any other study to see whether sitagliptin affects the expression of FGF19.

This study has some limitations. First, the number of patients is relatively small, although it is higher than that of many previous studies as mentioned above. Second, it is a single-center study making generalization of the results difficult. Third, a control group could be established using a different antihyperglycemic medication to compare the findings. Finally, we could not exactly compare our results because of a lack of similar studies in the literature. However, being the first study investigating the effect of sitagliptin on FGF19 in T2DM patients constitutes a strong aspect of the study. We believe that this study will be guiding for further more comprehensive, multi-center studies with larger populations to be conducted in the future.

Conclusions

This study did not show a significant effect of 3-month sitagliptin therapy on FGF19. However, T2DM variables such as postprandial blood glucose and HbA1c were significantly improved. Expression levels of FGF19 were moderately correlated with total cholesterol and LDL-c in negative direction and with triglycerides in positive direction. There is an urgent need for further studies to enlighten physiological functions of FGF19 in T2DM.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: OOG; Study Design: OOG, SC; Supervision: OOG, SC; Materials: OOG, SC; Data Collection and/or Processing: OOG, SC; Statistical Analysis and/or Data Interpretation: OOG, SC; Literature Review: OOG, SC; Manuscript Preparation: OOG, SC; Critical Review: OOG, SC.

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Original Article

Evaluation of the Effect of the COVID-19 Pandemic on the Distribution of Kidney Transplants in the World in 2019 and 2020

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ABSTRACT

Background The COVID-19 pandemic caused by SARS-CoV-2 has had adverse effects in every field. One of the affected areas is organ supply and transplantation. This study aimed to evaluate the impact of the pandemic period on the number of kidney transplants in 2019 and 2020 in countries with a population of 40 million and above.

Material and Methods We evaluated kidney transplants from living and deceased donors reported between 2019 and 2020 from the Global Observatory on Donation and Transplantation (GODT). We obtained the number of kidney transplants in countries with a population of 40 million and over before and after the COVID-19 pandemic.

Results The total number of kidney transplants performed in 2019 and 2020 of countries with a population of 40 million or more, which sent data to the GODT database, were respectively: Sudan 313 and 139, Algeria 270 and 91, Argentina 1,675 and 854, Spain 3,423 and 2,702, Colombia 947 and 526, Republic of Korea 2,293 and 2,280, Italy 2,139 and 1,907, France 3,643 and 2,595, UK 3,649 and 2,567, Thailand 679 and 712, Germany 2,132 and 1,909, Iran 2,101 and 1,240, Turkey 3,863 and 2,498, Philippines 300 and 132, Ethiopia 35 and 8, Japan 1,913 and 1,697, Mexico 2,976 and 913, Russian Federation 1,473 and 1,124, Bangladesh 205 and 155, Nigeria 164 and 165, Pakistan 1,306 and 129, Brazil 6,298 and 4,830, United States 24,273 and 23,644, India 9,751 and 5,486, China 12,124 and 11,037.

Conclusions Compared to 2019, deceased and living kidney transplants increased only in Thailand in 2020, while kidney transplants in other countries have decreased. Countries where deceased kidney transplants increased in 2020, were Thailand, Korea, and the United States. Total kidney transplants in Turkey decreased by 35.4% in 2020 compared to 2019.

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Introduction

The number of patients diagnosed with SARS-CoV-2 in the world in 2020 is 83,999,379.[1] According to the World Health Organization (WHO) data, 1,937,987 patients died in 2020.[2] 2.3% of all patients with SARS-CoV-2 infection died. The COVID-19 pandemic caused by SARS-CoV-2 has had adverse socio-cultural, economic and health effects. Organ supply and transplantation were also one of the affected areas. This study aimed to evaluate the impact of the pandemic period on the number of kidney transplants in 2019 and 2020 in countries with a population of 40 million and above.

Material and Methods

According to the Global Observatory on Donation and Transplantation (GODT) data, kidney transplants from living and deceased donors reported between 2019 and 2020 were examined.[3] The number of kidney transplants in countries with a population of 40 million and over before and after the COVID-19 pandemic was obtained.

Results

The number of kidney transplants performed in 2019 and 2020 (*Figure 1*) of countries with a population of 40 million or more, which sent data to the GODT database, were respectively: Sudan 313 and 139 (-55.59%), Algeria 270 and 91 (-66.30%), Argentina 1,675 and 854 (-49.01%), Spain 3,423 and 2,702 (-21.06%), Colombia 947 and 526 (-44.46%), Republic of Korea 2,293 and 2,280 (-0.57%), Italy 2,139 and 1,907 (-10.85%), France 3,643 and 2,595 (-28.77%), UK 3,649 and 2,567 (-29.65%), Thailand 679 and 712 (4.86%), Germany 2,132 and 1,909 (-10.46%), Iran 2,101 and 1,240 (-40.98%), Turkey 3,863 and 2,498 (-35.34%), Philippines 300 and 132 (-56.00%), Ethiopia 35 and 8 (-77.14%), Japan 1,913 and 1,697 (-11.29%), Mexico 2,976 and 913 (-69.32%), Russian Federation 1,473 and 1,124 (-23.69%), Bangladesh 205 and 155 (-24.39%), Nigeria 164 and 165 (-0.61%), Pakistan 1,306 and 129 (-90.12%), Brazil 6,298 and 4,830 (-23.31%), United States America (USA) 24,273 and 23,644 (-2.59%), India 9,751 and 5,486 (-43.74%), and China 12,124 and 11,037 (-8.97%). Compared to 2019, deceased and living kidney transplants increased only in Thailand in 2020. The number of kidney transplants in other countries has decreased.

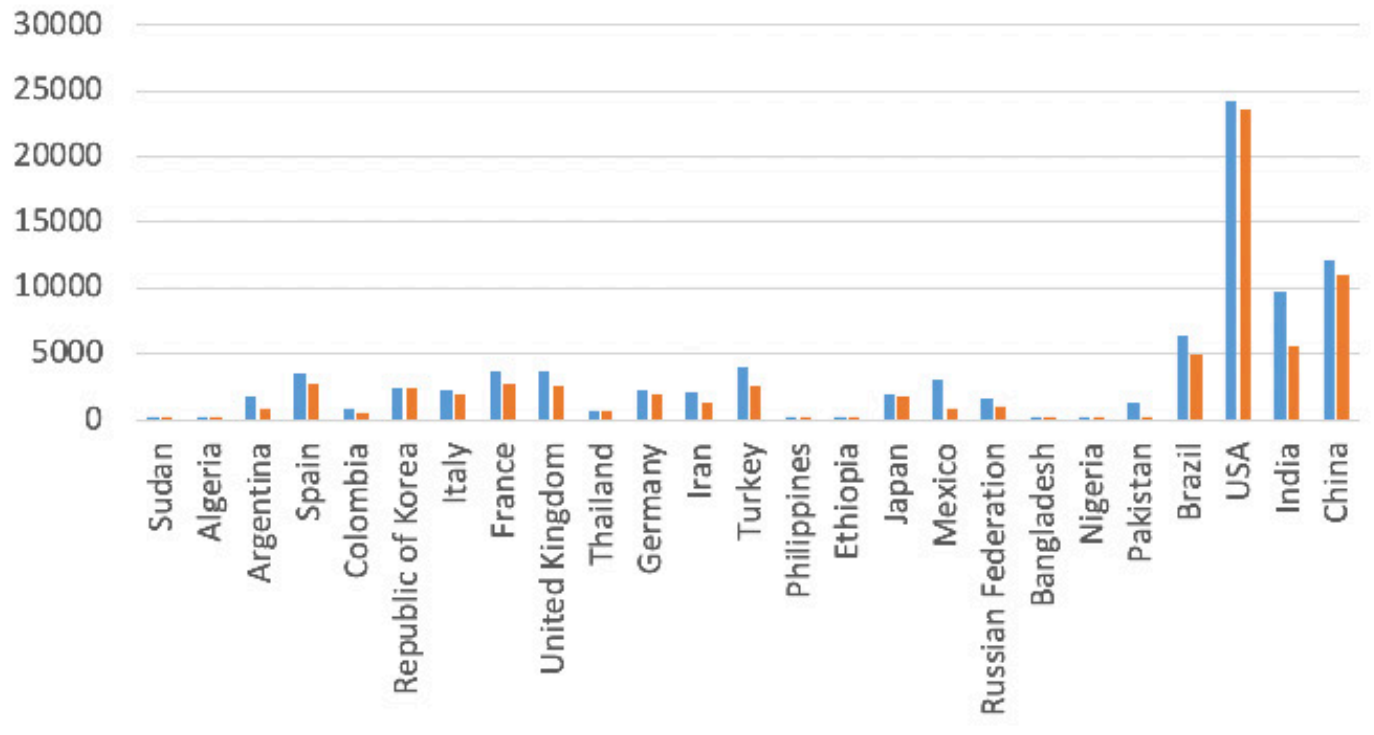

Figure 1. Total number of kidney transplants performed in 2019 and 2020.

The mean change in the total number of kidney transplants in these countries was -32.77±25.96%.

There was no transplant from a deceased donor in Sudan, Ethiopia, Bangladesh, Nigeria and Pakistan in 2020. When we compared 2019 and 2020 years, the changes in the number of kidney transplants from deceased donors in other countries were as follows: Algeria -100%, Argentina -45.32%, Spain 3-20.89%, Colombia -47.14%, Republic of Korea 6.80%, Italy -9.78%, France -29.62%, UK -23.52%, Thailand 3.21%, Germany -9.49%, Iran -39.44%, Turkey -69.18%, Philippines -29.41%, Japan -38.70%, Mexico -69.44%, Russian Federation -25.04%, Brazil -16.11%, USA 5.77%, India -54.66%, and China -9.53%. The three countries where the number of kidney transplants from deceased donors increased in 2020 compared to 2019 were the Republic of Korea, the USA, and Thailand (*Figure 2*). The mean change in kidney transplantation from a deceased donor in these countries was -31.07±27.71%.

Transplant numbers from living donors had decreased in all countries except Thailand (*Figure 3*). The changes in the number of transplants from living donors by country in 2019 and 2020 were as follows: Sudan -55.59%, Algeria -66.04%, Argentina -62.96%), Spain -22.69%, Colombia -32.96%, Republic of Korea -4.47%, Italy -16.47%, France -23.53%, UK -45.40%, Thailand 12.61%, Germany -13.46%, Iran -43.78%, Turkey -26.38%, Philippines -57.60%, Ethiopia -77.14%, Japan -7.55%, Mexico -69.27%, Russian Federation -14.21%, Bangladesh -24.39%, Nigeria -0.61%, Pakistan -90.12%, Brazil -58.45%, USA -23.78%, India -42.30%, and China -5.59%. The mean change in kidney transplantation from a living donor in these countries was -34.88±26.84%.

Discussion

The COVID-19 pandemic negatively affected the numbers of living and deceased kidney transplants in countries with 40 million and above, outside of Thailand, in 2019 and 2020. Only in Thailand has the number of kidney transplants increased. Total kidney transplants in Turkey decreased by 35.4% in 2020 compared to 2019. The rate of kidney transplants from living donors among all transplantations in Turkey increased from 79.13% in 2019 to 90.04% in 2020. In the USA,

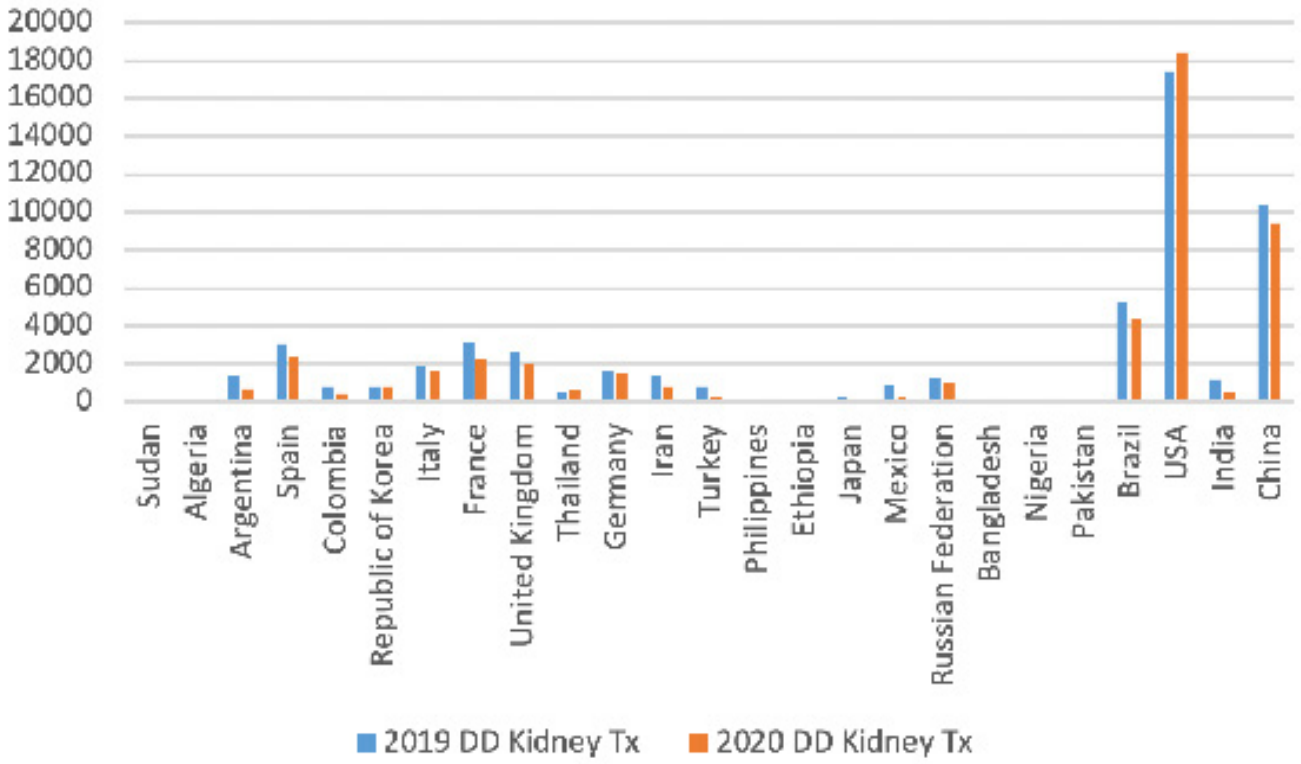

Figure 2. Number of kidney transplants from deceased donors (DD) in 2019 and 2020.

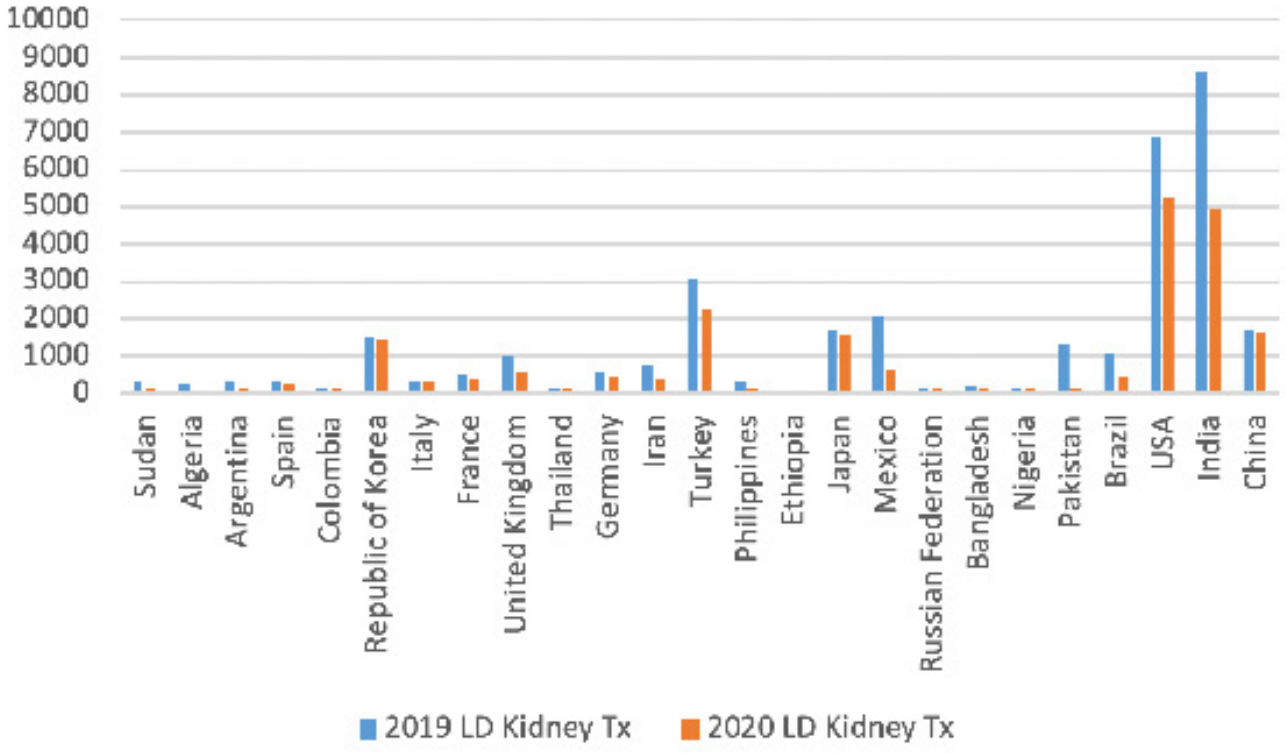

Figure 3. Number of kidney transplants from living donors (LD) in 2019 and 2020.

which has the highest transplant numbers, total kidney transplants decreased by 2.59% compared to 2019. However, the rate of transplants from deceased donors increased by 5.77%. The Organ Procurement Organization (OPO) activities in the states affiliated to the United Network for Organ Sharing (UNOS), which is used for organ harvesting in the USA, could have positively affected this increase.[4]

The COVID-19 pandemic also adversely affected the organ donation rates and organ supply in kidney transplantation.[5] During the pandemic period, transplant centres prioritized the management of patients with COVID-19 and the safety of healthcare personnel.[6] They have made different approaches periodically in living or deceased kidney transplantations.[7] In particular, the number of donations from living donors has decreased in most countries.

In some countries, the number of families applying for donations has decreased significantly. The limitation of face-to-face meetings between the coordinator and donor family members, which included emotional support and visual explanations regarding the medical condition, may have been effective in this decrease. In addition, intensive care units' increasing care for patients with COVID-19 infection and less detection of brain death may be another factor. Fewer donors have been admitted to the intensive care unit in Israel, and the number of donor organs has decreased.[8]

A group of researchers reviewed transplantation statistics from the World Health Organization website on June 15, 2021.[9] Comparing the average of global kidney transplant statistics between 2010 and 2019 with 2020 statistics, they found a significant decrease in kidney transplants from living donors. In Brazil, the number of solid organ transplants decreased significantly in 2020, and the number of active patients on the kidney transplant waiting list increased.[10] A Mexican study also found that transplants decreased more in public institutions than in private institutions (89% vs 57%).[11] COVID-19 has also negatively affected transplantation activities in general (public) transplantation centres in India.[12]

Conclusions

When we compared the years 2019 and 2020 in countries with populations of 40 million or more, the median changes were -28.76% (range: -90.12% to 4.86%, 25 countries) in total kidney transplantation, -27.22% (range: -100% to 6.80%, 20 countries) in deceased donor transplantation and -26.38% (range: -90.12% to 12.61%, 25 countries) in transplants from living donors.

As in the whole world, kidney transplantation activities in our country have slowed down during the pandemic. The Health Ministry declared the first official COVID-19 case in Turkey on March 11, 2020. The COVID-19 pandemic severely affected kidney transplantation in our country throughout 2020. The number of kidney transplants decreased from 3,863 in 2019 to 2,498 in 2020 (-35.34%). In 2020, the transplant rate from a deceased donor was 10%. This rate was generally low in the 18-25% band. This rate confirms a severe reduction in the activity of transplantation from deceased donors, which is already low. In our country, the decrease in organ transplantation from a deceased donor (from 808 in 2019 to 249 in 2020; -69.18%) was higher than in kidney transplantation from a living donor (from 3,055 in 2019 to 2,249 in 2020; -26.38%). This difference may be due to the decrease in brain death reporting and organ donation during the pandemic. Interestingly, the pre-emptive transplant rate increased from 46.1% in 2019 to 53.6% in 2020.[13]

As a result, many centres had to suspend kidney transplant activities due to the pandemic. Therefore, the COVID-19 pandemic has adversely affected the number of kidney transplants worldwide and in our country.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: EE; Study Design: EE, MS, AE; Supervision: AE; Materials: EE, KS, RO; Data Collection and/or Processing: EE, KS, RO, SEGB, MÇÇ, KÖG, AY, AO; Statistical Analysis and/or Data Interpretation: EE, AE; Literature Review: AE, EE; Manuscript Preparation: EE, AE; Critical Review: AE.

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Original Article

Evaluation of the Relationship Between Dehydroepiandrosterone Sulfate-Total Testosterone Ratio and Metabolic Parameters in Patients With Polycystic Ovary Syndrome

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ABSTRACT

Background In this study we aimed to evaluate the correlations between dehydroepiandrosterone sulfate-total testosterone (DHEAS/TT) ratio and insulin resistance, glycemic and lipid parameters.

Material and Methods A total of 35 patients with polycystic ovary syndrome (PCOS) and 34 healthy volunteers were included in the study. Anthropometric, clinical, biochemical, lipid and glycemic measurements were performed according to routine standards. Patients' demographic, clinical, anthropometric, biochemical, glycemic, lipid and hormonal parameters were measured and recorded. DHEAS/TT ratio was calculated in all patients. DHEAS/TT ratio and metabolic parameters were compared between the PCOS and control groups.

Results There were significant differences between the PCOS and control groups in terms of fasting blood glucose, total cholesterol, high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), triglycerides, insulin and homeostatic model assessment-insulin resistance (HOMA-IR) values (for all, $p<0.05$). Androstenedione and DHEAS/TT values were statistically significantly higher in the PCOS group. Pearson's correlation analysis revealed no statistically significant correlation between DHEAS/TT ratio and body mass index (BMI), HOMA-IR and lipid profile.

Conclusions In PCOS patients, glycemic and lipid parameters, HOMA-IR and DHEAS levels were significantly higher compared to the control subjects. In addition, the DHEAS/TT ratio was also significantly higher at limit in the PCOS group. However, no correlations were observed between DHEAS/TT ratio, BMI, glycemic and lipid parameters, suggesting that DHEAS/TT ratio is not an appropriate method to be used in prediction of metabolic status in patients with PCOS.

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Introduction

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine conditions, characterized by hyperandrogenic signs and symptoms, polycystic ovaries and ovulatory dysfunction. PCOS affects 10% to 20% of women of reproductive age with an increased risk of developing insulin resistance, dyslipidemia, obesity, diabetes, and cardiovascular disease.[1] Although different definitions of PCOS have been used based on the inclusion criteria until 2012, a consensus was reached at that time on the use of Rotterdam 2003 definition as it captures the broadest population of PCOS subjects (NIH). According to the Rotterdam 2003 diagnostic criteria, PCOS could be diagnosed after ruling out the related disorder by the following three diagnostic criteria: 1) oligo-anovulation, 2) clinical and/or biochemical signs of hyperandrogenism, and 3) polycystic ovaries.[2] The prevalence of PCOS among unselective reproductive-aged women has been reported between 15 and 20% based on the Rotterdam definition.[3-5]

PCOS is correlated with adiposity and insulin resistance that lead to hyperinsulinemia, which triggers increased androgen secretion.[6] The androgen excess is considered the major driving force in the development of signs and symptoms of PCOS. Excessive androgen production by ovaries and adrenals contributes to hyperandrogenism, which is among the diagnostic criteria of PCOS. Increased levels of testosterone is one of the most common manifestations of hyperandrogenism in women.[7] Total testosterone level has been reported to be a strong predictor of the presence and degree of hyperandrogenism.[8]

In women with PCOS, not only increased ovarian androgen, but in up to 50% of these patients increased dehydroepiandrosterone sulfate (DHEAS) levels are also observed. DHEAS is a pre-hormone produced by the adrenal cortex and can be converted into DHEA, which is considered as an active hormone with conversion into testosterone.[9] PCOS patients with higher DHEAS levels and excessive androgen have lower insulin resistance than those with lower DHEAS levels.[10] Although 40-70% of women with PCOS have increased levels of DHEAS, the exact mechanism that triggers production of androgens from the adrenal gland is yet to be clarified.[11]

Correlations between DHEAS, total testosterone, insulin resistance, dyslipidemia, obesity and diabetes in PCOS patients are complex and have not been fully understood. Some studies have claimed that investigation of adrenal versus ovarian androgen ratio may reflect associations between PCOS and metabolic parameters more clearly.[12] Recent studies have focused on the evaluating metabolic risks of women with PCOS using dehydroepiandrosterone sulfate- testosterone ratio.[13,14] Based on this information, in this study we aimed to evaluate the correlations between dehydroepiandrosterone sulfate-total testosterone (DHEAS/TT) ratio and insulin resistance, glycemic and lipid parameters.

Material and Methods

The study protocol was approved by our Institutional Review Board and was conducted in accordance with the Declaration of Helsinki. A total of 35 female patients diagnosed with PCOS according to the revised Criteria and followed-up in the Department of Endocrinology and Metabolism of our hospital and 34 healthy volunteer women as the control group were included in this prospective study. The control group consisted of age matched women who had no menstrual irregularity and clinical or biochemical signs and symptoms of hyperandrogenism, and who accepted participating in the study voluntarily. Patients with systemic diseases such as hypertension, diabetes mellitus, cardiovascular disease, renal failure, hepatic failure, gastrointestinal malabsorption diseases and malignancy, other androgen excess disorders and pregnant women were excluded from the study. Anthropometric, clinical, biochemical, lipid and glycemic measurements were performed according to routine standards.

Patients' demographic (age), clinical (Ferriman-Gallwey score [FGS], systolic blood pressure, diastolic blood pressure pulse), anthropometric (height, weight, body mass index [BMI], waist circumference, hip circumference, fat percentage), biochemical (urea, creatinine, aspartate transaminase [AST], alanine transaminase [ALT]), glycemic (fasting blood glucose, postprandial blood glucose, insulin, HOMA-IR), lipid (total cholesterol, HDL-c, LDL-c, triglycerides) and

hormonal parameters (total testosterone [TT], free testosterone [FT], dehydroepiandrosterone sulfate [DHEAS], androstenedione, follicle-stimulating hormone [FSH], luteinizing hormone [LH] and estradiol [E2]) were measured and recorded. DHEAS/TT ratio was calculated in all patients. DHEAS/TT ratio and metabolic parameters were compared between the PCOS and control groups.

The diagnosis of PCOS was established according to the 2003 Rotterdam ESHRE/ASRM PCOS Consensus Workshop Group Criteria.[15] Accordingly, patients with two of the following criteria were considered to have PCOS: oligomenorrhea-amenorrhea (menstrual dysfunction of >35 days and more than six cycles), clinical of biochemical signs and symptoms of hyperandrogenism, presence of polycystic ovaries detected on ultrasonography.

Standard anthropometric measurements were made in all participants. Waist circumference was measured in the standing position, at midpoint between the lower coastal margin and the iliac crest. Hip circumference was measured in the standing position as the greatest circumference over the buttocks. BMI value was calculated by dividing weight in kilograms by square of height in meters.

The blood samples were collected following an overnight fasting. Hormonal measures included TT, FT, FSH, LH, E_2, androstenedione and DHEAS. Hormonal analysis was made before the diagnosis of PCOS to rule out other causes of excess androgen. All hormonal parameters were analyzed with enzymatic chemiluminescence (Immulite 2000 Immunoassay System; Siemens Healthcare Diagnostics, Biermann, Germany). The other parameters measured in the fasting blood samples included lipid profile, fasting blood glucose, urea, creatinine, AST, ALT, and HOMA-IR.

Statistical Analysis

Analysis of the data obtained in this study was performed using SPSS version 23.0 (SPSS, Statistical Package for Social Sciences, IBM Inc., Armonk, NY, USA) software. Normal distribution of the variables was evaluated with the Kolmogorov-Smirnov test. Comparison of the continuous variables between the groups was made with the Mann-Whitney U test as the variables were skewed, while Chi-square test was used for comparison of the categorical variables. Continuous variables are expressed as mean ± standard deviation and categorical variables as number and percentage. Pearson's correlation analysis was used for the evaluation of correlations between the variables. $p<0.05$ values were considered statistically significant.

Results

A total of 69 subjects with 35 being PCOS patients and 34 control subjects were included in the study. The mean age was 26.48±4.22 years in the PCOS group and 27.58±3.50 years in the healthy control group. No statistically significant difference was found between both groups ($p=0.133$). Among the anthropometric parameters, the mean values of weight, BMI, waist circumference, hip circumference, and fat percentage were statistically significantly higher in the PCOS group compared to the control group (for all, $p<0.05$). The amount of hirsutism as measured by FGS was statistically significantly higher in the PCOS patients (11.55±4.99 vs 3.68±1.46; $p<0.001$). Anthropometric and clinical features and biochemical parameters of the subjects are given in Table 1.

Looking at the lipid and glycemic results of the subjects; there were significant differences between the PCOS and control groups in terms of fasting blood glucose, total cholesterol, HDL-c, LDL-c, triglycerides, insulin and HOMA-IR values (for all, $p<0.05$). Lipid and glycemic parameters of the groups are presented in Table 2.

In the hormonal analysis, androstenedione and DHEAS/TT values were statistically significantly higher in the PCOS group compared to the control subjects (both, $p<0.05$), while the mean estradiol value was significantly lower in the PCOS group. Hormonal results of the groups are given in Table 3. Pearson's correlation analysis revealed no statistically significant correlation between DHEAS/TT ratio and BMI, HOMA-IR and lipid profile. The correlations of DHEAS/TT ratio with BMI, FGS, glycemic and lipid parameters are shown in Table 4.

Table 1. Anthropometric, clinical and biochemical measurements of the groups.

	PCOS (mean±SD)	Control (mean±SD)	p value
Age (years)	26.48±4.22	27.58±3.50	0.133
Weight (kg)	74.79±17.75	61.31±12.76	<0.001*
Body mass index (kg/m^2)	28.27±6.76	22.77±5.04	<0.001*
Waist circumference (cm)	88.21±17.10	74.73±10.58	<0.001*
Hip circumference (cm)	105.13±10.87	99.45±7.94	0.011*
Fat percentage (%)	31.91±9.07	25.25±7.70	0.001*
FGS	11.55±4.99	3.68±1.46	<0.001*
SBP (mmHg)	109.00±7.44	112.50±6.70	0.037*
DBP (mmHg)	68.25±7.12	67.45±11.75	0.785
Urea (mg/dL)	20.95±5.93	22.18±5.38	0.232
Creatinine (mg/dL)	0.73±0.10	0.67±0.06	0.003*
AST (U/L)	17.95±6.38	15.98±3.60	0.159
ALT (U/L)	19.00±13.50	13.28±7.26	0.025*

PCOS: polycystic ovary syndrome, FGS: Ferriman-Gallwey score, SBP: systolic blood pressure, DBP: diastolic blood pressure, AST: aspartate transaminase, ALT: alanine transaminase.

Table 2. Lipid and glycemic values of the groups.

	PCOS (mean±SD)	Control (mean±SD)	p value
Fasting blood glucose (mg/dL)	88.61±8.85	81.48±7.88	0.001*
Total cholesterol (mg/dL)	186.71±35.39	166.38±36.69	0.049*
HDL-c (mg/dL)	46.32±8.00	54.30±10.91	0.002*
LDL-c (mg/dL)	116.94±32.46	97.75±24.49	0.014*
Triglycerides (mg/dL)	117.44±64.36	83.83±37.56	0.011*
Insulin (IU/mL)	14.07±7.11	7.89±4.74	<0.001*
HOMA-IR	3.25±1.84	1.60±0.99	<0.001*

PCOS: polycystic ovary syndrome, HDL-c: high density lipoprotein cholesterol, LDL-c: low density lipoprotein cholesterol, HOMA: homeostasis model assessment-insulin resistance.

Table 3. Hormonal analysis results of the groups

	PCOS (mean±SD)	Control (mean±SD)	p value
TT (ng/mL)	1.17±0.38	1.16±0.28	0.778
FT (pg/mL)	1.77±0.63	1.93±1.04	0.614
DHEAS (μg/dL	335.42±131.45	280.24±97.22	0.079
DHEAS/TT	282.35±91.92	245.90±70.58	0.049
Androstenedione (ng/mL)	4.57±1.54	3.31±1.30	<0.001*
FSH (mIU/mL)	4.66±1.15	5.17±2.39	0.921
LH (mIU/mL)	8.02±5.68	7.70±7.27	0.254
E2 (pg/mL)	63.18±70.57	105.18±75.31	0.002*

PCOS: polycystic ovary syndrome, TT: total testosterone, FT: free testosterone, DHEAS: dehydroepiandrosterone sulfate, DHEAS/TT: dehydroepiandrosterone sulfate-total testosterone, FSH: follicle-stimulating hormone, LH: luteinizing hormone, E2: estradiol.

Table 4. Correlation between DHEAS/TT and various parameters studied.

	DHEAS/TT	
	r	p
FGS	0.132	0.279
BMI	-0.064	0.6
Weight	-0.051	0.676
Fasting blood glucose	0.151	0.222
Total cholesterol	0.079	0.537
HDL-c	-0.015	0.905
LDL-c	-0.002	0.95
Triglycerides	0.116	0.365
HOMA-IR	-0.037	0.775

DHEAS/TT: dehydroepiandrosterone sulfate-total testosterone, FGS: Ferriman–Gallwey score, BMI: body mass index, HDL-c: high density lipoprotein cholesterol, LDL-c: low density lipoprotein cholesterol, HOMA-IR: homeostasis model assessment-insulin resistance.

Discussion

In the present study, we investigated DHEAS/TT ratio in patients with PCOS compared to healthy volunteer subjects. PCOS is a multifaceted disorder in relation with metabolic status as determined by obesity, lipid and glycemic parameters. Numerous studies have been conducted on PCOS since it was described first by Stein and Leventhal in 1935.[16] PCOS is one of the most common endocrine disorders in women of reproductive age. As expected, in the present study anthropometric measurements other than height were significantly higher in the PCOS group compared to the controls. Overweight and obesity affects approximately 60% to 80% of PCOS patients.[2] The main pathophysiological components of PCOS are gonadotropic dysfunction and insulin resistance, both of which are related to BMI. In our study, the mean BMI value was significantly higher in PCOS patients compared to the control subjects (28.77 vs 22.77, p<0.001). Bizon et al.[17] found BMI as 24.00 kg/m^2 in PCOS patients, while Neubronner et al.[18] reported this index as 25.14 kg/m^2. In this context, our findings are close to those of the other studies. In the present study, we investigated the correlation of DHEAS/TT ratio with BMI value, but could not find any association. Guducu et al.[14] reported a significant correlation between DHEAS/FT in PCOS patients. Kosus et al.[13] grouped their PCOS patients in patients with a DHEAS/TT ratio lower than 4.40 and those with a DHEAS/TT ratio higher than 4.40. They found a significant difference between the groups in terms of BMI with higher levels observed in the patients with a DHEAS/TT< 4.40. Since we did not group the patients in this way, we could not compare our results exactly. In that study, only PCOS patients with different DHEAS/TT were included without a control group. We believe that including a healthy group as in our study would give more comparable results. It has been proposed that HOMA-IR is a better marker for evaluating insulin resistance in women with PCOS (19). In our study, the mean HOMA-IR was significantly higher in PCOS patients (3.25 vs 1.60, p<0.001). Lerchbaum et al.[12] found the median HOMA-IR value as 1.2 in PCOS patients with elevated FT. This is higher than our findings, but in our PCOS group, FT was not elevated. Alebic et al.[20] found the median HOMA-IR values as 2.3, a closer value to our result of 3.25. The authors defined a cut-off value of 3.15 for HOMA-IR in prediction of IR.

Presence and pathogenesis of lipid abnormalities in PCOS remains controversial with some studies showing lipid disturbances in PCOS patients.[21] Ibrahim et al.[22] demonstrated that women with PCOS have atherogenic lipid profile characterized by increased cholesterol, LDL and triglycerides, especially in obese PCOS patients. Manjunatha et al.[23] reported dyslipidemia as the most common abnormality in PCOS with elevated total cholesterol, LDL-c and triglycerides and low levels of HDL-c. Similarly in the present study total cholesterol, LDL-c and triglycerides were increased and HDL-c was decreased in the PCOS patients compared to the control group.

In our study, DHEAS/TT ratio was statistically significantly higher in the PCOS group (p=0.049), indicating increased DHEAS values in PCOS. However, we could not find any correlation between DHEAS/TT ratio and BMI, HOMA-IR and lipid parameters in the patient group. This result indicates the need for further comprehensive studies with a larger series of patients to clarify this issue.

The major limitation of this study is the relatively small number of subjects. In addition to DHEAS/TT, DHEAS/FT could also be analyzed. However, this issue has been studied before and might complicate the study results. The strengths of our study include the detailed metabolic characterization. Further comprehensive multi-center studies are needed to enlighten relationships between PCOS and metabolic status indicators. New parameters with cut-off values calculated could be integrated to the existing criteria to refine the diagnosis of PCOS.

Conclusions

In PCOS patients, glycemic and lipid parameters, HOMA-IR and DHEAS levels were significantly higher compared to the control subjects. In addition, DHEAS/TT ratio was also significantly higher at the limit in the PCOS group. However, no correlations were observed between DHEAS/TT ratio, BMI, glycemic and lipid

parameters, suggesting that DHEAS/TT ratio is not an appropriate method to be used in prediction of metabolic status in patients with PCOS.

Acknowledgment

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: OOG; Study Design: OOG, SC; Supervision: OOG, SC; Materials: OOG, SC; Data Collection and/or Processing: OOG, SC; Statistical Analysis and/or Data Interpretation: OOG, SC; Literature Review: OOG, SC; Manuscript Preparation: OOG, SC; Critical Review: OOG, SC.

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Original Article

Investigation of Serum Neprilysin Levels in Overweight and Normal Weight Young Women

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ABSTRACT

Background In this study we aimed to evaluate biochemical, lipid and glycemic parameters and to compare serum neprilysin levels between overweight (OW) and normal weight (NW) young women who are more prone to gain weight.

Material and Methods A total of 28 overweight/obese women aged between 22-34 years and 34 age matched normal-weight women were included in this cross-sectional study on voluntary basis. of the subjects were performed, Participants' anthropometric measurements, hormone profiles, glycemic parameters and insulin resistance, and serum neprilysin levels were recorded and analyzed. Patients were evaluated in two groups as Group OW and Group NW.

Results The mean ALT, TSH and uric acid values were statistically significantly higher in Group OW compared to Group NW (for all, $p<0.05$). The mean HDL-c was statistically significantly lower in Group OW than in Group NW ($p<0.01$), while the mean triglyceride level was significantly higher in Group OW than in Group NW ($p=0.002$). The mean fasting blood glucose, insulin, HOMA, HbA1c and triglyceride values were statistically significantly higher in Group OW compared to Group NW (for all, $p<0.001$). The mean neprilysin (NEP) value was found as 1123.44±1327.60 mmol/L in Group NW and 1229.39±1315.17 mmol/L in Group OW with no statistically significant difference between the groups. No significant correlation was found between NEP and BMI values.

Conclusions In this study, no significant difference was found between serum neprilysin levels of overweight/obese and normal weight women, suggesting that neprilysin does not play a role in the pathogenesis of obesity, insulin resistance or diabetes.

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Introduction

Obesity represents a significant global public health problem with health care and socio-economic impacts. The increasing number of owerweight and obese people has been described as epidemic and even pandemic in the last few decades.[1] The impact and prevalence of obesity are disproportionately higher in women than men and are rapidly increasing. According to the 2017 Health Survey for England, the prevalence of obesity in women increased from 15% in 1994 to 29% in 2017 (available at: https://files.digital.nhs.uk/EF/AB0F0C/HSE17-Adult-Child-BMI-rep-v2.pdf). Obesity in women increases the risk of developing comorbidities including endocrine, cardiovascular and musculoskeletal diseases, malignities, infertility and depression.[2] In addition, overweight and obesity are known to be closely linked with insulin resistance, resulting in increased risk of metabolic syndrome.[3] It has been reported that young women (18-36 years) gain weight at a higher rate than women in any other age group, although little is known about the determinant of weight gain in young women.[4]

Also known as neutral endopeptidase, enkephalinase or EC3 4.24.11, neprilysin (NEP) is an integral membrane zinc metalloendopeptidase widely expressed on the surface of a wide spectrum of cells ranging from pancreatic islet cells to non-pancreatic endothelial, epithelial and smooth muscle cells to, cardiac myocytes and fibroblasts.[5,6] NEP breakdowns peptides at the N-terminal side of hydrophobic amino-acid residues and play a role in the degradation and inactivation of various bioactive peptides, including angiotensins I and II, bradykinin, atrial natriuretic peptide, enkephalins and chemotactic peptides, some of which are known to modulate glucose metabolism.[7] It is also involved in the regulation of insulin receptor pathways in pancreatic β cells. On the other hand, NEP is also produced by adipocytes, suggesting the possibility of its potential role as an adipokine in the regulation of adipocyte function.[8] In association with obesity, NEP has been reported to directly contribute to the development of insulin resistance.[9,10] and to correlate with body mass index, cholesterol and triglycerides.[11] Patients with obesity or heart failure have been reported to have absolute or relative NEP deficiency, respectively.[12] In animal studies, NEP activity was increased in metabolic tissues and plasma of mice with diet-induced obesity and NEP levels were correlated with reduced insulin sensitivity and reduced β cell functioning.[13] However, the data are less clear in humans. Although there is some evidence that plasma levels of NEP are positively correlated with BMI and other characteristics of metabolic syndrome, this needs to be confirmed with additional studies.[6] Therefore, the objective of this study was to compare serum NEP levels in overweight and normal weight young women who are more prone to gain weight.

Material and Methods

This cross-sectional study was conducted in the Department of Endocrinology and Metabolism of our hospital. Before the beginning of the study, ethics approval was obtained from the local ethics committee of our hospital. All participants were informed about the objective of the study in detail and gave informed verbal and written consent. The study was performed in line with the ethical principles of the Declaration of Helsinki.

A total of 28 overweight/obese volunteer women and 34 age matched normal-weight women were included in this cross-sectional study on voluntary basis between 2017 and 2019 Participants were divided into two groups as those with a body mass index (BMI) <25 kg/m^2 (Group NW) and subjects with a BMI ≥25 kg/m^2 (Group OW). After systemic examination and anthropometric measurements of the subjects were performed, participants' hormone profiles, glycemic parameters and insulin resistance, and serum neprilysin levels were recorded and analyzed. The variables studied included demographic features such as age, weight, height, BMI (dividing weight in kilos by height square in m^2), waist circumference, hip circumference, waist/hip ratio, waist/height ratio, fat percentage, systolic (SBP) and diastolic (DBP) blood pressures, pulse, fasting blood glucose, postprandial blood glucose, urea, creatinine, total cholesterol, high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), triglycerides, insulin, c-peptide, homeostatic model assessment-insulin resistance (HOMA-

IR), oral glucose tolerance test (OGTT), aspartate transaminase (AST), alanine transaminase (ALT), st4, thyroid stimulating hormone (TSH), uric acid, glycosylated haemoglobin A1c (HbA1c), NEP and fibroblast growth factor-19 (FGF19) levels. Subjects with cardiovascular disease or previously diagnosed diabetes mellitus and those who rejected participation were excluded from the study.

All anthropometric measurements were made as previously described. The measurements were repeated twice and the average value was recorded. Fasting blood glucose samples were collected from all participants for analysis and lipid subfractions, glucose, insulin and hemostatic factors were measured as previously described.[6] SBP and DBP levels were measured in subjects with a sitting position twice and the averaged result was noted. OGGT was measured at 0^{th} and 2^{nd} hours after administering 75 g glucose. Soluble NEP in plasma samples was determined with a Solid Phase Sandwich ELISA (R&D Systems, Minneapolis, MN, USA) method.

Statistical Analysis

Normality of the variables was tested with the Kolmogorov-Smirnov method. Mann-Whitney U test was used for comparison of the continuous variables and Chi-square for comparison of the continuous variables between the groups. Continuous variables are expressed as mean±standard deviation descriptive statistics and categorical variables as frequency (number, percentage). Correlations between the variables were evaluated with Pearson's correlation analysis. $p<0.05$ values were considered statistically significant. All statistical analyses were performed using SPSS v. 23 (SPSS, Statistical Package for Social Sciences, IBM Inc., Chicago, IL, USA) statistical software.

Results

The mean age was 27.60±3.07 years in all participants, 27.74±2.85 years in Group NW and 27.43±3.36 years in Group OW. No statistically significant difference was found between the groups in terms of the mean age (p=0.960). The mean BMI value was found as 21.42±2.14 kg/m^2 in Group NW and 31.91±4.85 kg/m^2 in Group OW (p<0.001). Demographic features and anthropometric measurements of the subjects are given in Table 1.

In the biochemical analysis, the mean ALT, TSH and uric acid values were statistically significantly higher in Group OW compared to Group NW (for all, p<0.05). No statistically significant difference was found between the groups in terms of the other biochemical parameters. Biochemical parameters of the subjects are presented in Table 2.

Table 1. Demographic and anthropometric characteristics of the groups.

	Group NW (mean±SD)	Group OW (mean±SD)	Total (mean±SD)	p value
Age (years)	27.54±2.85	27.43±3.36	27.60±3.07	0.96
Height (cm)	163.41±5.72	162.82±6.26	163.15±5.93	0.46
Weight (kg)	57.06±5.04	84.51±12.4	69.46±16.48	<0.001*
BMI (kg/m^2)	21.42±2.14	31.92±4.85	26.16±6.38	<0.001*
Waist circumference (cm)	71.47±5.64	96.62±11.52	82.37±15.23	<0.001*
Hip circumference (cm)	96.76±4.74	112.08±8.2	103.40±9.98	<0.001*
Waist/hip ratio	0.74±0.05	0.86±0.07	0.79±0.08	<0.001*
Waist/height ratio	0.44±0.04	0.60±0.07	0.51±0.1	<0.001*
Fat percentage (%)	23.14±4.42	37.33±5.14	29.42±8.52	<0.001*

*Mann-Whitney U test.
BMI: body mass index, SD: standard deviation.

Table 2. Biochemical laboratory values of the subjects.

	Group NW (mean±SD)	Group OW (mean±SD)	Total (mean±SD)	p value
SBP (mmHg)	110.59±7.36	112.50±6.45	111.45±6.98	0.226
DBP (mmHg)	66.12±12.10	70.71±7.16	68.19±10.36	0.080
Pulse (bpm)	79.32±5.46	78.75±5.15	79.06±5.29	0.557
Urea (mg/dL)	21.88±5.61	21.19±4.40	21.57±5.08	0.827
Creatinine (mg/dL)	0.67±0.07	0.71±0.10	0.69±0.09	0.141
AST (U/L)	16.59±4.28	18.26±17.33	17.33±5.64	0.312
ALT (U/L)	13.56±7.72	21.41±14.64	17.03±11.88	0.003*
ST4 (ng/dL)	1.16±0.20	1.15±0.14	1.16±0.17	0.420
TSH (mIU/L)	2.07±3.40	2.31±1.45	2.18±2.68	0.029*
Uric acid (mg/dL)	3.29±0.84	4.06±0.72	3.59±0.87	0.002*

*Mann-Whitney U test, p<0.05: statistically significant.
SBP: systolic blood pressure, DBP: diastolic blood pressure, AST: aspartate aminotransferase, ALT: alanine aminotransferase, TSH: thyroid stimulating hormone, SD: standard deviation."

When lipid profiles of the subjects were examined; the mean HDL-c was statistically significantly lower in Group OW than in Group NW (p<0.01), while the mean triglyceride level was significantly higher in Group OW than in Group NW (p=0.002).

In the analysis of glycemic parameters; the mean fasting blood glucose, insulin, HOMA, HbA1c and triglyceride values were statistically significantly higher in Group OW compared to Group NW (for all, p<0.001). The mean HDL-c value was significantly lower in Group OW than in Group NW (p<0.05). No significant difference was found between both groups in terms of the other glycemic parameters (for all, p>0.05). Lipid and glycemic parameters of the subjects are presented in Table 3.

The mean OGTT result was found as 88.4±6.95 mg/dL in Group NW and 94.5±9.42 mg/dL in Group OW at the 0th hour with nos significant difference between the groups (p=0.300). The mean OGTT result was found as 97.6±19.13 mg/dL in Group NW and 102.75±24.31 mg/dL in Group OW at the 2nd hour with nos significant difference between the groups (p=0.650). The mean FGF19 value was found as 88.68±45.09 pg/mL in Group NW and 90.21±71.47 pg/mL in Group OW with no statistically significant difference between the groups (p=0.815). The mean NEP value was found as 1123.44±1327.60 mmol/L in Group NW and 1229.39±1315.17 mmol/L in Group OW with no statistically significant difference between the groups (p=0.916) (*Figure 1*).

Correlations between the studied variables were examined using Pearson's correlation analysis. Accordingly, BMI was significantly correlated with glycemic and lipid parameters, while no correlation was found between NEP and BMI values (p>0.05) (*Table 4*).

Table 3. Lipid and glycemic parameters of the groups.

	Group NW (mean±SD)	Group OW (mean±SD)	Total (mean±SD)	p value
Fasting blood glucose (mg/dL)	81.82±9.09	89.0±9.23	85.06±9.77	0.001*
Insulin (mIU/L)	7.93±4.30	14.18±6.37	10.67±6.12	<0.001*
C-peptide (mcg/L)	1.94±0.77	2.44±0.91	2.11±0.85	0.083
HOMA-IR	1.61±0.97	3.13±1.52	2.28±1.45	<0.001*
HbA1c (%)	5.28±0.19	5.46±0.23	5.32±0.22	0.037*
Total cholesterol (mg/dL)	170.29±40.0	188.73±29.97	178.28±36.89	0.096
HDL-c (mg/dL)	55.44±9.79	44.04±7.38	50.50±10.45	<0.001*
LDL-c (mg/dL)	103.0±28.88	116.81±27.53	108.98±28.90	0.083
Triglycerides (mg/dL)	81.26±27.70	129.77±67.59	102.28±54.34	0.002*

*Mann-Whitney U test, p<0.05: statistically significant; HOMA: homeostatic model assessment; HbA1c: hemoglobin A1c test; HDL-c: high density lipoprotein-cholesterol; LDL-c: low density lipoprotein cholesterol SD: standard deviation.

Table 4. Correlation of NEP and BMI values with lipid and glycemic parameters.

	BMI		NEP	
	r	p	r	p
BMI (kg/m^2)	1	-	0.058	0.656
NEP (ng/mL)	0.058	0.656	1	-
Fasting blood glucose (mg/dL)	0.315	0.013*	-0.083	0.523
Insulin (mIU/L)	0.631	<0.001**	0.039	0.776
C-peptide (mcg/L)	0.386	0.009**	-0.114	0.455
HOMA-IR	0.639	<0.001**	-0.022	0.872
HbA1c (%)	0.393	0.022*	-0.085	0.631
Total cholesterol (mg/dL)	0.249	0.055	-0.094	0.473
HDL-c (mg/dL)	-0.589	<0.001**	-0.081	0.54
LDL-c (mg/dL)	0.289	0.025*	-0.173	0.185
Triglycerides (mg/dL)	0.52	<0.001**	-0.016	0.901

*Pearson's correlation analysis, *p<0.05: significant correlation; **p<0.001: strong correlation. NEP: neprilysin, BMI: body mass index, HOMA: homeostatic model assessment, HbA1c: hemoglobin A1c test, HDL-c: high density lipoprotein-cholesterol, LDL-c: low density lipoprotein cholesterol.

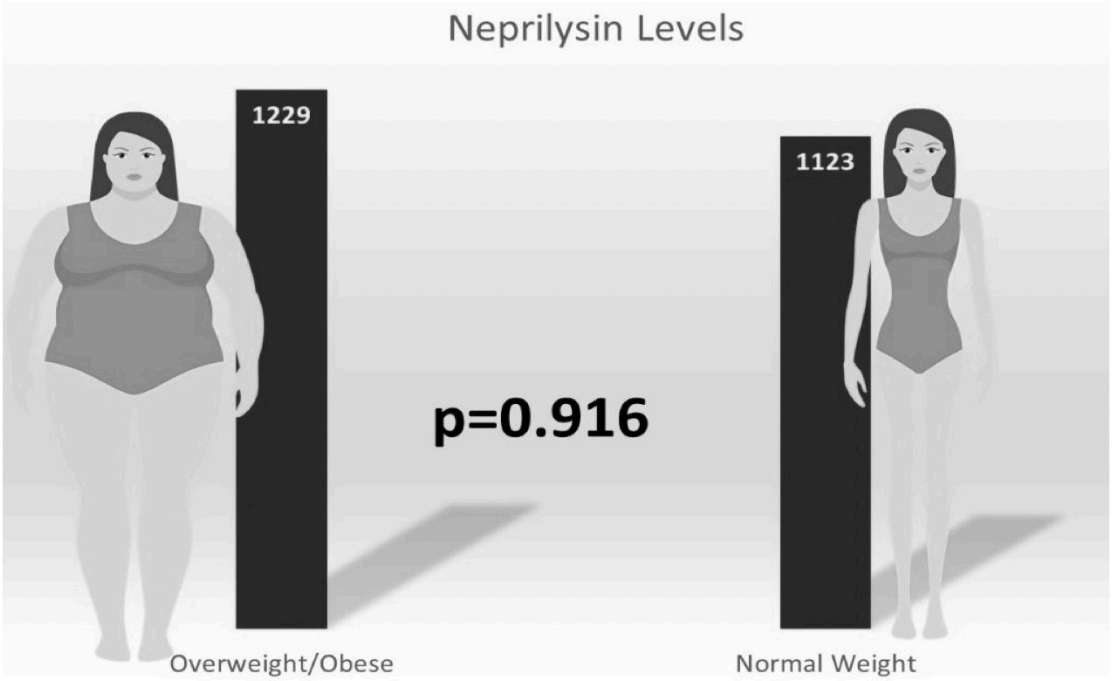

Figure 1. Comparison of neprilysin values between the overweight/obese and normal weight women.

Discussion

The steadily increasing global prevalence of obesity especially among young women, and developed and developing countries, had led research to focus on the biological changes associated with the pathogenesis of obesity in relation to a wide range of comorbidities and medical conditions including insulin resistance and diabetes mellitus. As the primary outcome of this study, we could not find any association between NEP and obesity.

The impact and prevalence of obesity have a female predominance and also lead to substantial health care costs with women accounting for 31% higher obesity-related expenditure than men.[14] This has prompted researchers to study obesity from a wide perspective and especially in women.[1,2,14-16] In the present study, we compared overweight/obese and normal weight young women in terms of biochemical, lipid and glycemic parameters.

Young women between 18-36 years have been reported to gain weight at a higher rate than in women in any other age group.[4] In our study, the mean age was found as 27.43 years. Jönsson et al. reported the mean age of obese women in their study as 30.90 years.[17] In this context, the mean age of our participants was consistent with the range reported in the literature. In the present study, anthropometric values were significantly higher in the overweight/obese group as expected.

Several biochemical parameters have been associated with obesity. Abdominal fat accumulation may represent a strong predictor of increased liver enzymes including AST and ALT.[18] In addition, BMI values, which is the primary indicator of obesity, has been associated with elevated ALT in non-diabetic people.[19] Similarly, in the present study, the mean ALT value was significantly higher in the overweight/obese group.

Serum uric acid is an end product which is produced by endogenous metabolism and exogenous urine.[20] Duan et al.[21] reported that high serum uric acid was positively associated with obesity in overweight and obesity groups. This association has been reported also by numerous studies.[22,23] In our study, the mean uric acid level was significantly higher in the over weight/obese women.

The interactions between thyroid function, weight control and obesity have been well-established. Obese people with a normal thyroid gland tend to have higher serum TSH and thyroid hormones in serum due to the activation of hypothalamic-pituitary-thyroid axis.[24] In the

present study, the mean TSH value was found to be statistically significantly higher in overweight/obese participants (p=0.02). On the other hand, lipid and glycemic parameters were significantly different in overweight/obese group as expected since their relationships with BMI and obesity are well-known.

NEP metalloendopeptidase has been proposed to have a potential role as an adipokine in the regulation of adipocyte function is it is also secreted by adipocytes.[8] Studies on the association between NEP and obesity are mostly animal experimental studies and research in humans lacks in the literature. Inhibition of NEP in obese insulin-resistant rats has been reported to improve insulin-mediated glucose disposal.[9] Standeven et al.[6] showed that adipose tissue levels of NEP were increased in obese insulin-resistant mice. Based on this finding and as NEP protein production in human adipocytes increased during cell differentiation, NEP increases with obesity. In addition, they claimed a correlation between BMI and NEP levels. Unlike these studies, we found no significant difference in NEP levels beetween overweight/obese young women and no significant correlation between NEP and BMI values. Of course it is not easy to compare these results and in order to draw more informed conclusions, this issue should be subjected to further studies to be performed on human subjects.

Study Limitations

Major limitation of our study is the relatively small sample size and being conducted in a single centre. However, this study is the first in the literature to investigate NEP in obese women as a strength, and lack of human studies on this issue make our study guiding for future studies. We believe that the main finding of our study will shed light on the research regarding the controversy about the role of NEP in obesity, insulin resistance and diabetes.

Conclusions

In this study, no significant difference was found between serum NEP levels of overweight/obese and normal weight women, suggesting that NEP does not play a role in the pathogenesis of obesity, insulin resistance or diabetes. However, further comprehensive studies are needed to support this finding.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: SC; Study Design: OOG, SC; Supervision: OOG, SC; Materials: OOG, SC; Data Collection and/or Processing: OOG, SC; Statistical Analysis and/or Data Interpretation: OOG, SC; Literature Review: OOG, SC; Manuscript Preparation: OOG, SC; Critical Review: OOG, SC.

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Medication Errors and Potentially Inappropriate Medication Use in Elderly Patients Admitted to the General Internal Medicine Outpatient Clinic of a University Hospital

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ABSTRACT

Background The frequency of chronic diseases, number of drugs used, and number of medication errors have increased in the elderly. In this study, we aimed to determine the prevalence of potentially inappropriate medication (PIM) use and medication errors in elderly patients admitted to a university hospital and to identify the influencing factors.

Material and Methods In this prospective cross-sectional study, the patients' characteristics, drug use patterns, and medication errors in the previous month were recorded in detail. Following this, PIM use was assessed according to the 2015 Beers Criteria.

Results A total of 721 elderlay patients (60.9% female and 39.1% male) were included in this study. The mean number of drugs used by the patients per day was 4.6±2.8 and the rate of polypharmacy was 49.4%. The rate of medication errors was 54.2%, that of PIM use was 30.1%, and that of adverse drug reactions was 22.5%; these rates were higher in patients with polypharmacy. The most common medication error, PIM use, and adverse drug reaction were the omission of a daily dose (36.5%), inappropriate use of proton pump inhibitors (10%), and gastrointestinal system-related symptoms (7.7%), respectively. Diabetes mellitus and depression were found to be independent factors associated with medication errors.

Conclusions In the present study, patient-related medication errors, PIM use, and adverse drug reactions were more frequently observed in elderly patients with polypharmacy. In addition, medication errors were more commonly observed in elderly with diabetes mellitus and depression.

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Introduction

In recent years, the elderly population has been increasing worldwide. Aging is associated with a decrease in organ functions and an increase in the frequency of chronic diseases and the number of drugs used. Changes in the pharmacokinetics and pharmacodynamics of drugs due to age-related physiological changes, an increased risk of adverse drug reactions (ADRs) and drug-drug interactions due to polypharmacy are the main factors that make the management of elderly patients difficult.[1,2]

Polypharmacy increases in the cost of treatment, need for hospitalization, rate of treatment nonadherence, and prevalence of medication errors.[2,3] Treatment nonadherence by the patient and the prescription of potentially inappropriate medications (PIMs) by the physician are the main medication errors observed in elderly patients. Omitting to take medication, taking the wrong dose of medication, taking medication at the wrong time than the recommended one, and taking the wrong medication are the main types of patient-related treatment nonadherence and medication errors.[4-6] PIM use in the elderly is also an important problem, and various criteria have been established to assess it in recent years, particularly the Beers Criteria and Screening Tool of Older Person's Prescriptions (STOPP) Criteria.[7,8] The present study included elderly patients admitted to the general internal medicine outpatient clinic of a university hospital. The aim of this study was to assess the patients' socio-demographic characteristics, concomitant chronic diseases, medication use features, frequency of polypharmacy and patient-related medication errors, and also rate of PIMs use according to the 2015 Beers Criteria and the influencing factors in order to contribute to the existing literature.

Material and Methods

This prospective cross-sectional study was conducted after obtaining approval from the local ethics committee. Patients aged ≥65 years who were admitted to the General Internal Medicine Outpatient Clinic of Bursa Uludag University Hospital in Turkey between July 1, 2012 and January 1, 2013 and provided informed consent were included in the study.

Patient information, such as age, gender, marital status, people they lived with, educational status, concomitant chronic diseases, drugs used, ADRs, and also patient-related medication errors in the previous month, were recorded on a questionnaire form via face-to-face interviews. The daily use of ≥5 drugs was accepted as polypharmacy, while that of ≥10 drugs was accepted as excessive polypharmacy in the present study.[9,10] The patients' PIM use was assessed according to the 2015 Beers Criteria.[7]

The main types of patient-related medication errors are as follows:

1. Dose omission error: Skipping or not taking the daily dose of at least one drug.
2. Wrong time error: Taking drugs outside the recommended time.
3. Wrong dose error: Taking drugs at a dose lower or higher than the daily recommended dose or duplicating the dose.
4. Wrong drug error: Taking drugs with an inappropriate indication or taking drugs prescribed to other family members by mistake.

PIMs are grouped as follows according to the 2015 Beers Criteria.[7]

1. Table 2-related PIMs: Taking drugs that should be avoided in the elderly.
2. Table 3-related PIMs: Taking drugs that should be avoided due to drug-disease or drug-syndrome interactions in the elderly.
3. Table 4-related PIMs: Inappropriately using drugs that should be used with caution in the elderly.
4. Table 5-related PIMs: Taking drugs that should be avoided due to clinically important drug-drug interactions in the elderly.
5. Table 6-related PIMs: Inappropriately using drugs that should be avoided or reduced in dosage due to renal impairment in the elderly.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21. Pearson's chi-square, Fisher's exact chi-square and Freeman Halton tests were used for comparing categorical variables. The Kruskal-Wallis test was used to compare more than two independent groups, and the Mann-Whitney U

test was used to compare two independent groups. Relationships between variables were analyzed using the Spearman correlation coefficient. Binary logistic regression analysis was performed to identify factors that independently affected medication errors. *p* values < 0.05 were considered statistically significant.

Results

A total of 721 patients admitted to the General Internal Medicine Outpatient Clinic for a period of 6 months were included in the present study. The sociodemographic characteristics of the patients are shown in Table 1.

Table 1. Demographic and anthropometric characteristics of the groups.

	Number (%)
Gender	
Female	439 (60.9)*
Male	282 (39.1)
Age group	
65-74 year-old	571 (79.2)*
≥75 year-old	150 (20.8)
Marital status	
Single	8 (1.1)
Married	472 (65.5)
Divorced	18 (2.5)
Widowed	223 (30.9)**
Household status	
Alone	111 (15.4)*
With spouse	471 (65.3)
With children	130 (18)**
With close relative	4 (0.6)
Nursing home	5 (0.7)
Educational status	
Illiterate	118 (16.4)**
Just literate	71 (9.8)
Primary school	314 (43.6)
Secondary school or above	218 (30.3)**

* p<0.01, ** p<0.001.

The number of female patients was higher in the present study. Moreover, most patients were aged 65-74. The mean age of the patients was: 70.9±5.1 years (females: 70.6±4.9 years, males: 71.5±5.3 years), and their median age was 70 years, (range: 65-89 years). The distribution of age groups was similar among female and male patients. The prevalence of losing their spouse, living alone, living with children and being illiterate was higher in female patients, while that of having secondary school and higher education levels was higher in male patients.

A total of 677 (93.9%) patients had at least one concomitant chronic disease. The mean number of concomitant chronic diseases in the patients was 2.5±1.4 (range: 0-7, median: 2), with the prevalence being significantly higher in females than males (2.7±1.3 vs 2.3±1.5, p<0.001). The most common chronic diseases were hypertension (n=473, 65.6%), diabetes mellitus (n=261, 36.2%), dyslipidemia (n=188, 26.1%), and coronary artery disease (n=136, 18.9%). Of the chronic diseases noted, the prevalence of hypertension, osteoporosis, goiter-hypo/hyperthyroidism (p<0.001), dyslipidemia, depression (p<0.01), and osteoarthrosis (p<0.05) was significantly higher in females, while that of coronary artery disease (p<0.001) was significantly higher in males. The patients' drug use characteristics are shown in Table 2, and their rates of polypharmacy, PIM use, and patient-related medication errors are shown in Table 3.

Cardiovascular system (CVS) drugs were the most commonly used drugs in both genders. The use of endocrine system drugs, psychiatric drugs (p<0.001), and analgesic-anti-inflammatory drugs (p<0.01) was higher in female patients. In terms of age groups, endocrine system drugs (p<0.05) were more commonly used in the "65-74 year-old" group, while CVS drugs (p<0.05) were more commonly used in the "≥75 year-old" group. In total, 162 patients (22.5%) experienced ADRs. ADRs were significantly higher in patients with polypharmacy (8.2% in patients taking 1-4 drugs per day vs 14.3% in patients taking ≥5 drugs per day, p<0.01), and there was no difference between genders and age groups. Moreover, 254 (35.2%) patients reported that they used non-prescription drugs, while 109 (15.1%) patients reported that they used alternative therapy. There was no difference between genders and age groups in this regard.

Table 2. Drug use characteristics of the patients.

	Number (%)
Most frequently used drug groups	
Cardiovascular system drugs	573 (79.5)
Endocrine system drugs	410 (56.9)
Gastrointestinal system drugs	192 (26.6)
Psychiatric drugs	108 (15)
Respiratory system drugs	97 (13.5)
Most frequently used drugs	
ASA	223 (30.9)
ACEI/ARB±hydrochlorothiazide	173 (24)
Beta blockers	170 (23.6)
Metformin	168 (23.3)
PPIs	152 (21.1)
Most frequently ADRs	
Gastrointestinal system intolerance	54 (7.5)
Allergic skin reaction	25 (3.5)
Hypoglycemia	25 (3.5)
Non-prescription drug use	
NSAIDs	128 (17.8)
Analgesics	96 (13.3)
Vitamins	28 (3.9)
Others	45 (6.2)
Alternative treatment use	
Herbal products	88 (12.2)
Massage-spa	11 (1.5)
Acupuncture	2 (0.3)
Others (fish oil, ozone etc.)	13 (1.8)

ASA: acetylsalisylic acid, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor bloker, PPIs: proton pump inhibitors, ADRs: advers drug reactions, NSAIDs: nonsteroidal antiinflammatory drugs.

The mean number of drugs used by the patients per day was 4.6±2.8 (range: 0-15, median: 4). Female patients used a significantly higher number of drugs than male patients (4.9±2.7 vs 4.1±3.0, p<0.001); however, there was no difference in the number of drug used between different age groups. A positive correlation was noted between the number of chronic diseases and the number of drugs used (r= -0.579, p<0.001). 35 (4.8%) patients were not taking any drug, while 686 (95.2%) patients were taking at least one drug. 356 (49.4%) patients had polypharmacy, with the rate of polypharmacy being higher in females than in males (56.2% vs 38.7%, p<0.01).

A total of 528 medication errors were noted in 391 (54.2%) patients (gender-wise distribution: 335 errors in 250 female patients and, 193 errors in 141 male patients; age-wise distribution: 411 errors in 314 patients in the 65-74 year-old group and 117 errors in 77 patients in the ≥75 year-old group); there was no difference between genders and age groups in this regard. The prevalence of medication errors was significantly higher in patients with polypharmacy (28.8% in patients taking 1-4 drugs per day versus 75.7% in patients taking ≥5 drugs per day, p<0.001). As the number of concomitant chronic diseases increased, the number of medication errors significantly increased (2.3±1.4 concomitant chronic diseases in patients without medication errors vs 3.0±1.4 in those with medication errors, p<0.001).

Retrospective binary logistic regression analysis was performed to assess the relationship between medication errors and age, gender, educational status, number of comorbid chronic diseases, most common concomitant chronic diseases, polypharmacy, non-prescription drug use, and alternative therapy use. The results revealed that polypharmacy (odds ratio [OR]: 1.12, 95% confidence interval [CI]: 1.05-1.19, p<0.001), diabetes mellitus (OR: 1.55, 95% CI: 1.1-2.1 p=0.009), and depression (OR: 2.6, 95% CI: 1.26-5.4, p=0.009) were independent factors associated with medication error.

In total, 264 instances of PIMs in 217 (30.1%) patients (gender-wise distribution: 168 instances in 136 female patients and, 96 instances in 81 male patients; age-wise distribution: 160 instances in 127 patients in the 65-74 year-old group, and 104 instances in 90 patients in the ≥75 year-old group). The rate of PIM use was significantly higher in patients with polypharmacy (17.6% in patients taking 1-4 drugs per day vs 47.5% in patients taking ≥5 drugs, p<0.001). As the number of concomitant chronic diseases increased, the rate of PIM use significantly increased. The number of chronic diseases in patients not using PIMs was

Table 3. Distribution of the number of drugs used, potentially inappropriate medications used, and patient-related medication errors by gender and geriatric age groups.

	Gender			Age group	
	Female	Male	Total	65-74 year-old	≥75 year-old
Number of drugs used					
1-4 drugs	178 (40.5)	152 (53.9)	330 (45.8)	255 (44.7)	75 (50)
5-9 drugs	222 (50.5)*	91 (32.3)	313 (43.4)	251 (44)	62 (41.3)
>10 drugs	25 (5.7)	18 (6.4)	43 (6)	32 (5.6)	11 (7.3)
Medication errors					
Dose omission error	165 (37.6)	98 (34.8)	263 (36.5) 206	206 (36.1)	57 (38)
Wrong time error	137 (31.2)	69 (24.5)	(28.6)	163 (28.5) 35	43 (28.7)
Wrong dose error	29 (6.6)	2 (7.8)	51 (7.1)	(6.2)	16 (10.6)
Wrong drug error	4 (0.9)	4 (1.4)	8 (1.1)	7 (1.2)	1 (0.6)
Total**	250 (56.9)	141 (50)	391 (54.2)	314 (55)	77 (51.3)
PIMs					
Table 2-related PIMs	121 (27.6)	70 (24.8)	191 (26.5)	122 (21.3)	69 (46.0)*
Table 3-related PIMs	12 (2.7)	7 (2.5)	19 (2.6)	12 (2.5)	5 (3.3)
Table 4-related PIMs	14 (3.2)	8 (2.8)	22 (3.1)	3 (0.5)	19 (12.7)*
Table 5-related PIMs	18 (4.1)	10 (3.5)	28 (3.9)	20 (3.5)	7 (5.3)
Table 6-related PIMs	3 (0.7)	1 (0.4)	4 (0.6)	3 (0.5)	1 (0.7)
Total***	136 (31)	81 (28.7)	217 (28.3)	127 (20.8)	90 (56.7)

*p<0.001, **Some patients have more than one medication error, ***Some patients have more than one potentially inappropriate medication use.

2.2±1.5, while that in patients using PIMs was 2.9±1.5 (p<0.001). The use of Table 2- and Table 4-related PIMs was higher in the ≥75 year-old group. No difference was found between gender and age groups with regard to the other categories of PIMs. The most common instances of Table 2-related PIM use were the inappropriate use of PPIs (n=72), potent anticholinergics (n=44), NSAIDs (n=24), antithrombotics (n=16), and digoxin (n=15), while those of Table 3-related PIM use was inappropriate drug use in patients with dementia (n=9) and heart failure (n=5). The most common Table 4-related PIM use was inappropriate use of acetyl salicylic acid (ASA) (n=22), while the most common Table 5-related PIM use was the combined use of antidepressants and ≥2 central nervous system-active drugs (n=19). With regard to Table 6-related PIMs, 4 patients used drugs without dose reduction in accordance with the degree of renal insufficiency.

Discussion

Polypharmacy is commonly observed in elderly. In community-based telephonic survey conducted in 1998 and 1999 in the USA,[10] the rates of polypharmacy and excessive polypharmacy were reported to be 57% and 12% in elderly females and, 44% and 12% in elderly males, respectively. Moreover, the rate of polypharmacy was reported to be 59.6% in a study conducted in patients living in a nursing home in Turkey,[11] 26.7% in a study conducted in 67 primary care practices in Germany,[12] 47.6% in a study on female patients in a geriatric outpatient clinic in Turkey,[13] and 45% in a study on patients aged ≥75 year-old who were admitted to the emergency services in England.[14] In the case of hospital-based studies, in a study on patients admitted to 5 hospitals in Norway,[15] the rate of polypharmacy on admission was reported to be 47%. In another study conducted

in 38 internal medicine wards in Italy,[16] the rate of polypharmacy was 51.9% on admission and 67% at discharge. Similarly, in the present study, the rates of polypharmacy and excessive polypharmacy were found to be 49.4% and 6%, respectively.

Chronic diseases are the most common cause of polypharmacy. In a study elderly females admitted to a geriatrics outpatient clinic in Turkey,[13] the most common chronic diseases were found to be hypertension (75.3%), depression (45.5%) and dementia (39.4%). Moreover, in a study on patients hospitalized in internal medicine clinics in Italy, the most frequent diagnoses were hypertension (57.8%), diabetes mellitus (24%) and coronary heart disease (23%).[16] In another study on patients hospitalized in Jordan, the most frequent diagnoses were hypertension (74.4%), diabetes (58.7%) and chronic kidney disease (34.2%).[17] Similarly, in the present study, the most common chronic diseases were found to be hypertension (65.6%) and diabetes (36.2%).

Medication errors may occur at various stages, such as prescribing the medication, supplying the medication, injecting the medication, and taking the medication home. PIMs associated with the prescription phase and medication errors made by patients at home were assessed in the present study.

The use of PIMs is common in the elderly. In a community-based study conducted at the homes of 423 elderly people in Brazil,[18] the rates of PIM use according to the 2012 Beers Criteria and STOPP Criteria version 2 were found to be 42.1% and 46.2%, respectively. The most common PIMs reported in that study were clonazepam-benzodiazepine, amiodarone-antiarrhythmic drugs, and glibenclamide/glyburide-sulfonylureas. In another study on patients who were admitted to a geriatrics outpatient clinic of a university hospital in Turkey[19] between 2010 and 2014, examination of the files of 667 randomly selected patients according to the 2012 Beers Criteria and STOPP Criteria version 2 revealed that the rates of PIM use were 33.3% and 39.1%, respectively. In that study, the 3 most common PIMs according to the 2012 Beers Criteria were antipsychotics, selective serotonin reuptake inhibitors (SSRIs) and nonsteroidal antiinflammatory drugs (NSAIDs). In another study on 835 patients who were admitted to an emergency department in Turkey,[20] the rates of PIM use according to the 2012 Beers Criteria and STOPP Criteria version 2 were found to be 52.9% and 51.6%, respectively. In that study, the most common PIMs according to the 2012 Beers Criteria were SSRIs, potent anticholinergics, NSAIDs, and ASA.

Moreover, in a study on 456 patients hospitalized in the department of geriatric care of a university hospital in China,[21] the rate of PIM use according to the 2012 Beers Criteria was found to be 44.7%, while that according to the 2015 Beers Criteria was found to be 53.5%. In that study, the most common PIMs according to the 2015 Beers Criteria were PPIs, benzodiazepines and benzodiazepine receptor agonists.

In a retrospective study examining the records of 95 elderly people in two assisted living facilities in the USA,[22] the rate of PIM use was found to be 60% according to the 2015 Beers Criteria. The most common PIM was central nervous system agents in that study. Moreover, in a study on 351 patients admitted to internal medicine and surgical wards in Jordan,[17] the rate of PIM use was 29.3% on admission and 47.2% during hospitalization according to the 2015 Beers Criteria. The most common PIMs before admission were PPIs (26.2%), alpha blockers (5.1%) and digoxin (4%) in that study. PPIs were also the most common PIMs during hospitalization (42.5%), followed by alpha blockers (4.8%) and metoclopramide (4.3%). In another study evaluating the data of 2231 patients using pharmacy records in Argentina,[23] 1623 patients (72.75%) were found to have received at least one PIM during the study period according to the 2015 Beers Criteria. In that study, the most common PIMs were anxiolytics (46.03%), PPIs (29.67%), and NSAIDs (22.37%).

Compared with the 2012 Beers Criteria, the most important changes in the 2015 Beers Criteria are the addition of 2 new tables on specific drug interactions and specific drugs requiring renal dose adjustment. In addition, PPIs and endocrine drugs have been added to the table of drug categories. PPIs have been added to the PIM list with instructions to ''avoid use for > 8 weeks except in high-risk patients (eg, patients taking oral corticosteroids or chronic NSAIDs) or those with erosive esophagitis, Barrett's esophagus, pathological hypersecretory condition, or therapeutic failure of H2 blockers''.[7,24] PPIs were

found to be the most frequently used PIM in the present study, according to 2015 Beers Criteria, similar to previous findings.

Patient-related medication errors are a relatively less researched issue. Instances of medication nonadherence in the form of dose omission error, dosage errors and wrong drug errors are frequently reported medication errors.[4] In a study conducted in the USA,[25] the rate of medication nonadherence in 147 elderly patients in a period of 2 weeks after discharge from the hospital was found to be 30.6%. In another study conducted by interviewing 382 elderly patients in Spain,[3] medication errors were noted in 75% of the patients. Moreover, 4% of the patients were found to have ≥ 4 medication errors. In the present study, 54.2% of the patients had medication errors, with the most common medication errors being dose omission (36.5%) and wrong time errors (28.6%); these errors were significantly higher in patients with polypharmacy ($p<0.01$).

The main limitation of the present study was that the data were obtained from a single center. However, we think that our data represent the patient profile of a tertiary university hospital in our country.[13] Another limitation was that the data of the drugs used by the patients were based on their own statements. However, to minimize this risk, the patients were asked to bring their drugs at the next visit, and were questioned in detail about their drug use patterns, medication errors and ADRs. In addition, the patients' files and the Social Security Institution prescription system were examined in order to obtain the most accurate information about the drugs used by the patients.

Conclusions

In conclusion, similar to previous findings, the present results revealed that the number of drugs used and the rates of polypharmacy increased with an increase in the number of chronic diseases. Consequently, the rates of medication errors, PIM use and ADRs also increased. Therefore, to reduce the potential risks in the elderly, a comprehensive geriatric assessment should be performed for all patients, drugs should be prescribed according to rational drug use recommendations and patients should be explained in detail about how to use their drugs. Following this, at each visit, patients should be carefully questioned how they use the drugs and about drug-induced adverse effects.

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: CD; Study Design: CD, EP; Supervision: CD, EP, DS; Fundings: EP, CD; Materials: EP; Data Collection and/ or Processing: EP, CD; Analysis and/or Interpretation: CD, EP, DS; Literature Review: EP, CD, DS; Writer: EP, CD, DS; Critical Review: CD, EP, DS; Statistics: DS.

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Original Article

Radiotherapy Could Increase the Efficacy of Immunotherapy in Non-small Cell Lung Cancer

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ABSTRACT

Background In non-small cell lung cancer (NSCLC), immunotherapy is a treatment option in patients without targetable mutations in second and later lines. Nevertheless, there is no validated test that can predict immunotherapy response.

Material and Methods Our study aimed to investigate the effect of radiotherapy (RT) on survival in patients with NSCLC receiving immunotherapy after first-line chemotherapy. Twenty-five patients diagnosed with NSCLC and received immunotherapy after at least one previous chemotherapy line were included in our study.

Results The median age of the patients was 61.7 (26.6-81.2) years. 19 (76%) patients were male. 11 (44%) of the patients had received immunotherapy in the second-line and 14 (66%) in ≥3 lines. Patients had received a median of 5 cycles (1-27) of immunotherapy. RT to immunotherapy interval was 6.4 months (1.0-11.8). Partial response was observed in 12 patients, stable disease in 8 patients, progression in 1 patient, and hyperprogression in 4 patients. Median progression-free survival (PFS) was 4.4 months (95% CI; 3.2-5.6), and median overall survival (OS) was 16.4 months (95% CI; 5.6-27.3). 14 (56%) of the patients had received RT. RT was administered to 12 patients before immunotherapy, and two patients received RT to bones during immunotherapy. The patients who received RT had statistically longer PFS (4.9 vs 3.9 months, p=0.012) and OS (18.7 vs 7.3 months, p=0.023) comparing those without RT.

Conclusions Our findings showed that RT significantly improved the survival in patients who received immunotherapy, pointing that RT may have an influential role in immunotherapy response.

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Introduction

Despite all the improvements in diagnosis and treatment options today, lung cancer is the most common cause of cancer-related death in men and women worldwide.[1] On the other hand, especially in non-small cell lung cancer (NSCLC), which constitutes approximately 85-90% of all lung cancers, a significant increase in survival rates has been achieved with targeted therapies and immunotherapy in the treatment of metastatic disease.[2,3]

The programmed death (PD)-1 receptor expressed by activated T cells interacts with the PD-ligand 1 (PD-L1) and -ligand 2 (PD-L2) expressed by tumor cells and infiltrating immune cells. As a result of this interaction, the T cell activation is inhibited, and the escape of the tumor from the immune system is supported. Immune checkpoint inhibition agents, such as anti-PD-1 antibodies, nivolumab, and pembrolizumab, an anti-PD-1 antibody, atezolizumab, disrupt PD-1 mediated signaling and restore anti-tumor immunity.[4-6] In several clinical trials, anti-PD-1 and anti-PD-L1 antibodies have shown durable responses in 20% of patients, which have not been reported in any trial studying chemotherapeutic agents in advanced NSCLC.[7-10]

Therefore, immunotherapy is an important treatment option in metastatic NSCLC patients who do not carry driver mutations such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), proto-oncogene tyrosine-protein kinase 1 (ROS1), and progress after primary chemotherapy. National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend pembrolizumab to patients with PD-L1 tumor proportion score (TPS) >1% and atezolizumab and nivolumab regardless of PD-L1.[3,11] However, there is no validated test to determine which patient group will benefit more from immunotherapy in the second or later treatment lines for metastatic NSCLC.[3,11]

Radiotherapy (RT) may be administered to lung cancer patients for curative intent in the locally advanced-stage or palliative treatment in the metastatic stage.[3] Radiotherapy is studied to have three main effects in tumor treatment. Firstly it reduces the tumor burden with a direct toxic effect. The second effect is that RT provides stimulation of antitumoral response far from the irradiated area. This effect was first described as the abscopal effect by Mole et al. in 1953.[12] Finally, RT may lead to an increase in PD-L1 expression in the tumor microenvironment, resulting in inhibitory PD-1 receptors to bind to T cells and inhibiting T cell anti-tumor response.[13] On the other hand, data showing the effects of RT regarding the increase in immunotherapy response in patients with NSCLC is quite limited. Our study aimed to investigate the effect of RT on immunotherapy efficacy in NSCLC patients receiving immunotherapy in the second-line or later treatment.

Material and Methods

Study Population and Data Collection

Twenty-five patients diagnosed with NSCLC in Bursa Uludag University Faculty of Medicine Medical Oncology Department between 2018-2020 and received immunotherapy after at least one previous chemotherapy line were included in our study. Patients under age 18, with known small cell lung carcinoma and missing clinical data in the electronic database, who possess targetable mutations such as ALK, EGFR, ROS1, BRAF, RET, c-MET, neurotrophin receptor tyrosine kinase (NTRK) had a history of pneumonitis, had received immunotherapy or systemic immunosuppressive therapy, and had an active autoimmune disease were excluded from the study.

PD-L1 levels were determined using the DAKO 22C3 antibody clone from paraffin blocks at the time of diagnosis. Patients bore the costs of immunotherapy due to the reimbursement system in the health policy in our country. Atezolizumab 1200 mg every 21 days, nivolumab 240 mg every 14 days, and pembrolizumab 200 mg every 21 days were administered by intravenous infusion on day 1 of each cycle. The patients' demographic characteristics and histopathological features, treatments, treatment-related side effects, and the effects of the treatment on survival were analyzed retrospectively using hospitals' electronic medical records.

Radiotherapy was recorded in two parts, during and before immunotherapy. If the patient received RT for the treatment of NSCLC at any

time point before the first immunotherapy course, the elapsed time between the date of the RT and the immunotherapy was recorded. Adverse events and laboratory abnormalities were assessed using the Common Terminology Criteria for Adverse Events version 4.0.

Our study complied with the ethical standards of the institutional research committee and the Helsinki declaration of 1964. The Clinical Research Ethics Committee of the Bursa Uludag University Faculty of Medicine approved the study (Approval number: 2020-19/21).

Outcomes

Response assessment was conducted according to Response Evaluation Criteria in Solid Tumors (version 1.1). The duration of response was defined as the time from first documented evidence of response until progression. Progression-free survival (PFS) was calculated from the beginning of treatment with immunotherapy until disease progression or death from any cause. Overall survival (OS) was determined from the beginning of the immunotherapy until death from any cause. Hyper-progression was defined as PFS <2 months, >50% increase in tumor burden, and >2-fold increase in progression pace.[14] Immunotherapy was maintained beyond progression in case of evidence of clinical benefit.

Statistical Analysis

Median (minimum-maximum) values expressed continuous variables, and categorical variables were expressed by frequency and corresponding percentage values. Life expectancy was analyzed by the Kaplan–Meier method, and the log-rank test was used to investigate the effect of radiation therapy, smoking, age, agent, and site of metastasis on survival. The data were statistically processed using the IBM SPSS version 22 software, and a 5% type-I error level was used for statistical significance.

Results

The median age of the patients was 61.7 (26.6-81.2) years. 19 (76%) patients were male. The demographic and clinicopathological characteristics of the patients are displayed in Table 1. Eastern Cooperative Oncology Group (ECOG) score was 1 for 18 (72%) patients. 56% of the patients had a smoking history. The pathological assessment of most patients (64%) was consistent with adenocarcinoma. Fifteen (60%) patients had a PD-L1 level of $\geq$ 50%. Nearly half of the patients (48%) had de novo metastatic disease. Lungs were the most common metastasis sites.

The immunotherapy agents, treatment steps, treatment responses, and duration of the treatment are presented in Table 2. There were 11 patients receiving pembrolizumab, 8 receiving atezolizumab, and 6 receiving nivolumab. Eleven (44%) of 25 patients had received immunotherapy in the second line and 14 (66%) in the third or later lines. The median duration of follow-up was 14.7 (4.9-19.6) months. The median duration of treatment was 6.9 (2.1-14.2) months. Patients had received a median of 5 cycles (1-27) of immunotherapy. Partial response was observed in 48% and stable disease in 32% of patients. There was progression in 1 and hyperprogression in 4 patients. The median duration of response was 6.3 (4.1-10.3) months. Chemotherapy was planned for patients who progressed after immunotherapy. The median OS was 16.4 months (95% confidence interval [CI]; 5.6-27.3) (Figure 1A), and the median PFS was 4.4 months (95% CI; 3.3-5.7) (Figure 1B).

The clinical features of the patients related to RT are given in Table 3. 56% of patients had received RT. Radiotherapy was administered to 12 patients before immunotherapy, and two patients received concurrent immunotherapy and RT to the bone metastasis. Radiotherapy to immunotherapy interval was 6.4 months (1.0-11.8). Thoracic radiotherapy was applied to 5 patients with a total dose of 50-60 Gy in 30 fractions. Palliative bone RT was given to 6 patients with 20-30 Gy in 5-10 fractions. One patient had progressive cervical lymph node metastasis, and RT was administered 30 Gy in 10 fractions palliatively. Whole-brain irradiation was administered with 30 Gy in 10 fractions in a patient who had brain metastases. In another patient with bone and brain metastases, a total of 30 Gy palliative RT in 10 fractions was applied to both metastatic sites.

Patients receiving RT had a statistically longer OS and PFS comparing those not receiving RT (for OS; 18.7 months [95% CI: 17.3-20.2] vs 7.3 months [95% CI: 5.2-9.3], p=0.023 and for PFS; 4.9 months [95% CI: 4.4-5.8] vs 3.9 months [95% CI: 3.3-4.2], p=0.012), respectively (*Figures 2A, 2B*). The

log-rank test revealed that there was no statistical difference in PFS in terms of gender (p=0.203), age (65< vs ≥65, p=0.156), ECOG performance (p=0.466), smoking (p=0.188), immunotherapetic agent (p=0.617), stage at diagnosis (non-metastatic vs de novo metastatic, p=0.813), treatment lines (2 vs ≥3, p=0.389), presence of liver metastasis (p=0.495), histopathological group (p=0.497) and PD-L1 status (50%< vs ≥50%, p=0.091). Except for smoking, these findings were similarly statistically insignificant for the OS analysis (p=0.837 for gender, p=0.730 for ECOG performance, p=0.858 for immunotherapetic agent, p=0.665 for stage at diagnosis, p=0.638 for treatment lines, p=0.281 for presence of liver metastasis, and p=0.330 for PD-L1 status). For PFS; PDL-1 level (50%< vs ≥50%, p=0.091) and for OS; histopathological subgroup (p=0.075) and age (p=0.052) showed a trend towards significance. The p-value for comparison between smokers and non-smokers in the log-rank test in terms of OS was 0.044, but confidence intervals were overlapping (18.7 months [%95 CI: 5.9-31.5] versus 10.0 months [%95 CI: 0.1-21.0], p=0.044), therefore the difference was not statistically significant.

Table 1. Demographic and clinicopathological features of the patients.

		n (%)
Gender	Male	19 (76)
	Female	6 (24)
Age	Median (range) (year)	61.7 (26.6-81.2)
ECOG performance status score	0	3 (12)
	1	18 (72)
	2	4 (16)
Smoking	Non-smoker	11 (44)
	Smoker	14 (56)
Histopathology	Adenocarcinoma	16 (64)
	Squamous cell carcinoma	9 (36)
PD-L1	< %50	8 (32)
	≥ %50	15 (60)
	Missed data	2 (8)
Stage at diagnosis	Non-metastatic	13 (52)
	Metastatic	12 (48)
Site of metastasis	Cranial	2 (8)
	Liver	8 (32)
	Lungs	20 (80)
	Bone	12 (48)
	Adrenal gland	3 (12)

ECOG: Eastern Cooperative Oncology Group performance status.

Table 2. Immunotherapy agents and treatment responses.

	n (%)
Immunotherapy agents	
Pembrolizumab	11 (44)
Atezolizumab	8 (32)
Nivolumab	6 (24)
Lines of immunotherapy	
2nd line	11 (44)
≥3rd line	14 (56)
Median	3 (2-5)
Immunotherapy cycles median (range)	5 (1-27)
Immunotherapy treatment response	
Partial response	12 (48)
Stable disease	8 (32)
Progressive disease	1 (4)
Hyperprogressive disease	4 (16)
Duration of follow up median (range) (month)	14.7 (4.9-19.6)
Duration of treatment median (range) (month)	6.9 (2.1-14.2)
Duration of response median (range) (month)	6.3 (4.1-10.3)
Progression on immunotherapy	19 (76)
Death	14 (56)

Table 3. The clinical features of the patients related to radiotherapy.

		n (%)
Radiotherapy history	Present	14 (56)
	Absent	11 (44)
Radiotherapy timing	Before starting immunotherapy	12 (85.8)
	Receiving immunotherapy	2 (14.2)
Radiotherapy sites	Bone	6 (43)
	Thorax	5 (35.7)
	Cranial and bone	1 (7.1)
	Cranial	1 (7.1)
	Neck lymph nodes	1 (7.1)
Radiotherapy to immunotherapy interval median (range) (month)		6.4 (1.0-11.8)

Table 4. Adverse effects observed with the use of immunotherapy.

Adverse effects	Grade 1-2 n (%)	Grade 3-4 n (%)
Fatigue	7	-
Hepatic enzyme elevation	4	-
Anaemia	3	-
Hypothyroidism	2	-
Hypercalcemia	-	2
Pneumonitis	1	-
Cough	1	-

Treatment-related adverse events are shown in Table 4. Except for 2 cases with grade 3-4 hypercalcemia, there were no grade 3-4 side effects in any of the cases. Grade 1-2 fatigue in 7 patients, grade 1-2 transaminase elevation in 4 patients, grade 1-2 anemia in 3 patients, grade 1-2 hypothyroidism in 2 patients, grade 1-2 cough in 1 patient, and grade 1 pneumonitis in 1 patient were reported. No deaths or withdrawal of treatment due to adverse events were reported.

Discussion

Our study revealed that patients who received RT had longer PFS and OS in patients with NSCLC lacking predictive test for immunotherapy response in the second and subsequent lines.

Irradiation of the tumor results in the release of tumor-associated antigens and molecules called damage-associated molecular patterns that can produce an immunogenic response. This phenomenon is defined as in-situ vaccination.[15] Calreticulin translocation on tumor cells' surface due to radiotherapy is described as cancer cells' immunological death.[16] Co-stimulants such as deoxyribonucleic acid, adenosine triphosphate, high-mobility group box-1, and interferon β released due to this death cause the activation of dendritic cells, which increases antigen presentation to cytotoxic T cells.[16] Radiotherapy leads to vascular normalization with increased nitric oxide secretion from macrophages. Chemokines such as CXCL10 and CXCL16 cause an increase in cytotoxic T-cell in the tumor microenvironment.[16] Schaue et al.[17] revealed that RT increases tumor-specific T cells in patients during and after treatment. Several have shown that PD-L1 expression is increased in tumors and myeloid cells of mice treated with RT.[17-19] PD-L1 is upregulated as an escape mechanism from the radiotherapy-induced anti-tumor immune response.[20] However, in low immunogenic mouse tumors and most cancer patients, RT alone is insufficient to provide an effective immune response.[21] Demaria et al.[22] first demonstrated the synergistic effect between RT and an anti-T-lymphocyte-associated protein-4 inhibitor in a mouse with metastatic breast cancer. Preclinical studies have shown that anti-tumor is combined with radiation therapy.[17-19] In Gong et al.[23], it was found that RT could increase PD-1/PD-L1 as an immunosuppressive effect, and the use of immunotherapy agents could reduce the immunosuppressive effect and increase the abscopal effect. In the secondary analysis of the KEYNOTE 001, phase 1 trial of pembrolizumab in advanced stage NSCLC patients, it was found that patients who had previously received RT had longer PFS and OS than those who did not.[24] In the randomized phase 2 study in patients with advanced NSCLC, higher response rates, and longer PFS were obtained in patients who received pembrolizumab after stereotactic body RT (SBRT) comparing pembrolizumab alone.[25] Fiorica et al.[26] studied immunotherapy plus RT versus immunotherapy alone in patients with metastatic NSCLC. They found a statistically significant difference in OS

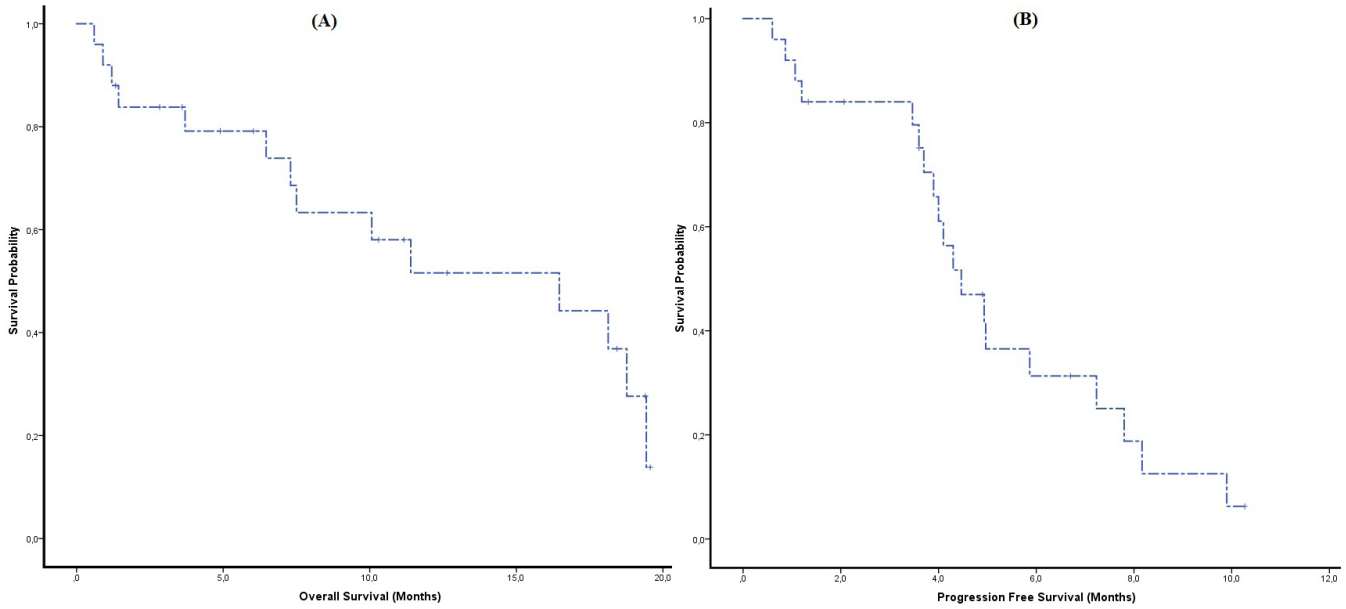

Figure 1. Overall survival (OS) (A) and progression-free survival (PFS) (B) of all patients.

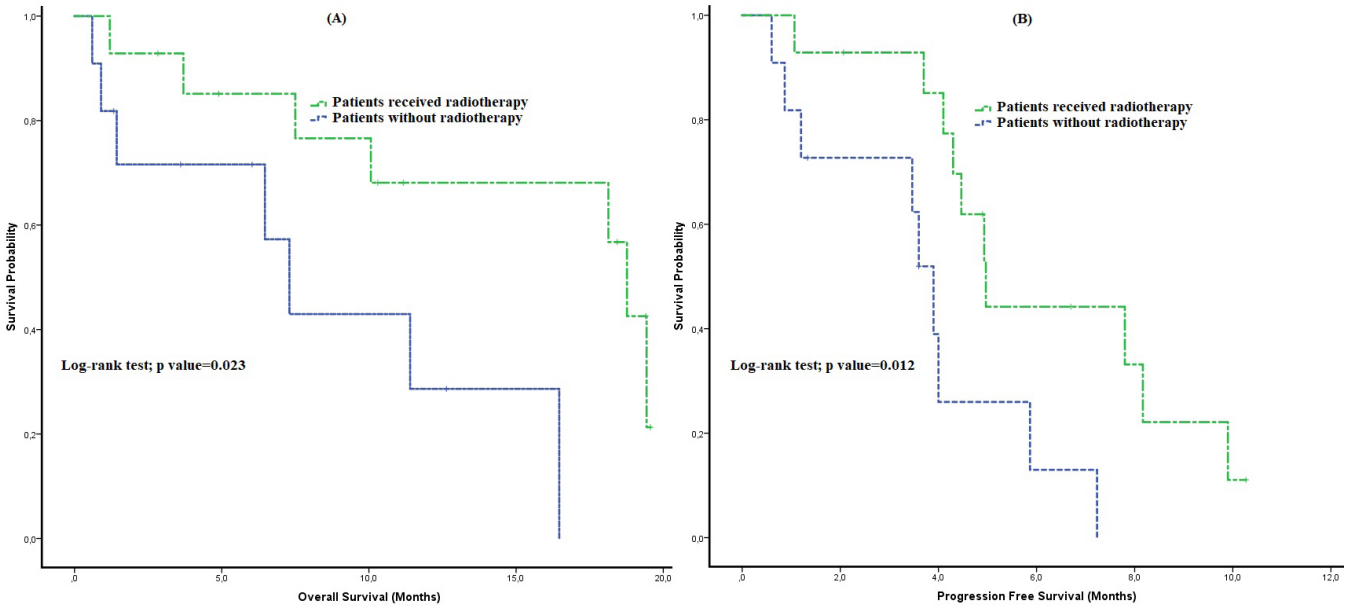

Figure 2. Overall survival (OS) (A) and progression-free survival (PFS) (B) according to radiotherapy.

and PFS in patients receiving hypofractionated RT plus nivolumab compared to those receiving nivolumab alone. Although these data support the effectiveness of RT on immunotherapy, there is no consensus on the RT dose and site (primary or metastatic site).[27] Therefore, there are no recommendations regarding RT in this setting in the current international guidelines.[3,11]

For immune cells to have a cytotoxic effect on tumor cells, tumor recognition via antigen presentation and T cell activation is required. Radiotherapy is considered to improve the anti-tumor immune response priming, and anti-tumor activity is obtained by removing checkpoint inhibition with immunotherapy.[28] We think that the better PFS and OS results obtained with immuno-RT compared to immunotherapy studies in the second and subsequent lines are due to the synergistic effect of RT on immunotherapy.[29-32]

There are concerns about increased side effects associated with the combination of RT and immunotherapy.[19,33] In patients who had previously received thoracic RT, pulmonary toxicity of any severity was observed in 63% (15 of 24 patients) in the KEYNOTE 001 trial.[24] In our study, the rate of grade 1 pulmonary toxicity was 20% (1 in 5 patients receiving thoracic RT). There is no consensus on how long immunotherapy treatment can be safely initiated after RT and which patient group is riskier for pulmonary toxicity in patients receiving thoracic radiotherapy. Patients who have previously received thoracic RT should be followed up more closely for pulmonary side effects.[24] Prospective randomized controlled studies are needed to address these uncertainties. Although stage 1-2 transaminase elevation was observed in two patients who received simultaneous immunotherapy and RT for bone metastasis and whose RT area was close to the lungs, pulmonary toxicity was not observed.

Limitations

Our study's main limitations are the retrospective nature, the limited number of patients, the use of different immunotherapy agents, and the inability to determine the PD-L1 level after RT. Also, we could not perform multivariate analysis due to the small number of patients.

Conclusions

It remains unclear which patient would benefit from immunotherapy in second-and later lines in NSCLC treatment. However, our findings have revealed that patients receiving RT had more prolonged survival significantly on immunotherapy in patients with NSCLC, claiming that RT may be used to increase immunotherapy efficacy. These findings should be supported by further studies involving a larger number of patients.

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: BO, SS; Study Design: BO, ABS; Supervision: BC; Data Collection and/or Processing: BO, BD, KG, BC; Statistical Analysis and/or Data Interpretation: BO, OT, ABS; Literature Review: BO, AD, EC, TE; Manuscript Preparation: BO; and Critical Review: SS, AD, OT, EC, TE.

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Original Article

Retrospective Evaluation of Microalbuminuria and GFR Levels of Diabetic Patients Taking DPP-4 Inhibitor, GLP-1 Analog, or SGLT-2 Inhibitor

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ABSTRACT

Background In our study, we determined the changes in microalbuminuria and GFR (glomerular filtration rate) values, which are important for diabetic nephropathy, within 1 year after starting treatment in our patients taking DPP-4 inhibitor (linagliptin), GLP-1 analog (exenatide) and SGLT-2 inhibitor (empagliflozin).

Material and Methods We evaluated the urea, creatinine, gfr and microalbuminuria levels of our patients who were treated with linagliptin, exenatide and empagliflozin on their 0th, 6th and 12th month visits. We included patients who were followed up for nephropathy for at least 1 year after starting treatment in each drug group.

Results When the 0th and 12th month GFR values of our 98 patients who were prescribed linagliptin were compared, an increase of 4.57% was detected ($p<0.01$). In this group, there were 55 patients whose microalbuminuria could be followed up at 12 months, and no significant change was detected ($p>0.05$). While no statistically significant difference was found in the 0th and 12th month GFR follow-ups of our 97 patients using exenatide ($p>0.05$); in this group, it was determined that the microalbuminuria decreased significantly in 12 months in 33 of our patients who could be followed up in terms of microalbuminuria ($p<0.05$). No statistically significant change was observed in the 0th and 12th month GFR follow-ups of our 99 patients taking empagliflozin ($p>0.05$); however, it was determined that microalbuminuria decreased significantly at the end of 1 year in our 79 patients who could be followed up for microalbuminuria in this group ($p<0.05$).

Conclusions Although there was no improvement in microalbuminuria in our patients taking linagliptin, an increase in GFR was observed; however, it was observed that this situation was associated with the discontinuation of the nephrotoxic agents used by the patients for the treatment of diabetes and switching to linagliptin. In our patients taking exenatide and empagliflozin, although no significant change was detected in the GFR value, a decrease in microalbuminuria was observed; this is important in order to prevent the progression of nephropathy in the early period. The results of our study suggest that the use of GLP-1 analog and SGLT-2 inhibitor in diabetic patients will provide a nephroprotective effect.

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Introduction

Diabetes mellitus is one of the most important causes of chronic kidney disease and end-stage renal disease worldwide.[1] Although it is thought that diabetic nephropathy classically starts with albuminuria (≥30 mg/day or ≥20 μg/minute or ≥30 μg/mg creatinine) that develops after diabetic retinopathy, some studies show that the estimated glomerular filtration rate (eGFR) may decrease even before albuminuria develops.[2] Thus, despite the limitations of "albuminuria as the earliest marker" of diabetic nephropathy, many scientists suggest that rapid eGFR decline is of prognostic importance.[3] Some patients with diabetes mellitus paradoxically have a high GFR early in the course of the disease, and this is called "glomerular hyperfiltration". Glomerular hyperfiltration has been associated with the risk of progression of albuminuria and impaired renal function.[4,5] High albuminuria levels and low eGFR in patients with diabetic nephropathy independently and additionally increase the risk of cardiovascular complications and death.[6-10] In this study, we retrospectively analyzed the changes in microalbuminuria and gfr levels in our patients taking DPP-4 (dipeptidyl peptidase 4) inhibitor, GLP-1 (glucagon like peptide 1) analog or SGLT-2 (sodium glucose cotransporter 2) inhibitor.

Material and Methods

The study was conducted after the approval of the local ethics committee in accordance with the Helsinki Declaration. In this retrospective study, patients who were started on linagliptin (DPP-4 inhibitor), exenatide (GLP-1 analog) or empagliflozin (SGLT-2 inhibitor) and continued for at least 12 months; changes in albuminuria and glomerular filtration rate levels were investigated before, 6 months after and 1 year after starting to take these medications. Adult (>18 years old) patients diagnosed with type 2 diabetes mellitus; patients who had been taking DPP-4 inhibitor, GLP-1 analog or SGLT-2 inhibitor for at least 12 months and patients with full hospital controls were included in the study. Patients with type 1 diabetes mellitus, those in the pediatric age group, women in pregnancy and lactation period, and patients whose hospital controls were missing after the medications was prescribed were excluded from the study. In total, the files of 546 patients were reviewed retrospectively (229 linagliptin, 140 exenatide, and 177 empagliflozin), and 100 patients from each drug group who met the criteria were included in the study and the data of 300 patients were analyzed. Age and gender distribution, changes in albuminuria and gfr levels at 0th, 6th and 12th months of treatment were evaluated in all three treatment groups.

Statistical Analysis

The conformity of continuous variables to the normal distribution was examined using the Shapiro-Wilk test. Variables are expressed as mean±standard deviation, median (minimum:maximum) or n (%). The Kruskal-Wallis test was used for comparisons between treatment groups according to the results of the normality test. In case of significance after the Kruskal-Wallis test, pairwise comparisons between the groups were made using Dunn's test. The Wilcoxon Signed Rank test or the t-test for paired samples were used in the analyses performed to compare the measurements obtained at the 6th and 12th months with the baseline values in the treatment groups. Intergroup comparisons of categorical variables were performed using Pearson's chi-square test, Fisher-Freeman-Halton test, or Fisher's exact chi-square test. All statistical analyses were performed using IBM SPSS Statistics version 21.0 and a p-value of 0.05 was considered statistically significant.

Results

The mean age was 62.19±12.02 years in our patients taking linagliptin, 56.23±10.76 years in patients taking exenatide, and 58.20±10.31 years in patients taking empagliflozin. There was a significant difference between the treatment groups according to age distribution. In subgroup analyses, the median age was found to be higher in patients taking linagliptin than in the exenatide and empagliflozin groups ($p<0.001$ and $p=0.026$, respectively) (*Table 1*). Gender ratio were 49% female in the linagliptin group, 81% in the exenatide group and 57% in the empagliflozin group ($p<0.001$) (*Table 1*).

Table 1. Comparison of age and gender between treatment groups.

	Linagliptin (n=100)	Exenatide (n=100)	Empagliflozin (n=100)	p value	Binary comparisons (group I vs group J)		
					PLin-Exe	PLin-Empag	PExe-Empag
Age (years)	64 (22:90) 62.19±12.02	57 (29:77) 56.23±10.76	59 (28:79) 58.20±10.31	<0.001[a]	<0.001[d]	0.026[d]	>0.999[d]
Gender							
Female	49 (49%)	81 (81%)	57 (57%)	<0.001[b]	<0.001[b]	0.257[b]	<0.001[b]
Male	51 (51%)	19 (19%)	43 (43%)				

Data were given as n (%), median (minimum:maximum) and mean±standard deviation.
a: Kruskal-Wallis Test, b: Pearson Chi-Square test, c: Fisher-Freeman-Halton test, d: Dunn test.

The median value of urea measurements in patients who were prescribed linagliptin treatment was 43.50 (12:115) mg/dL at 0 month, 39 (12:142) mg/dL at 6 month, and 38.50 (16:192) mg/dL at 12 month. In comparisons made with reference to month, no significant difference was found in terms of urea value at 6th month and 12th month (p=0.397 and p=0.660). The median value of creatinine measurements at 0th month was 1.03 (0.48:3.80) mg/dL, 1.09 (0.45:4.30) mg/dL at 6th month, and 1 (0.48:5.50) mg/dL at 12th month. In comparisons made with reference to month 0, no significant difference was found in terms of creatinine value at 6th and 12th months (p=0.897 and p=0.191). The median value of albuminuria level at 0 month was 51 (5:2,600) mg/day, 43.50 (5:2,100) mg/day at 6th month and 55.50 (6:2,597) mg/day at 12th month. In comparisons made with reference to month 0, no significant difference was found in terms of albuminuria level at 6th and 12th months (p= 0.833 and p=0.406). The median values of GFR measurements were 62 (12:123) mL/min/1.73 m^2 at 0th month, 65 (10:130) mL/min/1.73 m^2 at 6th month, and 64 (8:126) mL/min/1.73 m^2 at 12th month. In comparisons made with reference to month 0, it was observed that there was no significant change in GFR at 6th month (p=0.094), but there was an increase of 3.23% at the end of 12th month (p<0.01) (*Table 2*).

The median value of urea measurements in patients who were prescribed on exenatide treatment was found to be 28 (9:83) mg/dL at 0th month, 31(12:54) mg/dL at 6th month, and 28 (0.74:71) mg/dL at 12th month. In comparisons made with reference to month 0, no significant difference was found in terms of urea value at 6th and 12th months (p=0.365 and p=0.455). The median value of creatinine measurements at 0th month was 0.75 (0.55:1.76) mg/dL, 0.77 (0.53:1.57) mg/dL at 6th month, and 0.76 (0.57:1.87) mg/dL at 12th month. In comparisons made with reference to month 0, no significant difference was found in terms of creatinine value at 6th and 12th month (p=0.999 and p=0.277). The median value of albuminuria level at 0th month was 19.50 (6:995) mg/day, 18.50 (6:1643) mg/day at 6th month and 16 (5:1681) mg/day at 12th month. In comparisons made with reference to month 0, no significant difference was found in terms of albuminuria level at 6th month (p=0.789). At 12th month, a decrease of 17.95% was detected compared to the baseline (p=0.024). The mean of GFR measurements were 87.78±17.65 mL/min/1.73 m^2 at 0th month, 87.76±16 mL/min/1.73 m^2 at 6th month, and 88.57±15.24 mL/min/1.73 m^2 at 12th month. In comparisons made with reference to month 0, no significant difference was found in terms of GFR values at 6th and 12th months (p=0.623 and p=0.536) (*Table 3*).

The mean urea level of the patients who were prescribed empagliflozin treatment was 31.28±9.74 mg/dL at 0th month, 33.44±11.91 mg/dL at 6th month, and 33.89±17.71 mg/dL at 12th month. In comparisons made with reference to month 0, an increase of 6.91% was observed at month 6 (p=0.031). At the 12th month, no significant difference was found in terms of urea value compared to the baseline (p=0.098). The median values of creatinine measurements at month 0 were 0.79 (0.56:1.17) mg/dL, 0.79 (0.45:1.50) mg/dL at 6th month, and 0.80 (0.54:4.30) mg/dL at 12th month. In comparisons made with

Table 2. Comparisons for the linagliptin treatment group.

	Descriptive statistics	PC%	p value
Urea (mg/dL)			
Beginning (n=89) → 6th month (n=89)	43.50 (12:115) → 39 (12:142)	↓10.34%	0.397[e]
Beginning (n=98) → 12th month (n=98)	43.50 (12:115) → 38.50 (16:192)	↓11.49%	0.660[e]
Creatinine (mg/dL)			
Beginning (n=89) → 6th month (n=89)	1.03 (0.48:3.80) → 1.09 (0.45:4.30)	↑5.83%	0.897[e]
Beginning (n=98) → 12th month (n=98)	1.03 (0.48:3.80) → 1 (0.48:5.50)	↓2.91%	0.191[e]
GFR (mL/min/1.73 m^2)			
Beginning (n=89) → 6th month (n=89)	62 (12:123) → 65 (10:130)	↑4.84%	0.094[e]
Beginning (n=98) → 12th month (n=98)	62 (12:123) → 64 (8:126)	↑3.23%	<0.001[e]
Microalbuminuria (mg/day)			
Beginning (n=24) → 6th month (n=24)	51 (5:2,600) → 43.50 (5:2,100)	↓14.71%	0.833[e]
Beginning (n=30) → 12th month (n=30)	51 (5:2,600) → 55.50 (6:2,597)	↑8.82%	0.406[e]

Data were given as median (minimum:maximum) and mean±standard deviation.
PC: percentage change in mean or median, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GFR: glomerular filtration rate, e: Wilcoxon Signed Rank, f: t-test for paired samples.

Table 3. Comparisons for the exenatide treatment group.

	Descriptive statistics	PC%	p value
Urea (mg/dL)			
Beginning (n=91) → 6th month (n=91)	28 (9:83) → 31 (12:54)	↑10.71%	0.365[e]
Beginning (n=98) → 12th month (n=98)	28 (9:83) → 28 (0.74:71)	0%	0.455[e]
Creatinine (mg/dL)			
Beginning (n=90) → 6th month (n=90)	0.75 (0.55:1.76) → 0.77 (0.53:1.57)	↑2.67%	>0.999[e]
Beginning (n=98) → 12th month (n=98)	0.75 (0.55:1.76) → 0.76 (0.57:1.87)	↑1.33%	0.277[e]
GFR (mL/min/1.73 m^2)			
Beginning (n=91) → 6th month (n=91)	87.78±17.65 → 87.76±16	↓0.02%	0.623[f]
Beginning (n=97) → 12th month (n=97)	87.78±17.65 → 88.57±15.24	↑0.9%	0.536[f]
Microalbuminuria (mg/day)			
Beginning (n=12) → 6th month (n=12)	19.50 (6:995) → 18.50 (6:1643)	↓5.13%	0.789[e]
Beginning (n=33) → 12th month (n=33)	19.50 (6:995) → 16 (5:1681)	↓17.95%	0.024[e]

Data were given as median (minimum:maximum) and mean±standard deviation.
PC: percentage change in mean or median, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GFR: glomerular filtration rate, e: Wilcoxon Signed Rank, f: t-test for paired samples.

Table 4. Comparisons for the empagliflozin treatment group.

	Descriptive statistics	PC%	p value
Urea (mg/dL)			
Beginning (n=97) → 6th month (n=97)	31.28±9.74 → 33.44±11.91	↑6.91%	0.031[f]
Beginning (n=99) → 12th month (n=99)	31.28±9.74 → 33.89±17.71	↑8.34%	0.098[f]
Creatinine (mg/dL)			
Beginning (n=97) → 6th month (n=97)	0.79 (0.56:1.17) → 0.79 (0.45:1.50)	0%	0.681[e]
Beginning (n=99) → 12th month (n=99)	0.79 (0.56:1.17) → 0.80 (0.54:4.30)	↑1.27%	0.493[e]
GFR (mL/min/1.73 m^2)			
Beginning (n=97) → 6th month (n=97)	89.40±14.47 → 89.19±15.85	↓0.23%	0.577[f]
Beginning (n=99) → 12th month (n=99)	89.40±14.47 → 89.14±15.78	↓0.29%	0.567[f]
Microalbuminuria (mg/day)			
Beginning (n=52) → 6th month (n=52)	52.57±129.63 → 22.32±18.82	↓57.54%	0.052[f]
Beginning (n=79) → 12th month (n=79)	52.57±129.63 → 27.39±53.31	↓47.9%	0.027[f]

Data were given as median (minimum:maximum) and mean±standard deviation.
PC: Percentage change in mean or median, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GFR: glomerular filtration rate, e: Wilcoxon Signed Rank, f: t-test for paired samples.

reference to month 0, no significant difference was found in terms of creatinine value at 6th and 12th months (p=0.681 and p=0.493). The mean level of albuminuria at 0th month was 52.57±129.63 mg/day, at 6th month 22.32±18.82 mg/day, and at 12th month 27.39±53.31 mg/day. In comparisons made with reference to month 0, no significant difference was found in terms of albuminuria level at 6th month (p=0.052). There was a 47.9% decrease from the baseline at 12th month (p=0.027). The mean of GFR measurements were 89.40±14.47 mL/min/1.73 m^2 at 0th month, 89.19±15.85 mL/min/1.73 m^2 at 6th month, and 89.14±15.78 mL/min/1.73 m^2 at 12th month. In comparisons made with reference to month 0, no significant difference was found in terms of GFR values at 6th and 12th months (p=0.577 and p=0.567) (*Table 4*).

Discussion

When the previous studies on the renal effects of linagliptin, exenatide and empagliflozin treatments that we examined in our study were scanned, it was seen that the age range was 55-65 years.[11-20] It was determined that the mean age of patients taking linagliptin, which we included in the study, was 64, 57 in patients taking exenatide, and 59 in patients taking empagliflozin; this was in agreement with the literature.

While the gender distribution was consistent with the literature in patients taking linagliptin and empagliflozin, the proportion of female patients taking exenatide was higher than the literature. The reason for this is thought to be due to the fact that exenatide treatment can be started in diabetic patients with a body mass index >35 kg/m^2 in accordance with the SUT (health practices communiqué) and obesity is more common in women in Turkey.[21] In studies on DPP-4 inhibitors, SGLT-2 inhibitors or GLP-1 analogues, the rate of female patients was found to be around 35-45%.[12-16,19,22,23] In our study, the rate of female patients was 81% in the exenatide group.

While there was no significant change in

microalbuminuria, urea and creatinine values in our patients taking linagliptin, GFR increased by 3.23% at the end of one year. It is known that linagliptin has no renoprotective effect.[22] However, it is thought that this situation may be related to the discontinuation of the nephrotoxic diabetes treatment of the patients and switching to linagliptin, which has no nephrotoxic effect.

In our study, it was observed that there was no significant change in urea, creatinine and GFR levels in the patient group taking exenatide, and no GFR change was observed in other studies.[24,25] In the EXSCEL study, no significant change was found in the amount of albuminuria, but in our study, it was determined that the microalbuminuria level decreased by 7.95% at the end of one year after the treatment was started. In a study conducted in Croatia in 2016, it was observed that exenatide treatment in obese type 2 diabetes patients significantly reduced the amount of albuminuria 22 months after starting treatment.[26]

In the patient group taking empaglifilozin, no significant changes were detected in urea, creatinine and GFR levels during the 1-year follow-up. In the twelfth month of the treatment, a 47.9% decrease was observed in the microalbuminuria level. This is related to the renoprotective effect of SGLT-2 inhibitors.[27]

Conclusions

Our aim in conducting this study was to show the real-life projection of large studies and to see how much we could protect our patients who started taking SGLT-2 inhibitor or GLP-1 analogue from renal pathologies. As a result, we have seen that we can better protect patients who use GLP-1 analog and SGLT-2 inhibitor from albuminuria, which gives information about the prognosis of diabetic nephropathy. There are studies with different results in the literature with the renoprotective effects of DPP-4 inhibitors; therefore, there is a need for new studies on this drug group that have been tried in a larger patient group.

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: BG; Study Design: OOG, SC; Supervision: OOG, SC; Materials: BG; Data Collection and/or Processing: BG; Statistical Analysis and/or Data Interpretation: BG, OOG, SC; Literature Review: BG, OOG, SC; Manuscript Preparation: BG, OOG, SC; Critical Review: OOG, SC.

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Original Article

Retrospective Evaluation of Radioactive Iodine Ablation Therapy in the Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features (NIFTP) And Thyroid Tumors With Uncertain Malignity Potential

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ABSTRACT

Background Noninvasive Follicular Thyroid Neoplasm (NIFTP), Well diferantiated thyroid tumor with uncertain malignity potential (WDT-UMP), follicular thyroid tumor with uncertain malignity potential (FT-UMP), and Hurtle cell neoplasia with uncertain malignity potential (HCN-UMP) have been included in the classification of thyroid tumors by WHO, with the incidence of thyroid cancer increasing every passing year. There is no consensus regarding the follow-up and treatment processes of these tumors. Our study aims to shed light on our clinical practice by evaluating the follow-up processes of the groups with and without radioactive iodine ablation in patients followed up with these diagnoses.

Material and Methods The 49 patients older than 18 years of age and followed for at least 12 months, who were performed subtotal and total thyroidectomy between 2015 and 2020 and were diagnosed with WDT-UMP, FT-UMP, HCN-UMP, and NIFTP according to histopathological examination were included to the study.

Results Tumor type rates did not differ between the groups that received and did not receive RAI treatment (p=0.361). The mean follow-up period did not differ between the groups that received and did not receive RAI treatment. Also the rates of RAI treatment according to tumor size did not differ (p=0.413). Tumor size was larger than 4 cm in 13 patients, and 1 patient from this group had received RAI treatment. Recurrence was not detected in the 49 patients included in our study who received or not receive RAI treatment.

Conclusions Some studies recommend giving RAI to these borderline thyroid tumors larger than 4 cm. But in our study no recurrence was detected in patients who did not receive RAI. That supports the view that patients could be followed without RAI treatment even if they are large tumors.

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Keywords: *Noninvasive Follicular Thyroid Neoplasm (NIFTP), Well diferantiated thyroid tumor with uncertain malignity potential (WDT-UMP), follicular thyroid tumor with uncertain malignity potential (FT-UMP), Hurtle cell neoplasia with uncertain malignity potential (HCN-UMP), RAI ablation, recurrence.*

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Introduction

Thyroid cancers are the most common endocrine organ cancer.[1] It constitutes approximately 2.3% of newly diagnosed cancers all over the world.[2] It is the second most common cancer in women after breast cancer in Turkey, and it is seen approximately four times more frequently in women than in men.[3] There has been an increase in the incidence of thyroid cancers in the last three decades. With the increasing incidence of thyroid cancer each year, in addition to classical type differentiated thyroid cancers, an increase is observed in atypical thyroid tumors whose malignant potential is not fully determined.[4] Thereupon, the classification of thyroid tumors was revised in 2017 by WHO. Non-invasive papillary tumor features of follicular tumors (NIFTP), well-differentiated tumor with uncertain malignant potential (WDT-UMP), follicular tumor with uncertain malignant potential (FT-UMP), and Hurthle cell tumor with uncertain malignant potential (HCN-UMP) are included in the new classification.[4]

There are differences of opinion on how to manage the follow-up processes of these borderline tumors. Some researchers have stated that the evaluation of these tumors as carcinoma did harm more than benefit, resulting in treatment methods such as overtreatment, unnecessary total thyroidectomy, radioactive iodine ablation therapy, and suppression of TSH levels with levothyroxine is used.[5]

We aimed to light on our clinical practice by evaluating the results of the groups with and without radioactive iodine ablation in patients followed up with the diagnoses of NIFTP, WDT-UMP, FT-UMP, and HCN-UMP.

Material and Methods

Study Protocol

Our study has planned to evaluate the retrospective and cross-sectional data of patients followed up in our endocrinology outpatient clinic with the diagnoses of WDT-UMP, FT-UMP, HCN-UMP, and NIFTP. This study was carried out following the Helsinki Declaration decisions, the Patient Rights Regulation, and ethical rules. The study started after the local ethics committee approval was obtained with the decision dated 14 July 2022 and numbered 2020-1/17.

The files of 53 patients who underwent subtotal and total thyroidectomy between 2015 and 2020 were diagnosed with WDT-UMP, FT-UMP, HCN-UMP, and NIFTP according to histopathological examination were analyzed. Inclusion criteria were over 18 years of age, followed for more than 12 months, no concomitant papillary carcinoma. One patient was younger than 18, two patients were applied less than 12 months, and one patient had papillary thyroid carcinoma with the current diagnosis. The information was reviewed of the patients retrospectively from archive records and electronic media files in the hospital automation system. In detail, were examined the treatments and follow-up processes applied to the patients.

Statistical Analysis

The conformity of continuous variables to the normal distribution was examined using the Shapiro-Wilk test. According to the test results, the variables were expressed as mean ± standard deviation or median (minimum: maximum) values according to the results they were suitable. Categorical variables are given with numbers and percentages. Intergroup comparisons of continuous variables were made using the t-test for independent pair samples. Categorical variables between groups were compared using Fisher–Freeman–Halton and Fisher's chi-square tests. SPSS for statistical analysis (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) program was used, and type I error level was accepted as 5% in statistical analysis.

Results

A total of 47 patients were included in the study. While the mean total follow-up period was 33 months in patients who received RAI, it was 30 weeks in patients who did not receive RAI (p=0.266). Of eight patients who underwent RAI, two (25%) had WDT-UMP, three (37.5%) FT-UMP and three had (37.5%) NIFTP. In the RAI non-received group, WDT-UMP was present in 13 patients (33.3%), FT-UMP in 12 patients (30.8%), NIFTP in 6 patients (15.4%), and HCN-UMP in 8

Table 1. Comparison of pathological diagnosis rates and follow-up time between groups that received and did not receive RAI treatment.

	RAI (n=8)	Non-RAI (n=39)	p value
Pathological diagnosis			0.361[a]
WDT-UMP	2 (25%)	13 (33.30%)	
FT-UMP	3 (37.50%)	12 (30.80%)	
NIFTP	3 (37.50%)	6 (15.40%)	
HCN-UMP	0	8 (20.50%)	
Tracking time (months)	33.63±4.84	30.49±7.53	0.266[b]
Recurrent disease	0	0	
Tumor size*			0.413[c]
<4 cm	7 (20.60%)	27 (79.40%)	
≥4 cm	1 (7.70%)	12 (92.30%)	

Data were expressed as median (minimum:maximum) and n (%).
* Relevant percentage values were calculated according to tumor size variable.
a: Fisher-Freeman-Halton test, b: t-Test for independent samples, c: Fisher's Exact Chi-square test.

patients (20.5%). The tumor was larger than 4 cm in 1 (12.5%) of the patients who received RAI and in 12 (30.7%) of the patients who did not receive RAI (*Table 1*).

The rates of pathological tumor types did not differ between the RAI and non-RAI groups (p=0.361). WDT-UMP and NIFTP diagnoses were observed at the highest rate in the RAI group (37.5%); WDT-UMP (%33,30) and FT-UMP (30.8%) diagnoses were observed at the highest rate in the non-RAI received group (37.5%). In addition, it was determined that the mean follow-up period did not differ between the groups that received and not received RAI treatment. No signs of recurrence were detected in any of the patients who had or had not undergone RAI. Therefore, it was thought that RAI treatment had no effect on recurrence in these tumors with uncertain malignant potential, since no recurrent tumors were detected in patients who received or did not receive RAI treatment, regardless of tumor size and type.

Discussion

In this study; The RAI treatments of the patients followed in our hospital with the diagnoses of WDT-UMP, FT-UMP, HCN-UMP, and NIFTP were evaluated. In the comparison of the treatment modalities and follow-up processes of these four groups, no statistically significant difference was found between them, and no recurrence were detected in any of the patients who had or had not undergone RAI ablation therapy.

After the diagnosis of NIFTP started to be used, to these patients could be reached no consensus on giving RAI treatment. Although some studies suggest that RAI treatment is not needed in tumors <4 cm, but RAI treatment can be given in tumors ≥4 cm, there is no consensus.

In the study reported by Capucine Richard et al.[6] histopathological preparations of patients with PTC between 1975 and 2015 were re-examined, and 65 of these patients

were diagnosed with NIFTP. If this patient's was performed examination was 50 total thyroidectomy and 15 lobectomies, 45 (70.8%) RAI treatment. In the study reported by Bin Xu et al.[7], follow-up periods ranged from 1.9 to 27.3 years after the first treatment, and it was reported that all patients remained in complete remission during follow-up. The mean tumor size was 4.5 cm in 79 patients included in the study, in which NIFTP patients with a nodule diameter of ≥4 cm showed long-term follow-up results. There are 32 patients with a clinical follow-up of 2 years or more and who did not receive RAI treatment. No disease was observed in the patients in this group during the follow-up period. In our study, 7 of 10 patients had a tumor size of <4 cm and 3 of 10 patients was given RAI treatment. All those receiving RAI treatment had concomitant micropapillary carcinoma. Tumor size was >4 cm in 1 of the patients who received RAI treatment. No relapse was observed in any patient during the follow-up period. These data support that the malignant potential of tumors is very low and these patients have not required post-operative RAI treatment.

There is no established protocol for the treatment and follow-up management of WDT-UMP due to their unknown biological behavior to date. There was no consensus on the treatment of lobectomy, total thyroidectomy, and RAI in the treatment of this patient. The general view is that this group of tumors has a good prognosis and is very low recurrence rate. Lie et al.[5] stated that no recurrence was found during the 80-month follow-up of 20 WDT-UMP cases with follow-up data. In another study by Adela Nechifor-Boila et al.[8], 21 cases were taken from the four follower route and gave disease and recurrence. The mean follow-up period of the 15 WDT-UMP patients included in our study was 33.63±4.84.2 months of these patients had received RAI treatment, and the remaining 13 patients did not receive RAI treatment. Recurrence was not observed in any of the patients.

As in NIFTP and WDT-UMP, there is no consensus on the treatment and follow-up processes in patients with FT-UMP. It has been stated that RAI treatment could be considered in tumors with a diameter of ≥4 cm since they are tumors with very low malignanc potential. In the literature review, no study was found showing the treatment and follow-up results of patients with FT-UMP. In our study, 3 of the 15 patients followed up with FT-UMP were given RAI treatment, while the other patients were not. There were 2 patients with tumor size ≥4 cm, and two of them were not given RAI treatment. The mean follow-up period of the patients was 31.1 months. No recurrent disease was detected in the patients during the follow-up period. The data in our study support the view that FT-UMP, which has a very low malignancy potential, could be followed without RAI treatment.

Hurtle cell thyroid carcinoma all differentiated thyroid, It constitutes less than 5% of malignancies. It is of follicular cell origin, and its biological behavior differs from other thyroid cancer histologic. Minimally invasive, It can be classified as Hurtle cell carcinoma and widely invasive hurtle cell thyroid carcinoma. However, in recent studies, it has been reported that there are cases of hurtle cell carcinoma with uncertain malignant potential and that it should be added to the classification.[9] There are case reports supporting this in the literature. However, there is no study reporting post RAI treatment follow-up results of these patients in our knowledge. Christopher Juhlin et al.[9] published a case report on HCN-UMP. In this case, is presented a 50-year-old male patient. Tumor size was 30 mm in the operative pathology, RAI was not recommended to the patient, and no recurrence tumor was detected in the 4-month follow-up of the patient. In our study, there were 8 patients followed up with HCN-UMP. The patients followed up with HCN-UMP RAI was not applied to RAI. The mean follow-up period of the patients was 29.3 months, and no recurrence was observed in any of the patients.

Conclusions

As a result, in the literature since there is no study evaluating the radioactive iodine ablation treatment of all thyroid tumors in our country, our study is the first national study in this field. Of the 49 patients included in our study, 8 received RAI treatment, 41 did not, and none of them relapsed. The disease was not detected tumor size was large than 4 cm in 13 patients, and only one patient from this group had received RAI treatment. This supports the view that patients can be followed without RAI treatment in even large tumors, and it is thought that our study will contribute to the literature in this regard.

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: MRG; Study Design: OOG, SC; Supervision: OOG, SC; Materials: MRG; Data Collection and/or Processing: MRG; Statistical Analysis and/or Data Interpretation: MRG, OOG, SC; Literature Review: MRG, OOG, SC; Manuscript Preparation: MRG, OOG, SC; Critical Review: OOG, SC.

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Original Article

Retrospective Evaluation of the Efficiency of Therapeutic Plasmapheresis in Thyrotoxic Patients

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ABSTRACT

Background Therapeutic plasma exchange (TPE) is a treatment method that can be used to provide euthyroidism before permanent treatment in patients with severe thyrotoxicosis, in cases of thyroid storm and in cases where antithyroid drug (ATD) cannot be used due to side effects or ineffectiveness. This study presented our results and experience on TPE in thyrotoxic patients.

Material and Methods The data of 10 patients who underwent plasmapheresis for thyrotoxicosis in Bursa Uludag University Faculty of Medicine Endocrinology Clinic were retrospectively analyzed and compared with the literature.

Results Ten patients, 6 female and 4 male, were included. The cause of hyperthyroidism was Graves' disease in 8 patients and toxic multinodular goiter (TMNG) in 2 patients. It was observed that the reason for applying plasmapheresis in the patients was primarily due to toxic hepatitis. The mean number of plasmapheresis required to maintain euthyroidism was 4 (1-8). While no difference was found between the thyroid-stimulating hormone (TSH) results before and after TPE, free T4 (fT4) and free T3 (fT3) values were statistically significantly lower after TPE. It was observed that the leukocytes were considerably higher after TPE and the sodium and calcium values were markedly lower after TPE in the patients. After TPE, 7 patients underwent total thyroidectomy, 1 patient received radioactive iodine (RAI) treatment, and 2 were discharged with ATD treatment.

Conclusions TPE is an effective and safe treatment option that can be applied in cases where it is necessary to provide rapid euthyroidism before permanent treatments or non-thyroid surgical procedures or to treat life-threatening thyrotoxicosis. It requires experience in application and follow-up and provides rapid euthyroidism when performed in experienced centres.

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Introduction

Thyrotoxicosis; refers to the state of high thyroid hormone levels in the blood. It is called thyrotoxicosis with hyperthyroidism if it is caused by increased synthesis and secretion of thyroid hormones.[1] The most common causes of thyrotoxicosis with hyperthyroidism are Graves' disease, toxic adenoma, and toxic multinodular goiter (TMNG). The three most commonly used methods of treatment are antithyroid drug (ATD), radioactive iodine (RAI) and surgery. After patients are rendered euthyroid with ATD, permanent treatments such as RAI or surgery can be applied in necessary cases.[2] In patients with severe hyperthyroidism, in cases of thyroid storm and in cases where ATD cannot be used due to side effects or ineffectiveness, plasmapheresis therapy can be used to provide euthyroidism before permanent treatment.[3-8] Therapeutic plasma exchange (TPE) is the process of replacing patient plasma with albumin or fresh frozen plasma (FFP). During this treatment, thyroid hormones, high molecular weight substances, autoantibodies, immune complexes, cytokines, catecholamines and thyroid-binding globulins are also cleared from the patient's blood.[9] Anaphylaxis, hypotension, hypocalcemia, catheter-related complications and coagulation disorders may develop due to plasmapheresis.[10,11] This study aimed to retrospectively evaluate the pre-and post-TPE results of patients who underwent TPE for thyrotoxicosis with hyperthyroidism in our center and the complications that developed during the procedure.

Material and Methods

Ten patients who underwent TPE treatment for thyrotoxicosis with hyperthyroidism between January 2016 and December 2021 at Bursa Uludag University Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism Diseases were included in the study after the approval of the Ethics Committee. Patients with insufficient follow-up data were excluded from the study. Demographic and clinical characteristics of the patients, thyroid function tests and other biochemical parameters before and after TPE, treatment types after TPE, and the pathology results of the patients who went to surgery were evaluated retrospectively.

Plasma volume of the patients was calculated according to gender, height, weight and hematocrit information. The blood flow rate was set as 55-70 ml/min. Spectra Optia (Japan) devices were used for apheresis. While predominantly using FFP for apheresis, albumin was performed when there was difficulty in obtaining FFP, or in patients with an allergic reaction after FFP or multiple drug allergies. Vital signs were obtained at the beginning and end of each procedure, and patients were monitored for adverse events during apheresis procedures. Before each plasmapheresis, the procedure risks were explained in detail and then written informed consent was obtained from all patients. Intravenous 10% calcium gluconate was given to all patients to avoid severe hypocalcemia. Each apheresis session lasted 2.5-3 hours. Plasmapheresis was administered daily or every other day until normal thyroid function or clinical improvement was achieved.

Statistical Analysis

For statistical analysis, data were recorded in SPSS 25 (Statistical Package for the Social Sciences) software. Shapiro Wilk test was used for normality tests, and Student T-test was used for parametric tests in group comparisons. Non-parametric tests were analyzed with the Mann Whitney U test, and 2 dependent non-parametric samples were analyzed with the Wilcoxon test. Values with a p-value of <0.05 were considered statistically significant.

Results

Six of the 10 patients included in the study were female, and 4 were male, and the mean age of the patients was 44±17.1 years. Mean age was found to be 38.3±17 years in women and 52.5±15.3 years in men. The cause of hyperthyroidism was Graves' disease in 8 patients and TMNG in 2 patients. Of the 8 Graves' patients, 5 were women. The median time since diagnosis was 3.5 (0-240) months. While 60% of the patients had weight loss and palpitations as main symptoms, 40% had sweating and tremor. It was observed that the most common reason for patients to undergo plasmapheresis was toxic hepatitis, followed by

agranulocytosis, thyroid storm, unresponsiveness to high-dose antithyroid therapy, and to provide euthyroidism before emergency bypass surgery (one patient). The mean hospital stay of the patients was 14.3±5.4 days, and the mean number of plasmapheresis sessions required to maintain euthyroidism was 4±2.35 (min 1-max 8 sessions). Plasmapheresis sessions were performed with FFP in 7 patients and albumin in 1 patient. Both FFP and albumin were used in 2 patients. Due to the problem experienced in obtaining FFP in 1 patient, albumin was performed once and then FFP was used. In the other patient, first FFP was given and then continued with albumin after a minor allergic reaction. All patients used methimazole as ATD treatment before hospitalization, except for one unfollowed patient, and methimazole was discontinued in one patient just before hospitalization due to pregnancy. The median dose of methimazole they used was 15 (10-80) mg. The beta-blocker dose used before TPE was 71.5±45.34 mg, and after TPE 62±46.61 mg, no difference was found between the two groups (p=0.488). Details of patient characteristics and treatment data are given in Table 1.

Table 1. Patient characteristics and treatment data of patients who underwent therapeutic plasmapheresis for thyrotoxicosis with hyperthyroidism.

Variables	Findings
Female gender n (%)	6 (60)
Age (year)	44±17.1
Cause of hyperthyroidism n (%)	
Graves	8 (80)
TMNG	2 (20)
Reason for plasmapheresis n (%)	
Toxic hepatitis	3 (30)
Agranulocytosis	2 (20)
Thyroid storm	2 (20)
Unresponsiveness to ATD	2 (20)
Non-thyroid emergency surgery	1 (10)
Hospitalization duration (day)	14.3±5.4
Number of plasmapheresis sessions (n)	4±2.35
Time since diagnosis (month)	3.5 (0-240)
Additional treatment n (%)	
Lugol	7 (70)
Steroid	4 (40)
Definitive treatment n (%)	
Surgical	7 (70)
RAI	1 (10)
ATD	2 (20)

Data were given as mean±standard deviation, median (minimum:maximum) or frequency.
n: number, TMNG: toxic multinodular goiter, ATD: antithyroid drug, RAI: radioactive iodine.

While no difference was found between TSH results before and after TPE (p=0.14), fT4 and fT3 values were found to be statistically significantly lower after plasmapheresis (p=0.005, p=0.005, respectively), there was no statistically significant difference between TSH receptor antibody levels (TRAb) before and after TPE in patients with Graves' disease (p=0.18). The changes in thyroid hormone levels are shown in Table 2.

Patients had significantly higher leukocytes after TPE (p=0.011) and substantially lower sodium and calcium values after TPE (p=0.01, p=0.04, respectively), but they were not below the normal laboratory range and did not have a clinical effect. After TPE, 7 patients underwent total thyroidectomy, 1 patient received RAI treatment, and 2 were discharged with ATD treatment. The pathology of all 7 patients who underwent surgery was benign. Except for minor allergic reactions in 2 patients, no serious complications related to TPE were observed. Tables 3 and 4 show changes in complete blood count and biochemical parameters.

Discussion

In this study, we presented the data of 10 patients who underwent TPE treatment for thyrotoxicosis with hyperthyroidism. ATD, surgery and RAI constitute the three main treatment strategies used in thyrotoxicosis.[12] In cases of inadequate response to ATD treatment or side effects related to ATD, plasmapheresis can be used to provide euthyroidism before permanent treatment.[13,14]

Statistically, our study found a significant decrease in fT3 and fT4 hormone levels after plasmapheresis, similar to the two studies conducted in our country.[15,16] Another study from our country indicated a decrease in free hormone levels with no significant statistical difference.[17] The mean number of plasmapheresis required to provide euthyroidism in our patients was 4, and it has been found to be similar to the literatüre.[15,16] Although free thyroid hormone levels could not be brought to the normal laboratory range in three of our patients, the clinical findings of thyrotoxicosis were improved with plasmapheresis in all of our patients.

Hepatotoxicity is a side effect that can be seen due to ATD, and although cholestatic hepatitis is more common due to methimazole, toxic hepatitis can also be seen. A significant decrease in liver enzymes after plasmapheresis was reported in different studies, but this did not make a statistically significant difference.[1,18]

Agranulocytosis is a rare but severe life-threatening side effect that can be seen in 0.2-0.5% of ATD. In the literature, plasmapheresis has been found to be an effective and safe treatment option in cases with thyrotoxicosis who cannot use ATD due to agranulocytosis.[6,7,13,19] In our study, plasmapheresis was performed in two of our patients due to ATD-related agranulocytosis, and a significant decrease in free thyroid hormone levels was achieved. While one of our patients did not need granulocyte colony-stimulating factor (GCSF), the other patient was given GCSF treatment because neutropenic fever was accompanied.

Table 2. Data of thyroid function tests in patients who underwent therapeutic plasmapheresis for thyrotoxicosis with hyperthyroidism.

Variable (unit)	Pre-TPE	Post-TPE	Normal range	p value
TSH (mU/L)	0.009 (0.002-0.009)	0.009 (0.002-0.22)	0.35-4.94	0.14
fT4 (ng/dL)	3.04±1.21	1.55 (0.7-3.6)	1.71-3.71	0.005
fT3 (ng/dL)	10.8 (6.4-31)	3.95±1.9	0.7-1.48	0.005

Data were given as mean±standard deviation or median (minimum:maximum).
TSH: thyroid stimulating hormone, fT4: free T4, fT3: free T3, PTE: therapeutic plasma exchange.

Table 3. Complete blood count data in patients undergoing therapeutic plasmapheresis for thyrotoxicosis with hyperthyroidism.

Variable (unit)	Pre-TPE	Post-TPE	Normal range	p value
WBC (10^9/L)	7.4±3.4	11.2±3.1	1.3-3.8	0.011
Hb (g/dL)	12.2±1.48	12.4±1.3	12.5-16.5	0.65
Htc (%)	36.9 ±4.7	36.6(34.7-46.9)	33-44	0.20
Plt (10^9/L)	254±82.5	245±76	145-400	0.63

Data were given as mean±standard deviation or median (minimum:maximum).
WBC: leukocyte, Hb: hemoglobin, Htc: hematocrit, Plt: platelet, PTE: therapeutic plasma exchange.

Table 4. Biochemical parameters in patients who underwent therapeutic plasmapheresis for thyrotoxicosis with hyperthyroidism.

Variable (unit)	Pre-TPE	Post-TPE	Normal range	p value
Urea (mg/dL)	29.4 (21-66)	31 (16.4-63)	17.9-54.9	0.81
Creatinine (mg/dL)	0.55 (0.4-1.5)	0.5 (0.51.48)	0.7-1.1	0.59
AST (U/L)	22 (10-72)	25.1 ±12.1	13-30	0.44
ALT (U/L)	29.5 (9-289)	28 (16-104)	9-57	0.85
Total bilirubin (mg/dL)	0.55 ± 0.19	0.52±0.2	0.2-1.2	0.78
Direct bilirubin (mg/dL)	0.2 (0.1-0.4)	0.20±0.07	0-0.5	0.38
Na (mmol/L)	139.3±2	137±1.56	136-145	0.01
K (mmol/L)	4.4 ±0.36	4.2±0.3	3.5-5.1	0.07
Ca (mg/dL)	9.3±0.3	9±0.48	8.8-10	0.04
Albumin (g/L)	38.9±3.2	38.1±4.55	40-50	0.64
INR	1 (0.86-2)	0.95 (0.90-1.14)	0.85-1.15	0.46

Data were given as mean±standard deviation or median (minimum:maximum).
AST: aspartate aminotransferase, ALT: alanine aminotransferase, Na: sodium, K: potassium, Ca: calcium, INR: international normalized ratio, PTE: therapeutic plasma exchange.

Thyroid storm is seen in 0.22% of all thyrotoxicosis cases, and its mortality rate varies between 8-30%.[20] Conventional treatments such as ATD, steroid and potassium iodide are used as first-line treatment, but patients with severe symptoms despite these treatments or for whom these treatments are contraindicated should undergo plasmapheresis.[5,21,22] Two of our patients with a previously known diagnosis of Graves' were taken to plasmapheresis because of thyroid storm. One of our patients was a patient who voluntarily stopped taking the drug and the follow-up, and the other patient was a patient who presented with vaginal bleeding in the first trimester of pregnancy and had significant thyrotoxicosis findings. Although TRAb levels were also high at the time of admission, invasive molar pregnancy was detected in the patient in the follow-up, and she received surgical and chemotherapy treatments for a molar pregnancy. It was thought that molar pregnancy together with Graves' activation might affect developing thyrotoxicosis in this patient.

There are cases in the literature who underwent plasmapheresis due to molar pregnancy.[23,24] One of our patients had plasmapheresis to provide rapid euthyroidism before coronary bypass surgery. There are cases in the literature who underwent plasmapheresis before non-thyroid surgery, as in our case.[17,25]

Histopathologically, no malignancy was detected in any of our patients who underwent thyroidectomy. In the literature, there are also cases with malignancy in Graves' patients who underwent thyroidectomy after plasmapheresis (17.5%), and the majority of them were reported as thyroid papillary carcinoma.[16,26]

In our study, no significant decrease was found in hemoglobin and hematocrit levels after plasmapheresis. There is a study in the literature that supports our study.[15] On the contrary, there is a study that found a statistically significant decrease, but in this study, a reduction was not found to create a need for replacement in patients.[16] In addition, leukocyte level was found to be statistically significantly higher after plasmapheresis in our study. Similar to our research, there is a study in the literature with leukocyte elevation after plasmapheresis. It was thought to be due to a partial decrease in the metabolism of neutrophils in the foreground.[27] In another study in which plasmapheresis was performed due to the side effect of toxic hepatitis, leukocyte elevation was observed after plasmapheresis, as in our research. Still, no statistically significant difference was found.[14] In our study, sodium and calcium values after plasmapheresis were significantly lower after plasmapheresis, and this situation was not at a level that would create a clinical effect or require replacement. It is thought that this change in calcium and sodium levels may be related to citrate in patients given FFP and may be dilutional due to the water-retaining effect of albumin in patients using albümin.[28,29]

While serious side effects such as anaphylaxis, catheter infection, and coagulopathy may be seen due to plasmapheresis, no complications were observed in our study except for simple urticarial rash in one patient and itching in one patient.[30]

Conclusions

TPE is an effective and safe treatment option that can be applied in cases where it is necessary to provide rapid euthyroidism before permanent treatments or non-thyroid surgical procedures or to treat life-threatening thyrotoxicosis. It requires experience in application and follow-up and provides rapid euthyroidism when performed in experienced centres.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: FMS, CE; Study Design: CA, EE; Supervision: CE; Data Collection and/or Processing: OOG, EH; Statistical Analysis and/or Data Interpretation: EA, SC; Literature Review: FMS; Manuscript Preparation: FMS; and Critical Review: CE.

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Short Report

Evaluation of the Impact of COVID-19 on the Yearly Distribution of Brain Death Declarations in Turkey Between 2011 and 2020

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Keywords: *COVID-19, pandemic, world, kidney transplantation, deceased donor, living donor, transplant number.*

The 2020 data of the Turkish Society of Nephrology reveals that the number of patients receiving hemodialysis and peritoneal dialysis treatment in Turkey is 63,945.[1] According to the 2020 registered data of the Transplantation Dialysis Monitoring System (TDIS), the number of patients waiting for solid organs is 23,923. The number of organs used was 1,059 out of 1,391 brain death cases declared in 2020.[2] While solid organ transplantation could be performed in 4.42% of the patients enrolled in TDIS, 95.58% could not. Insufficient organ supply in our country adversely affects patients waiting for organs. Our study aimed to investigate the effect of the COVID-19 pandemic on the distribution of brain deaths declared in our country by years.

We examined the distribution of brain death data reported in our country between 2011 and 2020 from "Transplantation Dialysis Monitoring System - Decision Support Unit (TDIS-KDS) data" of the Ministry of Health. We evaluated the effect of the COVID-19 pandemic on this distribution retrospectively. In our country, the brain death numbers between 2011 and 2019 were as follows; 1,227, 1,145, 1,645, 1,776, 1,941, 1,997, 2,046, 2,178 and 2,309, respectively. In 2020, this number was 1,391.[3] While the number of brain death declarations increased from 2011 to 2019, during the COVID-19 pandemic, the rate of brain death notifications in 2020 decreased by 40% compared to the previous year (*Figure 1*).

The COVID-19 pandemic has significantly reduced the number of declared brain death, family organ donation and organs used in 2020. The upward trend reversed in 2020. During the pandemic, prohibitions have restricted human mobility, and therefore, the number of potential donors, especially from trauma, has decreased. The intensive care unit served patients with COVID-19, and bed capacities increased. Even the institution's intensive care teams and other health workers were affected and infected by the pandemic.[4] The increasing number of patients necessitated intensive work. This situation may have negatively affected the management and donation rates of patients diagnosed with potential

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brain death, which is less in 2020. TDIS 2020 registry data showed that 4.42% of 23,923 patients awaiting solid organs were transplanted.

As a result, the COVID-19 pandemic adversely affected patients awaiting solid organ transplantation. The pandemic has led to a pause in the increasing trend in organ transplantation from deceased donors in our country. Dialysis patients without a living donor had to wait longer for an organ.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: EE; Study Design: EE, AE; Supervision: AE; Materials: EE, KS, RO; Data Collection and/or Processing: EE, KS, RO, MFA; Statistical Analysis and/or Data Interpretation: EE, KS, RO; Literature Review: AE, AY, AO; Manuscript Preparation: EE, KS, RO, MCC, KOG; Critical Review: AE.

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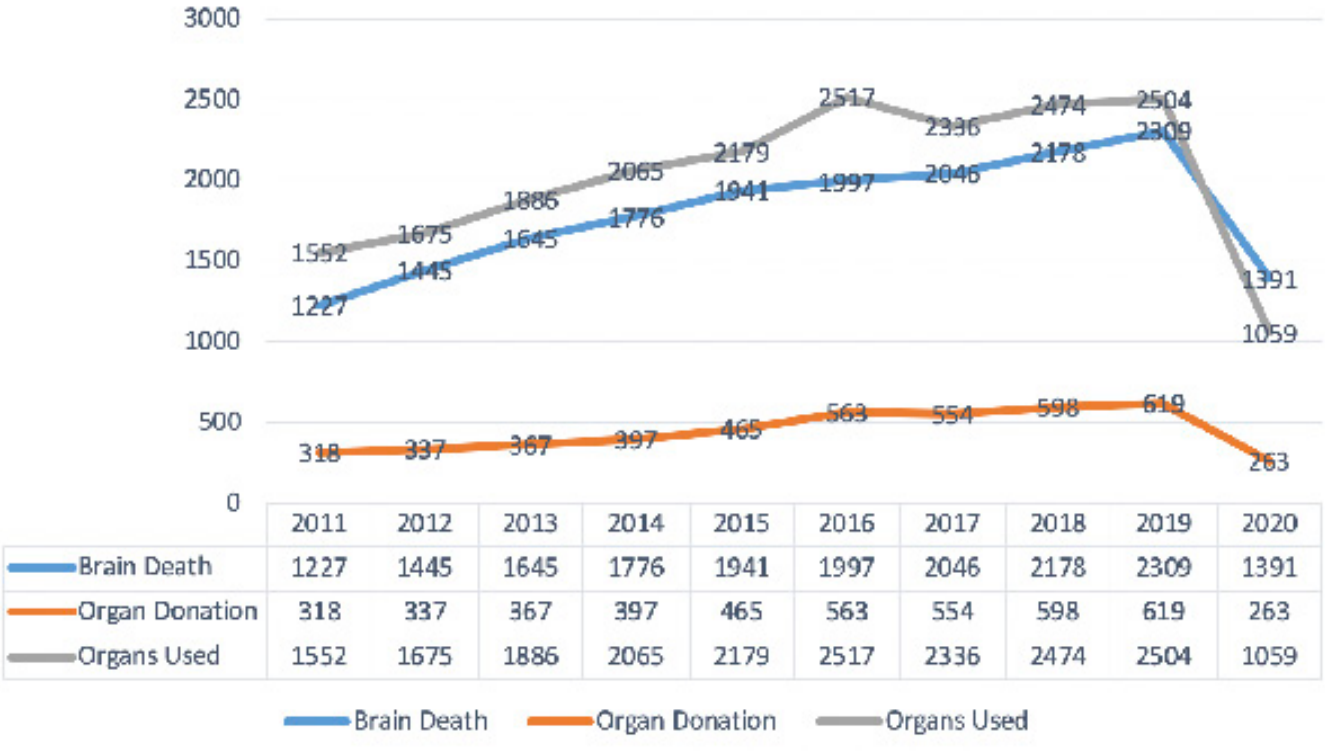

Figure 1. Brain death, organ donation and organ used rates in 2011-2020.

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Case Report

A Case of Proteinuria Developing Secondary to Solitary Renal Vein Thrombosis Due to Oral Contraceptive Use

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ABSTRACT

Renal vein thrombosis (RVT) is the presence of thrombi in major renal veins or their branches and is a rare clinical entity. RVT is one of the common thrombotic complications of nephrotic syndrome or renal cell carcinoma. Hormonal contraception can also rarely cause this complication. Herein, we presented a case of renal vein thrombosis accompanied by subnephrotic proteinuria after oral contraception.

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Keywords: *Renal vein thrombosis, proteinuria, nephrotic syndrome, oral contraception, thrombolytic therapy.*

Introduction

Common symptoms of renal vein thrombosis (RVT) are flank pain, hematuria, and acute kidney injury. The leading causes of RVT are nephrotic syndrome, renal cell carcinoma, trauma, kidney transplantation, hypovolemia, and hereditary procoagulant defects.[1] Recently, cases of COVID-19-related RVT have also been reported in the pandemic. Oral contraception is one of the rare causes of RVT.[2] Usually, RVT may occur due to hypercoagulation during the nephrotic syndrome, generally bilateral. We presented a case of renal vein thrombosis with subnephrotic proteinuria after oral contraception use.

Case Report

A 29-year-old female patient presented with complaints of left flank pain and nausea-vomiting for two days. She had a previous diagnosis of trigeminal neuralgia and history of nonsteroidal anti-inflammatory drug use. Her physical examination revealed left costovertebral angle tenderness and bilateral pretibial oedema (+/+). We learned that the patient was using oral contraceptives. The examination of urine sediment revealed 38 erythrocytes and 15 leukocytes per HPF. In urine, proteinuria was positive (++). Protein excretion in 24-hour urine was 2,562 mg. In the biochemistry tests, creatinine was 0.92 mg/dL, urea 10 mg/dL, albumin 31 g/L, D-dimer

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13 mg/L, LDH 351 U/L, and triglyceride 334 mg/dL. Contrast-enhanced computed tomography reported that a thrombus causing total occlusion in the left renal vein extended from the left renal vein to the inferior vena cava. We diagnosed acute RVT, and the interventional radiology unit performed thrombolytic therapy, thrombectomy and balloon angioplasty. After the procedure, they coded flow in both renal veins in the control doppler ultrasonography. ANA, ANA profile, anticardiolipin IgM and IgG, beta-2 glycoprotein IgM and IgG antibodies were negative. Heterozygous MTHFR mutations were positive in the thrombophilia panel. PAI 4g/5g, MTHFR c.1298A>C, FXIII p.V34L, prothrombin g.20210G>A, and FV Leiden c.11691G>A was normal. We thought that RVT developed secondary to oral contraceptive use in the patient. We followed up the patient with anticoagulant therapy after the procedure. She had no complaints at the outpatient policlinic control five months after, and urinary proteinuria (150 mg/24 hours) and kidney function tests were within normal ranges.

Discussion

Renal veins are rarely thrombosed, and the cause is usually almost always clear. The use of oral contraceptive drugs is known among the risk factors for RVT.[3,4] The relationship between the use of oral contraceptives and the risk of venous thrombosis was investigated in women aged 15-49 years without a history of cardiovascular or malignant disease in Denmark between 1995 and 2005.[5] In this cohort, out of a total of 4,213 venous thrombotic events, 2,045 were observed in current oral contraceptive users. The overall absolute risk of venous thrombosis per 10 000 women-years was 3.01 in non-users and 6.29 in current users of oral contraceptives.[5]

Pregnancy-postpartum, surgery and trauma can often trigger thrombotic events even in the general population. Clinicians should also look for the presence of a prothrombotic disorder if there are no obvious risk factors in oral contraceptive users who develop venous thrombosis. These conditions can cause acute renal vein thrombosis in the presence of a trigger such as oral contraceptive medication. Several case series in the literature have reported patients with RVT associated with hyperhomocysteinemia, elevated factor VIII levels, congenital disabilities of clotting inhibitors such as potential heterozygous true deficiencies of antithrombin III (low ATIII antigen and activity), a decreased protein C antigen to factor X antigen ratio, a heparin cofactor II deficiency, and a type I protein S deficiency after oral contraceptive use.[6-9] In our case, heterozygous MTHFR c.677C>T mutation was positive. This heterozygous mutation generally increases the susceptibility to arterial thrombosis.

A previously healthy 15-year-old female patient was taking oral contraceptives admitted with isolated, unilateral renal vein thrombosis. This patient had mild proteinuria (760 mg/24 hours).[10] Nephrologists often encounter RVT as a complication of nephrotic syndrome. However, we should be aware that RVT can lead to mild or nephritic proteinuria. Rapid diagnosis and intervention with radiological imaging are essential in patients with RVT. In some cases, thrombosis has been effectively treated with streptokinase.[11] After early diagnosis, we treated the present case with RVT with successful intervention and thrombolytic agents.

Conclusions

When patients use oral contraceptives with flank pain and hematuria, one of the differential diagnoses should be acute renal vein thrombosis. The treatment can change depending on the patient's prognosis and clinic. Patients without acute kidney injury can generally follow up with anticoagulant therapy. Thrombolytic treatment and thrombectomy should be considered primarily in patients with the presence of acute kidney injury, transplanted kidneys, and bilateral RVT or unilateral patients with a high thrombus load.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: MS, AG; Study Design: MS, AG, AE; Supervision: MS, AG, AE; Materials: MS, AG; Data Collection and/or Processing: MS, AG; Statistical Analysis and/or Data Interpretation: MS, AG, AY; Literature Review: MS, AG, AY; Manuscript Preparation:MS, AG; Critical Review: MS, AG.

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Original Article

A Rare Cause of Hypokalemia: Ectopic ACTH Syndrome

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ABSTRACT

The most common cause of adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome is a benign ACTH-producing pituitary tumour or, less frequently, ectopic ACTH production from non-pituitary tumours. Ectopic ACTH syndrome occurs more commonly in men and usually presents after 40 years. It is most commonly associated with small cell lung cancer. Although this syndrome is associated with severe hypercortisolemia, some findings of Cushing's syndrome, such as central obesity, may not be observed due to underlying malignant diseases. In these cases, rapid metabolic disruption, anorexia, myopathy, glucose intolerance, hypokalemic alkalosis, and hyperpigmentation accompany the patients' clinical condition. In the current case report, we aimed to emphasize that ectopic ACTH syndrome should be kept in mind in the differential diagnosis, especially in the presence of hypokalemia accompanying hypertension and proximal muscle weakness, if the patient also has progressive weight loss.

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Keywords: *Hypokalemia, ectopic ACTH syndrome, small cell lung cancer.*

Introduction

Cushing's syndrome (CS) is an endocrine disorder characterized by excessive cortisol production. Endogenous CS is a rare disease with an annual incidence of 0.7–2.4 per million. CS patients can show signs and symptoms such as moon face, trunkal obesity, hypertension, fatigue, amenorrhea, hirsutism, fragile skin that easily bruises striae, and osteoporosis.[1] The most common cause is iatrogenic CS due to long-term use of glucocorticoids. Endogenous CS occurs due to secretion of adrenocorticotropic (ACTH) and corticotropin-releasing hormone (CRH) from the pituitary and non-pituitary sources or excessive glucocorticoid secretion as a result of the adrenal gland's pathologies. The most common cause of ACTH-dependent CS is a benign ACTH-producing pituitary tumour (Cushing's disease; CH, 70-80%) or less frequently (15-20%) ectopic ACTH/CRH production from non-pituitary tumours.

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Ectopic ACTH secretion is a rare paraneoplastic syndrome associated with a large group of tumours, most of which are neuroendocrine cells.[2] Ectopic ACTH secretion is the first described paraneoplastic endocrine syndrome in the literature, and it accounts for only 10-20% of all ACTH-dependent CS cases.[3] It is most commonly associated with small cell carcinoma of the lung (SCLC).[4] Although this syndrome is associated with severe hypercortisolemia findings, some findings of CS, such as central obesity, may not be observed due to underlying malignant diseases. It should be considered in the differential diagnosis, especially if hypertension, proximal muscle weakness, hypokalemia and weight loss accompany. Herein we present a patient who developed ectopic ACTH syndrome due to SCLC.

Case Report

A 66-year-old male patient with a history of hypertension and coronary artery disease was admitted to our outpatient clinic with complaints of weakness, fatigue, proximal muscle weakness, hoarseness and weight loss for the last two weeks. There was no pathological finding in his physical examination, and he had a 40 pack/year smoking history. Laboratory tests revealed hypokalemia, metabolic alkalosis and hypercortisolemia (*Table 1*). The patient received oral and intravenous potassium replacement to correct hypokalemia. We performed a 1 mg dexamethasone suppression test (DST) due to high basal cortisol and ACTH levels. The cortisol level was 45 mcg/dL after DST. A pituitary magnetic resonance imaging

Table 1. Laboratory values of the patient at the time of admission.

Variables	Value (reference ranges)
Glucose (mg/dL)	107 (74-100)
Urea (mg/dL)	31 (19-49)
Creatinine (mg/dL)	0.66 (0.7-1.2)
AST (U/L)	35 (0-40)
ALT (U/L)	33 (0-41)
Sodium (mEq/L)	145 (136-145)
Potassium (mEq/L)	2.34 (3.5-5.1)
Corrected calcium (mg/dL)	8.4 (8.6-10.2)
Magnesium (mg/dL)	1.96 (1.6-2.69
pH	7.51 (7.35-7.45)
Bicarbonate (mmol/L)	34.7 (21-26)
Renin (ng/mL/h)	1.96 (0.98-4.18)
Aldosteron (ng/dL)	<5 (3-16)
ACTH (pg/mL)	311 (0-46)
Cortizol (µg/dL)	(6.2-19.4)
Basal	55
1 mg DST	45.3
8 mg DST	51

AST: alanine aminotransferase, ALT: aspartate aminotransferase, ACTH: adrenocorticotropic hormone, DST: dexamethasone suppression test.

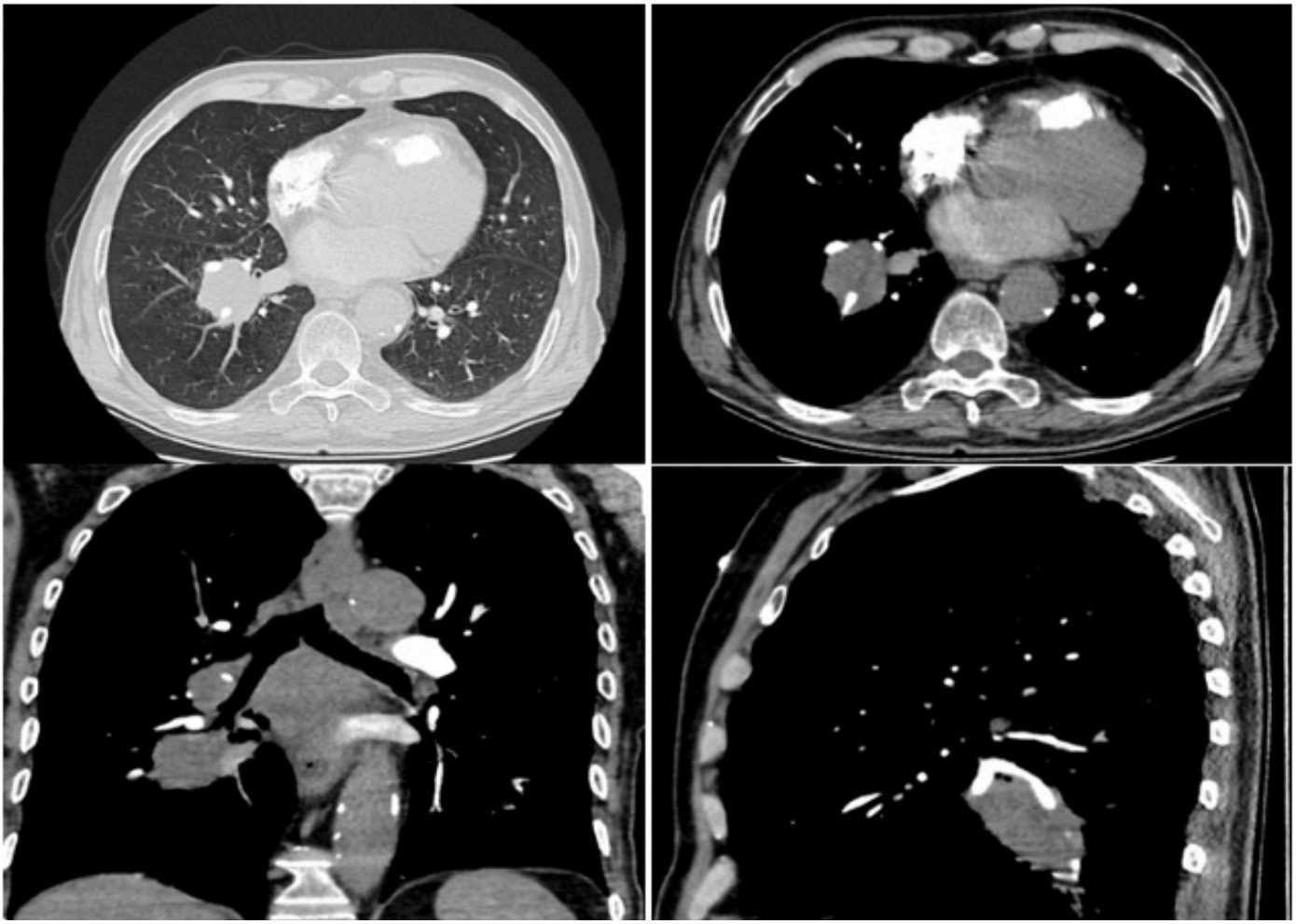

Table 1. Computed tomography images of the lesion in the lung.

(MRI) did not show adenoma in the pituitary region. There was no suppression of cortisol level in the high-dose DST test. On thoracic high-resolution computerised tomography (HRCT) imaging, a mass lesion measuring 4 cm and a soft tissue thickening of approximately 35 mm in the right hilar region was observed (*Picture 1*). The pathological examination of the biopsy taken from the mass was compatible with SCLC, and we referred the patient to the oncology policlinic for further assessment and treatment.

Discussion

Ectopic ACTH syndrome is a rare paraneoplastic syndrome caused by ACTH secreting tumour. SCLC and bronchopulmonary carcinoid tumours are the most common causes of ectopic ACTH release. Ectopic ACTH syndrome occurs most often in men, usually over 40 years. In addition to the typical symptoms of hypercortisolemia such as fatigue, proximal myopathy, and striae, findings related to high ACTH levels such as severe hypokalemia and hyperpigmentation may be observed.[5] Weight gain is not as prominent in ectopic ACTH syndrome as in CS patients because of the accompanying malignancy. Patients who developed ectopic ACTH syndrome related to malign tumours have more severe symptoms and faster disease progression due to higher serum ACTH and cortisol secretion. Resection of the tumour causing ectopic ACTH release is the optimal treatment method. However, chemotherapy treatment is at the forefront because SCLCs have a low resectability rate and respond well to systemic therapy.[6] In patients with ectopic CS, 1-year survival is reported as 84% and 5-year survival as 70%.[7] In this case, we emphasized that malignant causes lead to ectopic ACTH syndrome, and it should be considered in the differential diagnosis of patients with resistant hypokalemia.

Conclusions

When patients use oral contraceptives with flank pain and hematuria, one of the differential diagnoses should be acute renal vein thrombosis. The treatment can change depending on the patient's prognosis and clinic. Patients without acute kidney injury can generally follow up with anticoagulant therapy. Thrombolytic treatment and thrombectomy should be considered primarily in patients with the presence of acute kidney injury, transplanted kidneys, and bilateral RVT or unilateral patients with a high thrombus load.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: MT; Study Design: MC; Supervision: SK; Materials: RO, MT; Data Collection and/or Processing: MT; Statistical Analysis and/or Data Interpretation: SK; Literature Review: MT; Manuscript Preparation: MC; Critical Review: SIA.

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Case Report

A Case of Sinus Bradycardia in a Patient Treated with Pulse Steroids for Adult-Onset Still's Disease

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ABSTRACT

Adult Onset Still's Disease is a rare systemic inflammatory disease. The absence of a specific clinical presentation and diagnostic biomarkers causes delays in diagnosing and treating AOSD. Steroids used in treatment have many undesirable side effects. We presented a female case with AOSD who developed sudden bradycardia after pulse steroid therapy.

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Keywords: *Still's disease, adult, treatment, complication, methylprednisolone, pulse steroid, sinus bradycardia.*

Introduction

Adult-onset Still's Disease (AOSD) is a rare systemic inflammatory disorder characterized by fever, transient salmon-pink maculopapular rash, inflammatory polyarthritis, lymphadenopathy and sore throat.[1] The aetiology of AOSD is currently unknown. Non-specific clinical presentation, lack of diagnostic biomarkers, and AOSD rarity often result in a significant delay in diagnosis and treatment.[1] Steroids are the basis of therapy. In this case of a patient diagnosed with AOSD, we investigated clinical findings, treatment and the sudden bradycardia that occurred after the patient underwent pulse steroid therapy.

Case Report

In November 2021, a 30-year-old woman applied with transient whole-body maculopapular rash, sore throat and joint pain. The patient underwent empiric antibiotic therapy as an infection could not be excluded. However, the complaints of the patient did not regress. Rheumatological workup demonstrated normal renal and hepatic parameters, negative autoantibodies, ESR 63 mm/h, CRP 262 mg/L, ferritin 4,214 µg/L, and fibrinogen 890 mg/dL (*Table 1*).

Preliminary findings were compatible with AOSD; thus, methylprednisolone treatment was initiated. Arthralgia and rash regressed after pulse

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steroid treatment, supporting AOSD diagnosis. The patient was discharged with methotrexate and prednisolone; however, the patient applied to the hospital again with an attack after five days and was admitted. A pulse steroid of 1 g/day methylprednisolone was planned for three consecutive days. After two days of pulse steroid treatment, the patient's laboratory parameters and clinical signs didn't regress. Thus, anakinra was initiated. The patient, whose pulse was within the normal range in the previous follow-ups (*Figure 1*), developed asymptomatic sinus bradycardia (*Figure 2*) after three doses of pulse steroid therapy without deterioration of other vital parameters. The patient was monitored with a holter. However, a cardiac pathology that explains bradycardia was not found, and the case has been evaluated as isolated sinus bradycardia. Bradycardia of unknown aetiology was considered secondary to pulse steroid therapy. The patient, whose clinical and laboratory parameters improved with pulse steroid and anakinra treatment, was discharged.

Discussion

Physicians frequently encounter side effects of pulse steroid therapy such as hyperglycemia, hypertension and electrolyte disturbances. However, the side effect of bradycardia is not well known. There are a few cases of sinus bradycardia developing following steroid infusion in the literature. These cases, which are usually asymptomatic, resolved spontaneously after stopping the infusion.[2] Although there is no current data in the literature, a small-scale study conducted in the patient group diagnosed with multiple sclerosis found the prevalence of steroid-induced bradycardia to be 41.9%.[3] Although this side effect mainly develops following intravenous treatment, there are a few case reports of sinus bradycardia after oral methylprednisolone.[4] The pathogenesis of sinus bradycardia developing following steroid infusion has not been fully elucidated. However, the sympathetic nervous system can exert bradycardic effects by suppressing cytokine production and function.[5]

There was no comorbid disease or drug use in our case. While other vital parameters were stable in our young patient, sinus bradycardia developed following pulse steroid therapy. It spontaneously

Table 1. The course of the patient's laboratory tests.

	Admission	Second day	10th day	Discharge
Leukocyte (/mm^3)	27,100	13,040	10,440	11,400
Neutrophil (/mm^3)	24,600	11,900	6,740	8,060
Hemoglobin (g/dL)	11	11.5	10.4	12.4
Platelet (/mm^3)	501,000	479,000	264,000	257,000
INR	0.84	0.98	0.93	0.84
Fibrinogen (mg/dL)	890	822	238	274
Ferritin (mcg/L)	4,981	3,458	835	648
CRP (mg/L)	186	78	<2	<2
ESR (mm/h)	-	61	12	13
Procalcitonin (µg/L)	0.05	0.02	0.02	0.04
ALT (U/L)	23	69	31	29
AST (U/L)	27	41	17	22
Creatinine (mg/dL)	0.53	0.60	0.57	0.64

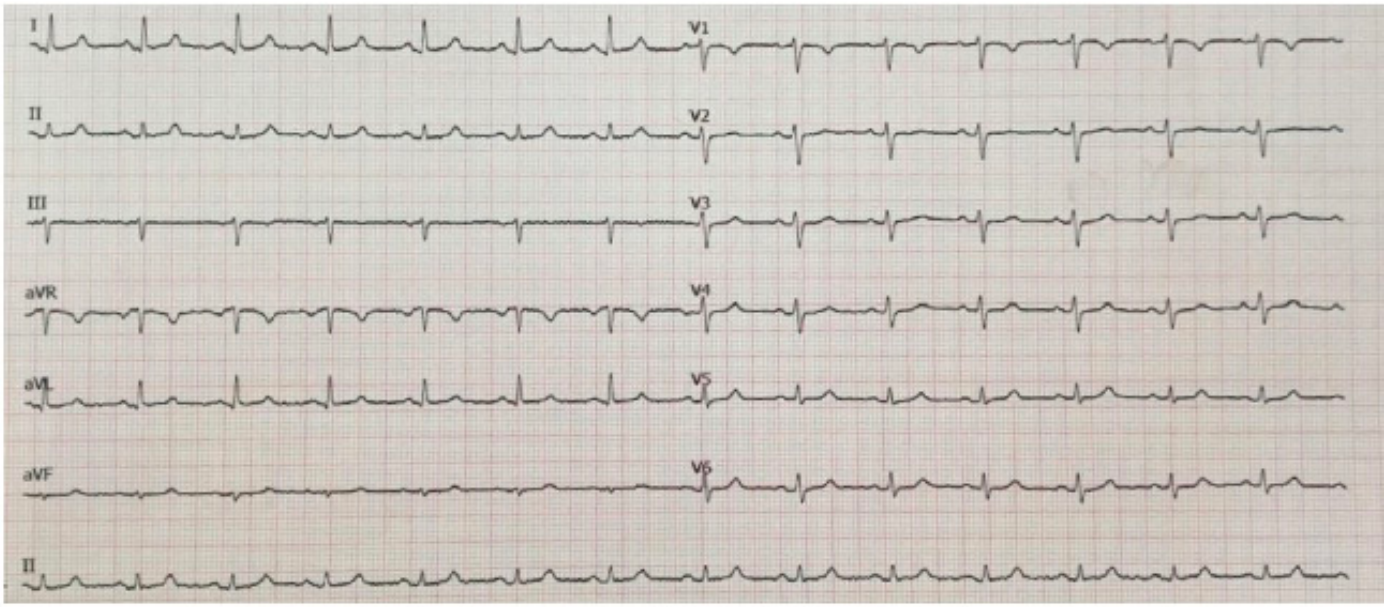

Figure 1. Electrocardiography before methylprednisolone treatment.

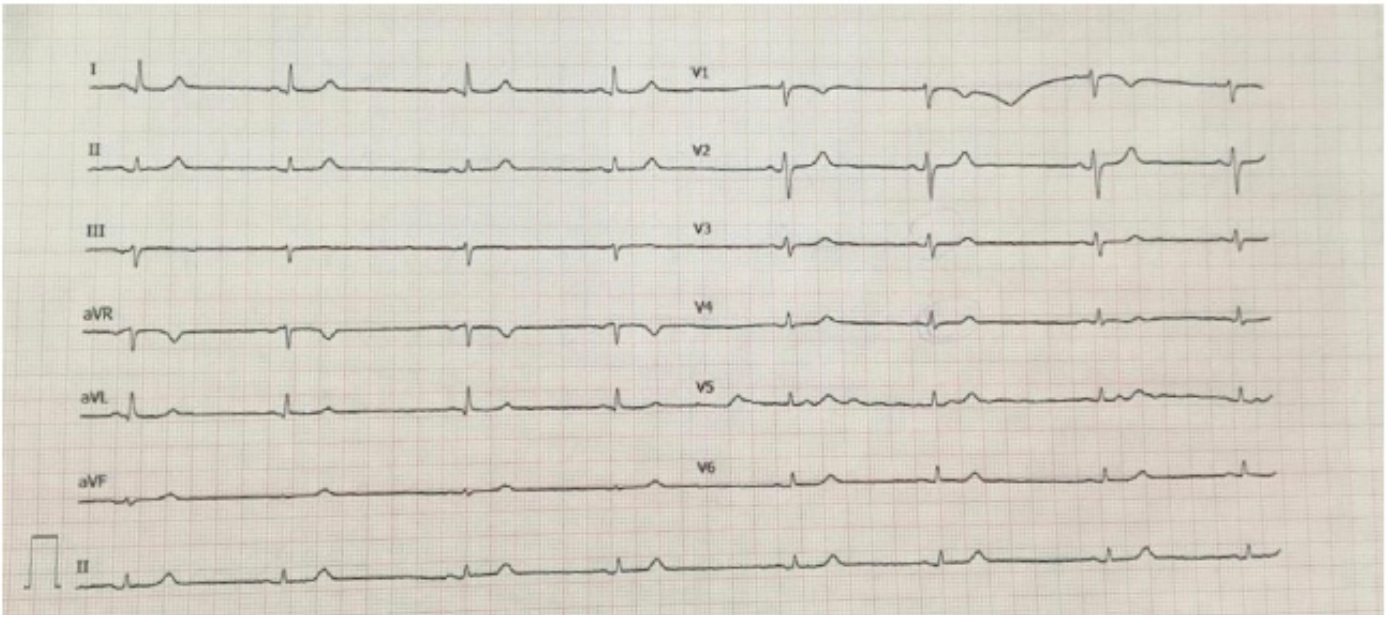

Figure 2. Electrocardiography after methylprednisolone treatment.

returned to normal rapid sinus rhythm within a few days after stopping the infusion. Therefore, we thought that sinus bradycardia was secondary to pulse steroid therapy. In the patient, the Naranjo drug side effect scale score was calculated as +6.[6] Electrolyte imbalance, underlying cardiac pathology, or steroid infusion rate increase the risk of bradycardia. Although this side effect is often asymptomatic, Guillen et al.[7] reported a case with a history of coronary artery disease that developed hypotension, bradycardia, and asystole after pulse steroids. For these reasons, bradyarrhythmia risk during pulse steroid therapy should be considered. In cases with cardiac pathology, it would be a more accurate approach to monitor the patient during the infusion and prefer prolonged infusion.

Acknowledgment

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: SI, BNE; Study Design: SI, AE, BNE; Supervision: BNC, YP; Data Collection and/or Processing: SI, BNE, AE, ED; Statistical Analysis and/or Data Interpretation: SI, AE, BNC, BNE; Literature Review: SI, AE, BNC; Manuscript Preparation: SI, BNE, YP; Critical Review: BNC, SI.

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Case Report

Bilateral Gouty Arthritis Developing After COVID-19 Infection: A Case Report

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ABSTRACT

Viral infections can lead to acute arthralgia and arthritis. Reactive arthritis has been reported after COVID-19 infection, but gouty arthritis. A 76-year-old male patient with a history of chronic kidney disease, hypertension and coronary artery bypass was hospitalized due to COVID-19 PCR positivity. On the 14th day of his hospitalization, the patient developed pain in both big toes, which started suddenly at night and worsened in the morning and was diagnosed with bilateral gouty arthritis. In this case, we thought that gouty arthritis was a secondary condition to the COVID-19 infection.

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Keywords: *COVID-19, infection, arthritis, uric acid, gout, treatment.*

Introduction

The SARS-CoV-2 virus started in Wuhan, China, in 2019 and caused the COVID-19 pandemic by affecting the whole world in a short time. It usually causes pneumonia, along with diseases in many systems.[1,2] Arthralgia is one of the symptoms seen after COVID-19 infection and can be seen in 14.9% of the cases. However, data on rheumatic and inflammatory symptoms such as arthritis are scarce.[3] Herein, we presented a case of gouty arthritis, possibly associated with COVID-19 infection.

Case Report

A 76-year-old male patient with chronic kidney disease, hypertension and a history of coronary artery bypass using saphenous veins in both legs 12 years ago was admitted to the emergency department with chest pain and increasing fatigue. The patient's medications regularly were isosorbide mononitrate 50 mg/day, metoprolol tartrate 25 mg/day, valsartan 80 mg/day, acetylsalicylic acid 300 mg/day, and trimetazidine dihydrochloride 35 mg/day. The cardiologist evaluated the patient who did not have other symptoms due to chest pain

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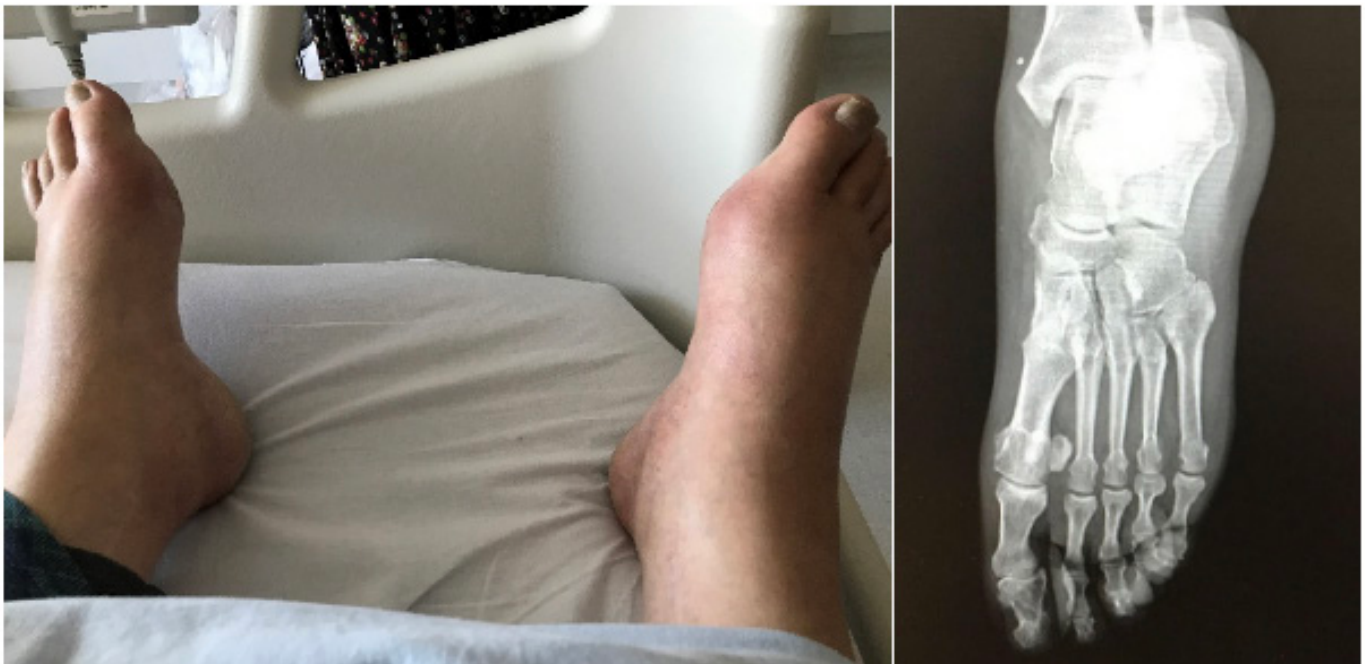
with blood results and electrocardiography and was not considered prominent cardiological pathology. Thoracic computerised tomography of the patient revealed patchy infiltration areas in the appearance of ground glass-cobblestones, predominantly in the upper lobes and subpleural peripheral areas in both lungs, and were radiologically reported as highly suspicious for COVID-19 pneumonia. We were hospitalized after the COVID-19 PCR result was positive. At his admission to the service, his vitals were measured as a body temperature of 36.2 °C, blood oxygen saturation (SpO2) of 97%, blood pressure as 130/80 mmHg and heart rate of 85/min with 4 L nasal oxygen support. In the hospitalized blood of the patient, urea 98 mg/dL, serum creatinine 1.84 mg/dL (baseline serum creatinine 1.52 mg/dL), D-dimer 0.44 mg/L, procalcitonin 0.03 µg/L, ferritin normal, white blood cell 4,710, hemoglobin 14.5 g/dL, C-reactive protein (CRP) 0.0515 g/L. We started methylprednisolone (80 mg/day), favipiravir, and enoxaparin sodium treatment at admission and tapered off methylprednisolone dose over 12 days. The patient's need for oxygen support decreased over time, and SpO2 remained 92% and above without oxygen support. On the 14th day of hospitalization, the patient complained of pain around both toes that started suddenly at night and intensified in the morning (*Picture 1*). In his history, the patient stated that he had completely similar complaints several times with an interval of one year in the last three years and that it resolved spontaneously in 10-15 days.

On his physical examination, there is little redness, swelling and tenderness in the bilateral foot metatarsophalangeal joints, and bilateral distal pulses are palpated clearly. There is a graft scar on the bilateral leg, and the foot skin is dry. It is not accompanied by hematuria, malar rash, Raynaud's history, mouth-nose sores, and hemoptysis. In the blood tests of the patient, uric acid 9.8 mg/dL, serum creatinine 1.67 mg/dL, D-dimer 0.33 mg/dL, procalcitonin 0.13 µg/L, ferritin 342 µg/L, white blood cell 12,460, neutrophil count 81.9%, sedimentation rate 26 mm /h., CRP was determined as 0.086 g/L. The patient who was not considered to have cellulitis was evaluated as having bilateral gouty arthritis according to the 2015 gout classification criteria (ACR/EULAR). We started colchicine (3x0.5 mg) with methylprednisolone treatment. Non-steroidal anti-inflammatory drugs were not given due to chronic kidney disease, and paracetamol was preferred for pain relief. At the end of the 6th day of the treatment, the findings in his physical examination started to improve, and the complaint decreased. At the end of the 14th day, a complete recovery was achieved.

Discussion

Viral infections (hepatitis B virus, hepatitis C virus, parvovirus, Epstein-Barr virus, HIV, alphavirus) are known causes of acute arthralgia and arthritis.[4] In the literature, there are many examples of reactive arthritis cases developing after COVID-19 infection.[5-8] One of the side effects of favipiravir, one of the active substances used to treat COVID-19, is to increase the uric acid level in the blood.[9] The blood uric acid level rises only temporarily after favipiravir treatment, and the probability of a gout attack is considered low. In the literature, cases of gout attacks during favipiravir are rare.[10] Gouty arthritis, the most common form of inflammatory arthritis, is characterized by elevated blood uric acid levels and monosodium urate accumulation in synovial fluid and other tissues.[11] Acute gouty arthritis most often affects the first metatarsophalangeal joint in the foot. Although the involvement in gouty arthritis is monoarticular, the first finding is polyarticular in approximately 20% of the cases, and this rate increases in later attacks and hospitalized patients.[12,13]. The final diagnosis is made by arthrocentesis of the affected joint and seeing intracellular monosodium urate (MSU) crystals under a polarized light microscope. However, if this is impossible, a clinical diagnosis can also be made.[13]

The patient was evaluated according to 2015 gout classification criteria (ACR/EULAR); he got 2 points for MTP joint involvement (during mono- or oligoarticular arthritis episodes), 1 point for having erythema on the affected joint, 1 point for inability to withstand the pain for touch and pressure on the affected joint, 1 point for difficulty in using the joint, 1 point for the maximum amount of pain lasting less than 24 hours, the attack passing within 14 days and returning to the normal state



Picture 1. Appearance and direct x-ray of the left foot with arthritis were taken with the patient's consent on the 13th day of hospitalization.

between attacks, 3 points for the uric acid value. He exceeded 8 points with a total of 9 points and he was diagnosed with gout arthritis.[14] Secondary hyperuricemia is an expected finding in chronic kidney disease. Since arthritis in our patient developed after the COVID-19 infection, it is likely secondary to the illness and/or treatment. However, since there were similar complaints in the history of this case, COVID-19 and/or favipiravir may also have triggered bilateral gouty arthritis. Similar case reports are needed to clarify the relationship between COVID-19 and gouty arthritis.

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Conflict of interest

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Authors' Contribution

Study Conception: SHA, DTG; Study Design: SHA, DTG; Supervision: SHA, DTG; Materials: SHA, DTG; Data Collection and/or Processing: SHA; Statistical Analysis and/or Data Interpretation: SK; Literature Review: SHA; Manuscript Preparation: SHA, DTG; Critical Review: SHA, DTG.

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TURKISH JOURNAL OF INTERNAL MEDICINE
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Case Report

Cetuximab-Induced Acneiform Eruption: A Case Report

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ABSTRACT

Epidermal growth factor receptor (EGFR) monoclonal antibody inhibitors are used to treat metastatic colorectal cancers. Cetuximab, an EGFR inhibitor drug, targets specific molecular pathways and does not cause the severe systemic side effects seen in cytotoxic chemotherapy. Herein, we presented a case who developed acneiform eruptions during cetuximab treatment.

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Keywords: *Colorectal cancer, metastasis, epidermal growth factor receptor inhibitors, cetuximab, adverse effect.*

Introduction

Colorectal cancer is the third most common cancer globally.[1] About a quarter of them are metastatic at diagnosis, and metastasis develops in 40-50% of early-stage cancers.[2] Epidermal growth factor receptor (EGFR) monoclonal antibody inhibitors are used to treat metastatic colorectal cancer without Ras mutation and are reported to prolong patient survival.[1] Cetuximab is an EGFR inhibitor drug used to treat metastatic colorectal, head and neck cancers. Since EGFR inhibitors target specific molecular pathways, they do not cause systemic severe side effects seen in cytotoxic chemotherapy and have less systemic toxicity than traditional antineoplastic agents.[3] Cutaneous side effects have been reported frequently during cetuximab treatment.[4] Acneiform eruptions, one of the severe side effects of cetuximab treatment, are usually reversible but rarely lead to dose reduction or discontinuation.[5] We presented a case with cetuximab-induced acneiform eruption.

Case Report

A 54-year-old male patient without known comorbid disease was undergone an emergency operation due to colonic obstruction in March 2020 and was diagnosed with colon adenocarcinoma after a left hemicolectomy operation. The systemic evaluation at the diagnosis revealed multiple liver metastases. Because the patient did not have K-ras/nras/braf mutations, mFOLFOX (folinic acid + fluorouracil + oxaliplatin) plus cetuximab was started in April 2020. The patient, who had no history of rash (acneiform) and had not used systemic steroids recently, developed pruritic papules and pustular lesions on the nose and sides of the nose and in the nasolabial grooves after the ninth cycle of chemotherapy (*Picture 1*). We observed no pathology in evaluating the skin and mucosa of the whole body, except for the lesions. Comedones did not accompany the lesions. Laboratory examinations were unremarkable. The patient was diagnosed with cetuximab-

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Picture 1. Papules and pustules on the erythematous ground on and around the nose.

Picture 2. Response after treatment.

induced acneiform eruption based on the current clinical findings. We applied clindamycin and 10% sodium sulfacetamide cream once a day and recommended protection from sunlight. On the seventh day of the treatment, the skin lesions regressed almost wholly (*Picture 2*), we continued his treatment at the current dose. In the outpatient follow-ups, there was no recurrence.

Discussion

Cetuximab is a chimeric (mouse/human) monoclonal antibody administered by intravenous infusion, which binds to EGFR and inhibits it.[3] It was first approved by FDA in 2009 for the treatment of metastatic colon cancer without K-ras mutation after it was found to be ineffective in patients with colon cancer with K-ras mutation. This is the first genetic test to be included in the management of cancer treatment.[3] Cetuximab's mechanism of action is to inhibit tumor proliferation by inhibiting EGFR, but besides this effect, it also inhibits the EGFR pathway in the skin, causing various dermatological side effects by impairing keratinocyte proliferation, differentiation, and hair follicle development.[6] Although systemic side effects are rare in patients using cetuximab, the frequency of cutaneous side effects has increased.[3] Among these dermatological side effects associated with EGFR inhibitors, the acneiform eruption is the most common and the earliest.[1] Papulopustular rash, nail and hair disorder, xerosis, telangiectasia, hyperpigmentation, seborrheic dermatitis are other cutaneous side effects.[1] Acneiform lesions

are usually seen on the face, scalp, trunk, and upper back. Unlike acne, comedones are not seen. In mild cases, topical metronidazole, clindamycin, salicylic acid; Systemic tetracyclines can be used in moderate and severe cases.[4] It is recommended that patients be protected from sunlight during cetuximab treatment and up to 2 months after the end of treatment, and sunscreens are recommended.[7]

In conclusion, it should be kept in mind that skin rashes developing in patients using cetuximab may be related to treatment. Recognition and treatment of lesions are necessary for the patient to continue cetuximab therapy.

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: SOO, BG; Study Design: SOO, BG; Supervision: TE; Materials: BG, SOO; Data Collection and/or Processing: BG; Statistical Analysis and/or Data Interpretation: TE; Literature Review: BG; Manuscript Preparation: BG, SOO; Critical Review: TE.

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Case Report

Colchicine Intoxication: A Case Report

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ABSTRACT

Colchicine is produced from the essence of the lily plant that has been cured for many sicknesses such as familial Mediterranean fever, recurrent pericarditis, gout since it has anti-inflammatory properties. This anti-inflammatory drug's acute intoxication has a high mortality rate and is a critical clinic to follow but not very common. The intoxication severity and mortality are directly depending on the ingested dose. However, although its treatment is principally symptomatic, if left untreated, it is a clinical effect that can be fatal depending on the dose taken directly. In our case, we aimed to present the patient hospitalized in the intensive care unit due to 30 tablets of colchicine intaken and finally was discharged in good health.

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Keywords: *Colchicine, poisoning, overdose, leukocyte dysfunction.*

Introduction

Acute colchicine poisoning is a rare clinical entity that causes multiple visceral failures. The severity of colchicine poisoning depends on the doses received. We presented a 34-year-old female patient that ingested colchicine for suicidal purposes and was discharged in good health.

Case Report

A 34-year-old female patient with a diagnosis of familial Mediterranean fever (FMF) was admitted in the emergency department after 4 hours of voluntary ingestion of 1 mg x 30 colchicine pill and 2 antibiotics of unname for suicide. At admission, she had abdominal pain and vomiting, and she was conscious. Vital data at admission; body

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Table 1. The course of the patient's laboratory tests.

Test (reference values)	1st day of hospitalization	2nd day of hospitalization	3rd day of hospitalization	4rd day of hospitalization
BUN (8-23 mg/dL)	6	6	8	11
Creatinine (0.57-1.1 mg/dL)	0.34	0.38	0.79	0.5
AST (5-34 IU/L)	36	37	33	24
ALT (0-55 IU/L)	15	15	18	17
Sodium (136-145 mmol/L)	132	138	137	138
Chlorine (98-107 mmol/L)	108	107	105	103
Calcium* (8.4-10.2 mg/dL)	6.7	9.3	8.7	8.3
Potassium (3.5-5 mg/dL)	7	4.3	4.8	3.9
Magnesium (1.6-2.6 mg/dL)	1	2.4	1.3	1.9
Leukocyte (3.5-10.5/mcL)	9.2	9.1	7.1	6.6
Hemoglobin (12-15.5 g/dL)	11.8	12	11.7	11
Platelet (150-450 k/mcL)	414	428	399	346
INR (0.8-1.2 kU/L)	1.1	1.2	0.9	0.8
PT (10.5-14.5 sec)	14.2	15.3	11.9	10.7
aPTT (21-35 sec)	24.3	22.6	24.6	21.7
D-dimer (0-0.50 mg/dL)	3.7	4.8	1.6	1.4

*corrected with serum albumin.

temperature 36 °C, blood pressure 110/70 mmHg, pulse 80/min, oxygen saturation 100%, pH 7.29, paO_2 126 mmHg $paCO_2$ 245 mmHg, HCO_3 20 mg/dL, lactate 4.6 mg/dL, base deficit -4.3 in blood gas, creatinine 0.43 mg/dL, BUN 8 mg/dL, potassium 7 mmol/L, calcium 7.7 mmol/L. After gastric wash was achieved and given activated charcoal treatment, she was admitted to the intensive care unit (ICU). During her stay in ICU, the patient was ventilated with a nasal mask (6 L/min) for oxygen support. In addition, the patient was administrated isotonic salin (100 cc/hour). Oral intake of the patient was closed. Urine output and electrolyte follow-up were closely monitored. The progression of laboratory findings is shown in Table 1. No clinical arrhythmias or respiratory problems were observed during her stay. On the 2nd admission day, she had profuse diarrhoea, abdominal pain and vomiting while stopped on the 3rd day of follow-up. On the 8th hospital day, her general condition was good, whose hemodynamics was stable and laboratory values returned to normal, and was referred to the internal medicine clinic.

Discussion

Colchicine is a fat-soluble, rapidly absorbed alkaloid from the gastrointestinal tract, and its biological effect is related to its plasma concentration level. The time required for this effect is between 30-120 minutes.[1] Since it binds to plasma proteins, the use of hemodialysis is limited in its treatment, and there is no known antidote. Since it is known that oral activated charcoal enters the enterohepatic circulation and reduces the absorption of colchicine, we administered oral activated charcoal to our patient, and We did not give any other special treatment for poisoning.[2] Colchicine exerts its effect by dose/time-dependent tubulin polymerization and mitosis inhibition. It causes minor toxicity at low doses (<0.5 mg/kg) and an early stage (<24 hours). It has major toxicity and 10% mortality at higher doses (0.5-0.8 mg/kg). There is a risk of cardiogenic shock/arrhythmia and higher mortality at doses >0.8 mg/kg and in the late course (>24 hours).[3] However, the amount of drugs taken and the severity/prognosis of clinical

findings are not directly proportional. It may start with gastrointestinal (nausea, diarrhoea, etc.) symptoms and multiorgan failure and respiratory depression. Haematological changes such as severe granulocytopenia/thrombocytopenia or metabolic changes such as hypophosphatemia, hyponatremia, hypokalemia, hypocalcemia, metabolic acidosis frequently occur.[4] Patients who survive the acute phase usually recover, and after the first week, many systems improve. In our case, severe electrolyte imbalances were observed on the second day of hospitalization. Necessary replacements were made, and he was healthily transferred to the clinic without any complications.

Our patient observed nothing except for the early-stage characteristic features (diarrhoea, abdominal pain, and vomiting). There was no bone marrow suppression or elevation in liver enzymes in the follow-up. Although infectious complications are widespread in the second stage of colchicine poisoning due to neutropenia, our case did not occur.

Conclusion

Although colchicine intoxication is a fatal condition, early diagnosis and close follow-up can positively affect the prognosis. Gastrointestinal findings may not be easily recognized because their appearance may resemble other systemic diseases. Promising specific treatments such as Fab fragment antibodies may be effective but are unfortunately not commercially available.

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: ACE, MeS, MuS; Study Design: ACE, MeS, MuS; Supervision: ACE, MeS, MuS; Materials: ACE, MeS, MuS; Data Collection and/or Processing: ACE, MeS, MuS; Statistical Analysis and/or Data Interpretation: SK; Literature Review: ACE, MeS, MuS; Manuscript Preparation: ACE, MeS, MuS; Critical Review: ACE, MeS, MuS.

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Case Report

COVID-19 Presenting with Diabetic Ketoacidosis: A Case Report

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ABSTRACT

Diabetic ketoacidosis (DKA) is one of the most common fatal complications of diabetes and is often associated with severe underlying disease. The COVID-19 infection follows an intense course in patients with comorbidities such as diabetes. Herein we presented a case of diabetic ketoacidosis caused by COVID-19 infection.

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Keywords: *COVID-19, infection, diabetes mellitus, complication, diabetic ketoacidosis, treatment.*

Introduction

Diabetic ketoacidosis (DKA) is one of the most common complications of diabetes and has the highest mortality rate among hyperglycemic emergencies. Diabetes mellitus is a chronic inflammatory process, and DKA itself is considered an inflammatory condition but is often associated with severe underlying disease. Influencing infections, drug compliance, cerebrovascular accidents, and acute coronary syndromes can be considered facilitating factors for DKA. DKA has been reported in COVID-19 disease and other concomitant serious infections. The expected DKA mortality in non-COVID-19 patients with a confirmed diagnosis is approximately 3% to 8%[1], with the small case series reporting a mortality rate of up to 50% in patients with COVID-19.[2] Herein, a case of DKA caused by COVID-19 infection was discussed.

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Case Report

A 71-year-old female patient with a known diagnosis of type 2 diabetes mellitus, whose blood sugar was not regulated, was admitted to the emergency service with weakness and general condition deterioration. On physical examination, she had clouding of consciousness. There were no rales and rhonchi on auscultation of the lung sounds. On abdominal palpation no rigidity or rebound tenderness was spotted. Oxygen saturation in room air was 97%. The patient had sinus tachycardia and was prone to hypertension. Arterial blood pressure was 140/75 mmHg, heart rate was 123 bpm. There was severe metabolic acidosis with increased anion gap in the obtained venous blood gas sample. The pH was 6.8, the bicarbonate was 5 mmol/L. There was leukocytosis in the laboratory examinations on arrival. D-dimer 4.12 mg/L, blood glucose 740 mg/dL, creatinine 2.04 mg/dL, sodium 121 mmol/L, potassium 5.39 mmol/L, chlorine 88 mmol/L, C-reactive protein (CRP) 1.60 mg/dL, and hemoglobin A1c were obtained as 15.4%. In the complete urinalysis, glucose and ketone were 3+. After the patient's COVID-19 rapid antigen test was positive. Polymerase chain reaction (PCR) test was taken and it was confirmed that the patient was positive for COVID-19. The patient was not vaccinated against COVID-19. Low-dose thoracic computed tomography (CT) revealed bilateral mild ground-glass infiltrates (*Image 1*). Aggressive hydration, bicarbonate infusion and insulin infusion were started to the patient. Blood glucose, blood gases, electrolyte and kidney function tests were obtained with short intervals. During the close follow-ups, the metabolic acidosis of the patient, who was not desaturated in room air, was conscious and oriented, cooperative, and normouric, regressed, and the creatinine value decreased to 1.12 mg/dL. The patient, whose general condition and ketoacidosis improved, was followed up with COVID-19 supportive treatment and steroid treatment. Insulin infusion was stopped and quadruple subcutaneous insulin therapy was started. However, on the 9th day of the COVID-19 infection, the patient whose oxygen demand increased, was transferred to the intensive care unit and intubated (*Image 2*). The patient, who was intubated for 23 days, was then transferred to the internal medicine ward and was discharged 52 days after her first hospitalization, due to her general condition improving.

Discussion

Patients with diabetes mellitus are at risk for serious COVID-19 complications. DKA can also be counted as one of these complications. Since it was seen in previous studies that COVID-19 may present with DKA as the first symptom, it should be considered that COVID-19 may cause DKA even in patients who have not been diagnosed with diabetes before. Among DKA admissions during

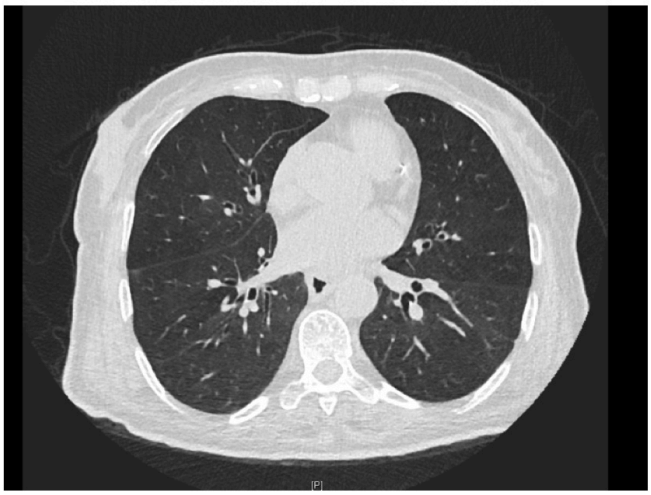

Image 1. Low dose thoracic CT, dated 28.09.2022.

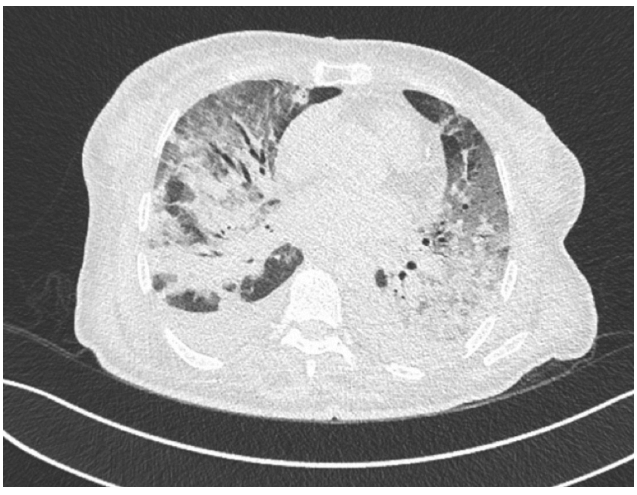

Image 2. Low dose thoracic CT prior to intubation, dated 05.10.2022.

the first wave, 12% had a diagnosis of COVID-19. 6% of admissions with type 1 diabetes, 23% with type 2 diabetes, and 7% with newly diagnosed diabetes had concurrent COVID-19.[3] SARS-CoV-2 infects the pancreas through angiotensin-converting enzyme 2 (ACE2), where it is highly expressed compared to other organs, leading to pancreatic damage with subsequent impairment of insulin secretion and development of hyperglycemia even in non-diabetic patients.[4] Data obtained underline that SARS-CoV-2 infection in diabetic patients is more severe and associated with poor clinical outcomes due to preexistence of comorbidities and inflammation disorders. SARS-CoV-2 infection impairs glucose homeostasis and metabolism in diabetic and non-diabetic patients due to cytokine storm (CS) development, downregulation of ACE2, and direct injury of pancreatic β-cells.[4] SARS-CoV-2 infection leads to dysregulation of insulin homeostasis, induction of apoptosis-associated signaling pathways, along with cell apoptosis, mainly in β-cells. These key observations support a mechanism through which SARS-CoV-2 can directly drive β-cell damage to cause clinical type 1 diabetes linked to hyperglycemia.[5] These factors are thought to have a role in the worsening of pancreatic beta cell function and the emergence of DKA in our patient.

Corticosteroids used in the management of COVID-19 infection aggravate hyperglycemia, complicating glycemic control in DKA. In our patient, 250 milligrams of methylprednisolone was started during the course of COVID-19, which resulted in the patient becoming hyperglycemic again and DKA redeveloping. Therefore, close follow-up with frequent blood gas control should be provided in patients whom glycemic control can not be achieved. Cases of COVID-19 presenting with DKA is rare in the literature and its pathogenesis has not been fully elucidated. In this case, we wanted to draw attention to the fact that COVID-19 may present with DKA.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: IBG, SEY; Study Design: IBG, SEY; Supervision: YO, IBG; Materials: BO, YO; Data Collection and/or Processing: BO, YO; Statistical Analysis and/or Data Interpretation: IBG, SEY; Literature Review: BO, YO; Manuscript Preparation: SEY, IBG; Critical Review: BO, YO.

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Case Report

Ground Glass Appearance During the Pandemic Period: Everolimus Induced Interstitial Pneumonia

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ABSTRACT

Ground glass appearance is a nonspecific finding that can see in diseases such as chronic interstitial disease, acute alveolar disease or infection; however, it is most commonly encountered in COVID-19 pulmonary involvement today. The mammalian target of rapamycin (mTOR) plays a regulatory role in cell proliferation and growth. Everolimus is an allosteric mTOR inhibitor used in ER+ breast cancers and inhibits the mTOR functional complex. Here, we present a case of interstitial pneumonia due to everolimus, which can be confused with COVID-19 pneumonia due to its ground-glass appearance during the pandemic period.

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Keywords: *Everolimus, mTOR, ground glass, interstitial pneumonia, COVID-19, breast cancer.*

Introduction

Interstitial lung diseases (ILD) are diseases that include many non-infectious diseases affecting the lung parenchyma. Etiologically, ILD is divided into nine main groups: idiopathic interstitial pneumonia, connective tissue disease, smoking-related, vasculitis, granulomatous disease, environmental/occupational, drug-induced, hereditary, and other causes.[1] In drug-induced interstitial pneumonia, the drug causes inflammation in the lung interstitium, resulting in fibrosis in the lung.

Ground glass appearance is a nonspecific finding that can see in COVID-19 lung involvement (which we see most today), pulmonary oedema, aspiration, *Pneumocystis jirovecii* pneumonia, nonspecific interstitial pneumonia, alveolar haemorrhage, and drug-related lung toxicity.[2] Dominant computed tomography (CT) findings in COVID-19 pneumonia include ground-glass opacification, consolidation, bilateral involvement, peripheral and diffuse distribution.[3] Herein, we wanted to present one of the etiologies that can be confused with the ground glass appearance, one of the radiological findings of COVID-19 pneumonia.

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Case Report

A 48-year-old female patient who received hormonal therapy and chemotherapy due to breast cancer and bone metastasis was admitted to the emergency room with low saturation, dyspnea, and worsening general condition. The patient had fever, cough and sputum. On the physical examination, her general condition was good. She was conscious, oriented, and cooperative. On the lung auscultation, basal and midline fine rales were present. There were no tenderness, rigidity or rebound in the abdominal examination. Oxygen saturation was 97% with 3 L/min oxygen support from the nasal cannula and 85% at rest in room air. The patient was started on teicoplanin and ciprofloxacin as antibiotic therapy. Lung computerized tomography (CT) on 23.06.2021 has been reported as "In addition to the COVID-19 sequelae identified in the examination on 12.06.2021 (*Image 1*), ground-glass consolidations in the lung parenchyma from the apex to the basal and vascular-bronchial clarifications in these areas are compatible with the second COVID-19 infection and active inflammation and it appears to be progressive compared to the examination on 12.06.2021." (*Image 2*). The patient was previously treated with a diagnosis of lung CT positive COVID-19 pneumonia. However, all of the patient's COVID-19 polymerase chain reaction (PCR) test results were negative. On 24.06.2021, the SARS-CoV-2 antibody test and PCR test were negative, and we excluded the diagnosis of COVID-19 from the patient. She had been using everolimus for the past four months. The reason for the ground-glass appearance in low-dose thoracic CT was thought to be related to interstitial pneumonia. We evaluated the patient with the oncology department and considered having interstitial pneumonia due to everolimus. Interstitial lung involvement, occasional pneumonic consolidation, ground-glass appearances and hyperaeration findings suggested bronchiolitis and interstitial pneumonia in the patient after consultation with chest diseases. Bronchoscopy, transbronchial biopsy or bronchoalveolar lavage were recommended to the patient to distinguish between agents and pathogens and to determine whether there was a drug lung or not. The patient refused. In the other tests, CMV IgM was negative and IgG positive. Candida beta-glucan antigen was negative. Aspergillus Galactomannan antigen

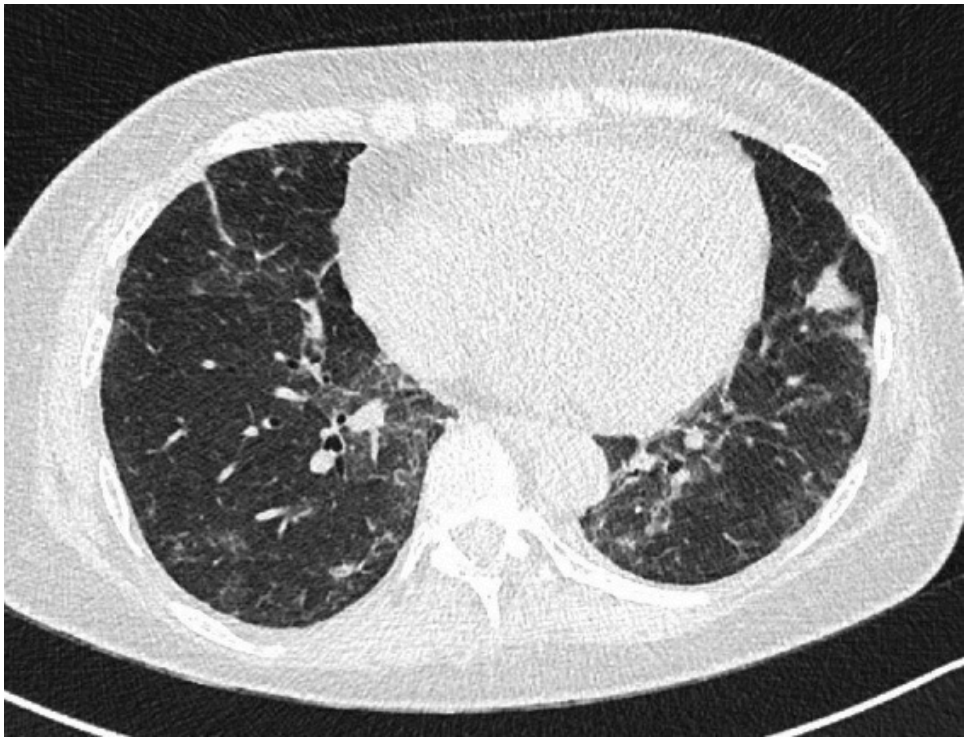

Image 1. Consolidation areas with ground glass appearance considered as a previous COVID-19 infection.

was negative. We started the patient with 100 mg of methylprednisolone and warned her not to use everolimus. On the 4th day of the patient's use of 100 mg methylprednisolone, the patient's room air saturation was 91%, and there were no rales or rhonchi on lung auscultation. The patient's admission CRP value was 33.05 mg/dL and decreased significantly after starting methylprednisolone. It was 1.31 mg/dL at the patient's discharge. The patient was ordered 100 mg of prednol for seven days on hospitalization. The patient showed significant improvement and did not get desaturated at room air and was discharged with the recommendation to continue using 32 mg methylprednisolone for 15 days at home.

Discussion

There are two mechanisms in drug-induced interstitial pneumonia; direct or dose-related toxicity and the other is an immune-mediated mechanism.[4] Mammalian target of rapamycin (mTOR) stimulates cellular anabolism and affects macromolecule formation with many mechanisms such as nucleic acid, protein, lipid production, ribosome biogenesis and protein translation. mTOR also inhibits catabolic processes such as lysosome biogenesis and autophagy. mTOR integrates anabolic processes induced by environmental stimuli by modulating metabolic pathways for cell proliferation, growth and metabolism.[5] mTOR is often downregulated in cancer, and activating somatic mutations of mTOR have recently been identified in several cancer types, thus making mTOR a therapeutic target. mTOR inhibitors have previously been widely used as immunosuppressants and are now approved to treat malignancies.[5] Everolimus inhibits mTOR functional complex 1 as an allosteric mTOR inhibitor used in ER+ breast cancers.[6]

Diagnosing interstitial pneumonia can be challenging for clinicians because the diagnosis is a diagnosis of exclusion. An analysis of data from three extensive controlled clinical studies of everolimus used in solid organ transplantation in one study found the incidence of everolimus induced interstitial lung disease to be 0.4%. (6 patients out of 1473). The onset of symptoms after patients started using everolimus was highly variable in these three studies, similar to the cases described in literature reviews. This period varies between 4 weeks and 15 months.[7]

The patient was diagnosed with everolimus-induced interstitial pneumonia because we excluded infectious causes. The patient's clinical status improved with steroid therapy, and the radiological and clinical findings were consistent with drug-induced pneumonitis. It is essential to consider other etiologies in the differential diagnosis, especially during the pandemic period, as the ground glass appearance leads clinicians to diagnose COVID-19.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

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Case Report

Drug Eruptions with Cases: Fixed Drug Eruption and Dress Syndrome

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ABSTRACT

Cutaneous drug reactions usually occur with mild and self-limiting lesions, but severe forms can be life-threatening. Non-steroidal anti-inflammatory drugs, antibiotics, and anticonvulsants often cause drug reactions. Herein, we presented two cases of immunological drug reaction, one with mild and localized fixed drug eruption and the other with more severe and diffuse DRESS syndrome.

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Keywords: *Drug eruptions, skin, drug-related side effects, adverse reactions.*

Introduction

Adverse drug reactions are undesirable side effects of routinely used or newly started drugs and are most common in the skin. Cutaneous drug reactions (CDR) are common and usually occur with mild and self-limiting lesions, and some of its severe forms can be life-threatening.[1,2] CDR may occur due to non-immunological (90-95%) and immunological (5-10%) mechanisms. Examples of non-immunological drug reactions are pharmacological side effects, drug-drug interactions, and drug toxicity. Immunological drug reactions are mainly divided into four types: Type 1 (IgE-mediated), Type 2 (cytotoxic), Type 3 (immune complex-mediated), and Type 4 (delayed-type/cell-mediated reactions).[3] However, some unclassifiable, immunological skin reactions include maculopapular skin rashes with specific T cell reactivation, fixed drug eruption, and specific drug-associated hypersensitivity syndromes.[4,5] Risk factors for non-immune drug reactions are female gender, renal impairment, liver disease, severe comorbidity, polypharmacy, HIV infection, herpes infection, systemic lupus erythematosus and alcoholism. Risk factors for immunological skin reactions are female gender, being an adult, HIV infection, history of drug hypersensitivity, asthma, beta-blocker use, concurrent viral infection, systemic lupus erythematosus.[6]

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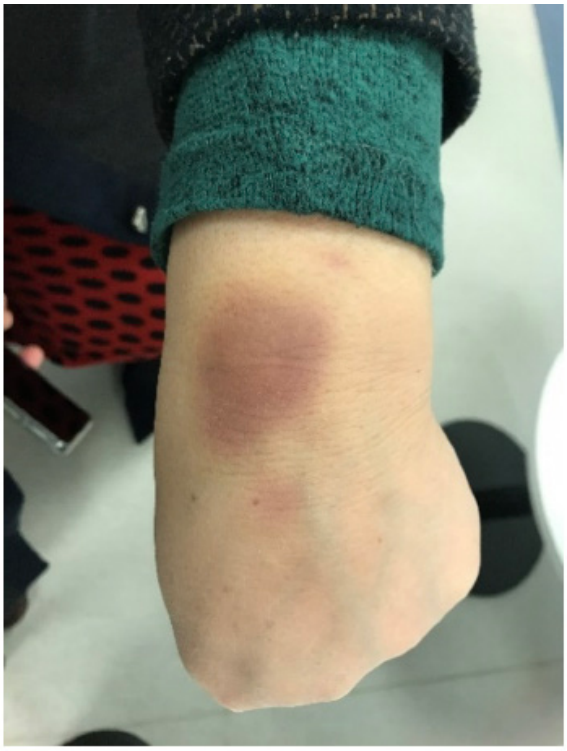
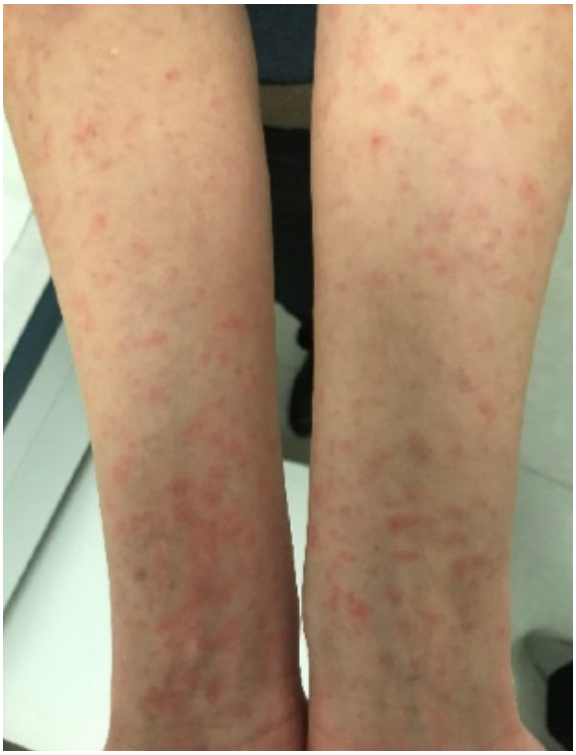
Physicians of all branches should be familiar with cutaneous drug reactions for early diagnosis and treatment since they may encounter it frequently in their daily practice.[5] There are nearly 30 skin-drug reactions, and the most common forms are exanthematous drug eruptions and urticarial.[6,7] Fatal skin reactions with skin detachment or necrosis on large areas of the body include Steven-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and drug rash with eosinophilia and systemic symptoms syndrome (DRESS).[6] The drug groups to often cause drug reactions for the skin are non-steroidal anti-inflammatory drugs, antibiotics and anticonvulsants.[8] Herein, we presented two cases of immunological drug reaction, one with mild and localized fixed drug eruption and the other with more severe and diffuse DRESS syndrome.

Case Report

The first case was a 56-year-old female patient diagnosed with ankylosing spondylitis and was receiving 40 mg of adalimumab every two weeks for three years. She stated that she was using diclofenac sodium 50 mg oral tablets and sometimes intramuscular injections of diclofenac sodium and thiocolchicoside due to the joint pain she experienced from time to time over the past year. Neither she uses other drugs, nor does she smoke. The patient applied to the dermatology outpatient clinic with a sharply defined, hyperpigmented macular-looking lesion on the dorsal aspect of the left hand (*Picture 1*). The patient stated that similar lesions had appeared in the same area from time to time in the last year. When it first appeared, it was a more vivid purple colour. The colour of the lesions became brownish over time and was accompanied by complaints such as itching and burning. The blood tests of the patient were no pathological findings. We diagnosed the patient with fixed drug eruption due to a history of diclofenac sodium drug use and lesion characteristics. We discontinued the suspected diclofenac sodium drug and gave topical corticosteroid treatment.



Picture 1. Hyperpigmented macular lesion of the dorsal left hand of the patient developing a fixed drug eruption.



Picture 2. Erythematous maculopapular lesions are seen on the inner sides of the bilateral forearms and throughout the body of the patient with DRESS Syndrome.

The second case, a 35-year-old female patient, started treatment of carbamazepine 400 mg/day with the diagnosis of epilepsy one month ago, and the patient did not have an additional disease or a history of any other drug use. The patient applied to the hospital with the complaint of a widespread erythematous maculopapular rash on the body (*Picture 2*) and itching, which started three days ago and is becoming increasingly severe. The patient had a fever reaching 38 °C from time to time, and in her dermatological examination, there were no findings in the oral and genital mucosa. She had bilateral cervical lymphadenopathy in lymph node examination. The laboratory evaluation revealed a more than ten-fold increase in liver function tests (AST: 313 U/L, ALT: 624 U/L, ALP: 291 U/L, GGT: 261 U/L). We diagnosed the patient with DRESS syndrome with clinical and laboratory findings, discontinued the carbamazepine drug, and replaced it with 1,000 mg/day levetiracetam. She was hospitalized for systemic steroid treatment and further examination in the dermatology service.

Discussion

Fixed drug eruptions are common cutaneous drug reactions with recurrent characteristic lesions on the same areas of the skin or mucosa after repeated administration of the causative drug. Among the drug groups, antibiotics (trimethoprim-sulfamethoxazole, tetracycline, penicillin, erythromycin) are first, and non-steroidal anti-inflammatory drugs (diclofenac sodium, aspirin, naproxen, ibuprofen) are in the second place of cause.[9,10] Acute lesions can be seen usually 30 minutes to 8 hours after ingestion of the causative drug. However, this period can last up to 2 weeks.[11,12] In the first case, diclofenac sodium was the causative drug for fixed drug eruption. Fixed drug eruptions can usually be seen characteristically in the same region after drug intake. They may also observe in different body parts with repeated drug doses. Lesions are often sharply delimited by round or oval, itchy, erythematous plaques that may sometimes turn dark purple and sometimes become vesiculobullous.[9] The most common site of involvement for men is the genital area, and for women, it is the extremities.[11] In this case, the location of the observed itchy lesion, which has a more vivid purple colour at first and becomes a paler plaque over time, was the dorsal aspect of the hand.

DRESS syndrome is a drug-associated hypersensitivity reaction that may be accompanied by haematological abnormalities such as generalized mucocutaneous rash, fever, lymphadenopathy, hepatitis, eosinophilia, leukocytosis or atypical lymphocyte, and sometimes with eosinophilic infiltration, especially kidney, heart, lung and pancreas organ involvement.[13] The aetiology role played by the drugs used between 3 weeks and three months is a picture that differs from other cutaneous drug reactions with multiorgan involvement.[13] The drug groups that most often cause DRESS syndrome include anticonvulsants (carbamazepine, phenytoin, lamotrigine, phenobarbital), allopurinol and antibacterials.[14] Scoring criteria established by the RegiSCAR (registry of severe cutaneous adverse reactions) group are often used to confirm or exclude a diagnosis of DRESS syndrome.[15,16] The patient also used carbamazepine as a suspected agent. 6 out of 7 potential DRESS cases determined by the RegiSCAR group were seen for the case. When evaluated with advanced diagnostic criteria, it was considered a possible DRESS case with a rate of 3/9. Haematological abnormalities such as eosinophilia are not always seen in DRESS cases at diagnosis but may develop over time.[14,16] Hematological abnormalities were not observed at the diagnosis for that case.

As a result, physicians of all branches should be familiar with cutaneous drug reactions that they may frequently encounter in their daily practice for early diagnosis and treatment. When cutaneous drug reactions are suspected, it is necessary to approach the patient holistically and systematically. First of all, the characteristic of the primary lesion should be identified, and its distribution determined. All prescription/nonprescription drugs used by the patient in the last three months should be questioned. The patient should be evaluated regarding mucosal involvement, fever, lymphadenopathy, and internal organ involvement. In all CDRs, it is essential to discontinue the known/suspected agent at the first stage. In the presence of a severe cutaneous

drug reaction, immediate referral to an advanced centre or consultation with the relevant branch is required.

Acknowledgment

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Case Report

A Rare Cause of Anemia Aetiology: Gastrointestinal Stromal Tumours

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ABSTRACT

Gastrointestinal stromal tumours (GIST) are rare neoplasms originating from the interstitial cajal cell in the gastrointestinal tract. Herein, we presented a 51-year-old male patient with GIST which we investigated the aetiology of iron deficiency anaemia and found the tumour.

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Keywords: *: Gastrointestinal stromal tumors, iron deficiency anemia, small bowel disease.*

Introduction

Gastrointestinal stromal tumours (GIST) constitute 1-2% of gastrointestinal system tumours.[1] The predominant localization of GISTs seems to be the stomach and small intestine, but GISTs may develop any level of the gastrointestinal tract and sometimes in the omentum, mesentery, and peritoneum. In our case, iron deficiency anaemia associated with GIST was considered suitable for the presentation because of its rare occurrence.

Case Report

A 51-year-old male patient was evaluated by abdominal ultrasonography at an external centre eight months ago with pain in the right upper abdomen. The patient with cholelithiasis had a laparoscopic cholecystectomy operation. The patient was re-evaluated in another centre with complaints of weakness, fatigue, swelling in the right upper abdomen and weight loss of 12 kg in the last six months. Because of iron deficiency anaemia, he received iron treatment after transfusion of 2 units of erythrocyte suspension. Upper gastrointestinal system endoscopy and colonoscopy had no abnormal findings. The non-contrast abdominal CT revealed duodenal wall thickening. His complaints continued to increase. In the patient's physical examination, the vital signs were unremarkable. His conjunctiva was pale, and there was fullness in the epigastric region. The haemoglobin value was 7.5 mg/dL, consistent with iron deficiency anaemia. MR enterography investigated small bowel diseases because the patient's endoscopic evaluations were normal. A

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mass lesion of approximately 13.5x15.5x16 cm in size at the level of the 3-4th part of the duodenum was detected. The mass had a connection with the intestinal lumen and was monitored for air and fluid levels in its central unit. Contrast-enhanced abdominal CT showed diffuse wall thickening in a 14 cm segment in the distal part of the duodenum. An exophytic mass, approximately 14x8 cm, was observed with cavitation in the centre. Combined MR and CT evaluations reported that the mass lesion described was consistent with GIST, a malignant mass. We referred the patient to the general surgery department. Biopsy was taken from the mass during the operation, and pathological examination resulted in a high-grade malignant mesenchymal tumour. Morphological and immunohistochemical findings were interpreted as compatible with GIST. We referred the patient to the oncology department, and they started imatinib treatment as preoperative chemotherapy.

Discussion

18% of cases are asymptomatic and diagnosed during CT scans, endoscopic procedures or surgical procedures.[2] GISTs can be identified on ultrasound examination of the abdomen, computerized tomography (CT) scanning, magnetic resonance imaging (MRI), and positron emission tomography (PET). The definitive diagnosis of GIST is made by histopathological examination and immunochemistry.

Symptoms such as nausea, vomiting, early satiety, abdominal pain, and rarely a palpable mass can be seen in GIST cases. The most common clinical finding is gastrointestinal bleeding resulting from mucosal ulceration.[3,4] Chronic bleeding can lead to anaemia. In patients with iron deficiency anaemia, the underlying gastrointestinal system losses should be investigated.

Treatment of GIST includes surgery, endoscopic therapy, and chemotherapy. Standard endoscopic procedures do not mean that there is no gastrointestinal disease. Other small bowel diseases such as GIST, which are rare, should also be investigated.

Acknowledgment

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: HS; Study Design: HS; Supervision: HS, AK; Materials: HS, EB, TD; Data Collection and/or Processing: SHA; Statistical Analysis and/or Data Interpretation: HS, AK; Literature Review: HS, AK; Manuscript Preparation: HS; Critical Review: HS.

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Case Report

A Finding That Is Not Clear What Will Emerge When You See It: Hypoalbuminemia

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ABSTRACT

Malnutrition can cause hypoalbuminemia. Gastrointestinal malignancies are among the causes of protein-losing enteropathy. Herein, we presented a case of protein-losing enteropathy due to gastrointestinal malignancy presenting with symptoms such as hypoalbuminemia and oedema in the hands and legs.

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Keywords: *Malnutrition, hypoalbuminemia, oedema, protein-losing enteropathy, gastrointestinal malignancy.*

Introduction

Hypoalbuminemia can occur for many different reasons, such as chronic kidney damage, nephrotic syndrome, chronic liver diseases, malnutrition, and dermatological losses. Gastroscopy, colonoscopy, and in some cases, enteroscopy can be used to demonstrate that protein loss originates from the gastrointestinal system. Protein-losing enteropathy can be caused by inflammatory bowel disease due to mucosal surface damage, gastrointestinal malignancies, lymphoma, erosive gastritis, multiple ulcerations, primary intestinal lymphangiectasia due to lymphatic obstruction, and many multisystemic causes.[1] Gastrointestinal malignancy, which generally presents with bleeding, obstruction, and changes in defecation habits, may rarely present with symptoms related to hypoalbuminemia.[2] Herein, we presented a case of protein-losing enteropathy due to gastrointestinal malignancy presenting with symptoms such as hypoalbuminemia and oedema in the hands and legs.

Case Report

A 67-year-old male patient with no known history of chronic disease had come to the emergency department with an increase in swelling in both legs that had increased, soft, pitting oedema for the last

week. He applied with the complaint of swelling in both hands and legs. In laboratory examinations of the patient, albumin level was 19.7 g/L, hemoglobin 10 g/dL, MCV 82 fL, leukocyte 4.5 K/uL, platelet 220 K/uL, creatinine

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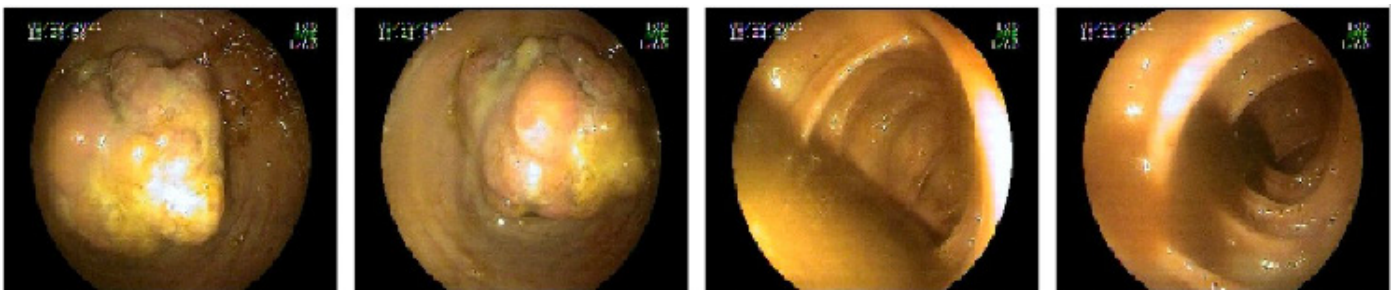
0.9 mg/dL, AST 12 IU/L, ALT 15 IU/L, and total protein 4.25 g/L. The patient had a history of colonoscopy due to dyspepsia two months ago, colonoscopy was found to be normal, and pangastritis was present in the gastroscopy. The patient was admitted to our internal medicine clinic for a hypoalbuminemia examination. The patient's echocardiography was normal (EF: 60, no valve pathology, right insufficiency and diastolic dysfunction). Bilaterally leg lower extremity venous doppler ultrasonography for oedema of both legs showed acute deep vein thrombosis in both legs. We started low molecular weight heparin at the treatment dose. Abdominal ultrasonography and abdominal tomography were unremarkable. Liver function tests requested for the possible liver disease were normal ranges. Albumin loss was not dependent on renal causes, but urea and creatinine levels were normal (urea: 32 mg/dL, creatinine 0.73 mg/dL), urinary ultrasonography was unremarkable, and 24-hour urine protein level was 0.03 mg/day.

There were no malnutrition findings in our research on malnutrition, which may be the cause of hypoalbuminemia. In evaluating the patient's malnutrition, the Nutritional Risk Screening had a low risk (as 0) in 2002. In the gastrointestinal system screening that the patient's current protein loss may be from the gastrointestinal tract, contrast-enhanced abdominal tomography showed diffuse asymmetrical wall thickness increase in a segment of approximately 12 cm extending from the hepatic flexure to the mid-right half of the transverse colon. Then the patient underwent colonoscopy. Colonoscopy revealed an ulcerovegetant mass in the transverse colon that almost completely occluded the lumen (*Picture 1*). The biopsy was taken from the patient resulted in colon adenocarcinoma. Since there was no distant metastasis in the PET-CT taken later, we transferred the patient to the general surgery service for operation.

Discussion

Hypoalbuminemia is an essential clinical condition that needs to be examined from a detective perspective. In this case, who underwent colonoscopy two months ago, systematically reviewing the causes of hypoalbuminemia and excluding other reasons, and advocating the idea that the case was of gastrointestinal origin, led to the renewal of the colon screening the patient and the early detection of malignancy. Although there was another aetiology such as deep vein thrombosis that could cause peripheral oedema, examination of hypoalbuminemia also helped for the accurate diagnosis of malignancy in the patient. The pathophysiology of protein-losing enteropathy is the loss of plasma proteins entering the gastrointestinal lumen. Protein-losing enteropathy may result from lymphatic obstruction or mucosal damage. It can develop as primary or secondary.[3] In acute situations, albumin infusion can increase the oncotic plasma pressure. In some cases, the use of corticosteroids or heparin may be required.

In conclusion, although there are gastrointestinal and cardiac diseases in the aetiology of protein-losing enteropathy, it can be seen as a rare complication of many diseases. Clinically, hypoalbuminemia, low total protein, diarrhoea, and weight loss can be seen. The most important approach to consider in a case of suspected protein-losing enteropathy is the exclusion of hepatic and renal causes.[4] Although its prognosis is not known precisely, it is crucial to correct the underlying pathology.[5]



Picture 1. Colonoscopy revealed an ulcerovegetant mass in the transverse colon that almost completely occluded the lumen.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

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Authors' Contribution

Study Conception: ES; Study Design: ES; Supervision: MVK; Materials: MVK; Data Collection and/or Processing: MVK; Statistical Analysis and/or Data Interpretation: EI; Literature Review: EI; Manuscript Preparation: EI; Critical Review: ES.

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Indomethacin Induced Toxic Hepatitis: A Case Report

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ABSTRACT

Nonsteroidal anti-inflammatory drugs deare widely used worldwide for analgesic, antipyretic and anti-inflammatory purposes. Indomethacin is a potent nonsteroidal anti-inflammatory drug and can cause severe liver damage. Few cases of idiosyncratic toxic hepatitis have been reported. Here, we present a case of indomethacin-induced toxic hepatitis that improved with methylprednisolone treatment.

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Keywords: *Nonsteroidal anti-inflammatory drugs, adverse effect, indomethacin, liver damage, idiosyncratic toxic hepatitis, methylprednisolone treatment.*

Introduction

Indomethacin is a potent nonsteroidal anti-inflammatory drug typically used for chronic inflammatory arthritis.[1] Fewer than a dozen cases of indomethacin related toxic hepatitis have been reported in the literatüre.[2-7] In this report, we discussed a case of indomethacin related toxic hepatitis, which recovered with palliative care and methylprednisolone treatment.

Case Report

A 23-year-old female patient, who had been well except for a history of hypothyroidism and levothyroxine 100 mcg/day use for 14 years, was referred to our centre with jaundice, dark urine, pale stool and itching. Due to low back pain, the patient received 25 mg/day for five days. The patient was admitted to the clinic to investigate the aetiology. The patient had liver damage in the hepatocellular pattern (R index: 11.5). The course of laboratory values was shown in Table 1.

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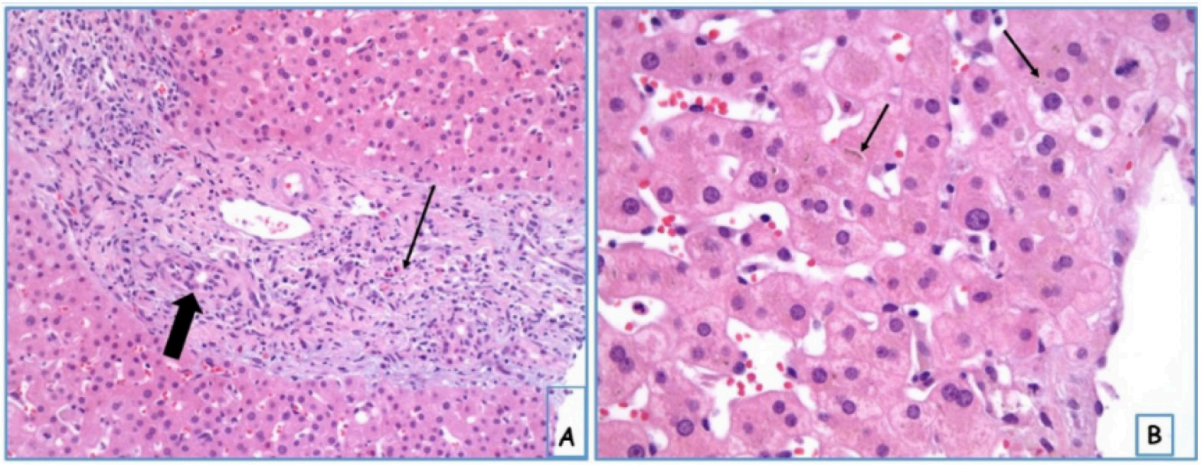
Table 1. The course of the patient's laboratory values.

Time after the onset of indomethacin	Event	AST (U/L)	ALT (U/L)	Bilirubin (mg/dL)	ALP (U/L)	GGT (U/L)	INR	Albumin (g/L)
Day 5		79	237	5.78	-	-	0.9	-
Day 10		86	230	7.69	-	67	1	47
Day 14		208	336	10.25	-	48	1	45
Day 18	Liver biopsy Methylprednisolone 1 mg/kg	296	473	9.86	220	45	1.1	42
Day 21		923	1,571	10.12	208	43	1	42
Day 24		1,533	3,019	7.54	180	68	1	44
Day 28		681	2.695	4.44	184	176	0.95	48
Day 38	Methylprednisolone 0.75 mg/kg	162	1.027	2.33	130	297	0.97	48
Day 48		88	358	1.48	109	305	0.9	47
Day 60	Methylprednisolone 0.5 mg/kg	64	157	0.6	82	250	1	47
Day 75		44	103	0.47	78	200	1	49
Day 90		34	55	0.67	84	113	1.1	45
Day 100	Discontinuation of methylprednisolone	33	49	0.41	83	83	0.94	44
Day 120		22	27	0.47	74	61	1	49

AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, INR: the international normalized ratio.

There was no alcohol or herbal medicine use and mushroom eating in the patient's history. Hepatitis A, B, C, and E, Epstein-Barr IgM, cytomegalovirus IgM, herpes simplex virus IgM and brucella agglutination tests were negative. Ceruloplasmin, 24-hour urine copper, ferritin, transferrin saturation and alpha-1-antitrypsin, IgM and IgG levels were within normal ranges. Kayser-Fleischer ring was not found in the ophthalmic examination. ANA, AMA, ASMA, LC-1, SLA/LP, LKM-1, c-ANCA, p-ANCA, PR3, MPO were negative. Anti-tissue transglutaminase IgA was negative. Abdominal ultrasonographic imaging revealed normal liver parenchyma and echogenicity. The bile ducts and gall bladder were normal.

Drug-induced toxic hepatitis was considered due to the emergence of hepatitis in the patient after taking the drug. There was no liver transplantation indication according to King's College criteria[8] in the patient who did not have an elevated INR and did not develop encephalopathy. The RUCAM (Roussel Uclaf Causality Assessment Method) score was calculated as fifteen.[9] A liver biopsy was performed. The biopsy result (*Picture 1*) was compatible with toxic cholangiopathy or hepatitis, and we started methylprednisolone 1x60 mg/day. The patient, who was followed up in the clinic for ten days, was discharged because there was no prolongation in the INR value and no development of encephalopathy. The patient's INR did not increase in the outpatient clinic controls, and bilirubin and transaminase levels returned normal. The methylprednisolone treatment was tapered and discontinued within three months.



Picture 1. Morphological evaluation of liver biopsy material; A: enlargement in the portal area, mixed inflammatory infiltration containing polymorphic nuclei and eosinophil leukocytes (thin arrow) and degenerative changes in bile duct epithelial cells (thick arrow) (HEx200), B: hepatocanalicular bilirubinocytosis (thin arrow) in the lobular area and hydropic degeneration of hepatocytes (HEx200).

Discussion

Toxic hepatitis is a disease that often occurs due to drugs and herbal substances. It encompasses a broad spectrum of clinical illnesses ranging from mild biochemical abnormalities to acute liver failure.[10] Mild and transient elevations in serum aminotransferase levels are found in up to 15% of patients taking indomethacin. Frank liver injury with jaundice from indomethacin is rare. The latency to onset symptoms or jaundice is variable but is usually within eight weeks of starting. Patients present with anorexia, nausea and vomiting followed by jaundice. Hepatocellular patterns of enzyme elevations are most common, but cholestatic and mixed patterns have been reported. The injury is usually self-limited, resolving in 1 to 3 months, but several fatal cases have been reported. Rechallenge may lead to recurrence and should be avoided.[11] Serum bilirubin values two times higher than normal and aminotransferases three times higher than normal are associated with poor prognosis.[12-14] Studies show that corticosteroid therapy may be beneficial.[15]

In the case presented, there was liver damage in the hepatocellular pattern. Her symptoms started one week after starting the drug. With the discontinuation of the drug and corticosteroid therapy, the patient's liver enzymes returned to normal within two months. Although indomethacin is known to cause liver damage, severe damage is rare. Therefore, in patients using indomethacin; If symptoms such as jaundice and dark urine colour develop, drug-related toxic hepatitis should be considered.

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Conflict of interest

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Authors' Contribution

Study Conception: OS, TT, SGN, NU; Study Design: OS, TT, SGN, NU; Supervision: OS, TT, SGN, NU; Materials: OS, TT, SGN, NU; Data Collection and/or Processing: OS, TT, SGN, NU; Statistical Analysis and/or Data Interpretation: OS, TT, SGN, NU; Literature Review: OS, TT, SGN; Manuscript Preparation: OS, TT, SGN, ; Critical Review: OS, TT, SGN.

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Juvenile Idiopathic Arthritis Complicated with Atlantoaxial Subluxation: A Case Report

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ABSTRACT

Juvenile idiopathic arthritis is a rheumatological disease that starts before 16 years and involves joints. Many complications such as bone erosions and joint destruction can be seen in the course of the disease. Herein, we presented a case of juvenile idiopathic arthritis complicated by atlantoaxial subluxation followed for 14 years.

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Keywords: *Juvenile idiopathic arthritis, arthritis, bone, complication, atlantoaxial subluxation.*

Introduction

Juvenile idiopathic arthritis (JIA) is a disease that onsets before the age of 16, and manifestations persist for at least six weeks, cannot be explained by any other reason, and can progress with uveitis and arthritis involving one or more joints. It is known that rheumatoid factor (RF) and antinuclear antibody (ANA) positivity can occur, and genetic predisposition (HLA-B27 or HLA-DR4) can be detected. JIA is further categorized as Systemic JIA, oligoarticular JIA (which can be persistent or extended), RF negative polyarticular, RF positive polyarticular, enthesitis-related, psoriatic arthritis, undifferentiated (none of which can be classified or characterized by more than one group) JIA.[1] Bone erosions and joint destruction, osteopenia and osteoporosis, temporomandibular joint (TMJ) anomalies, mobility problems due to contractures, and ocular complications such as anterior uveitis can be seen in the course of JIA. We aimed to present our case diagnosed in pediatric rheumatology and followed up in adult rheumatology, which was complicated by atlantoaxial subluxation.

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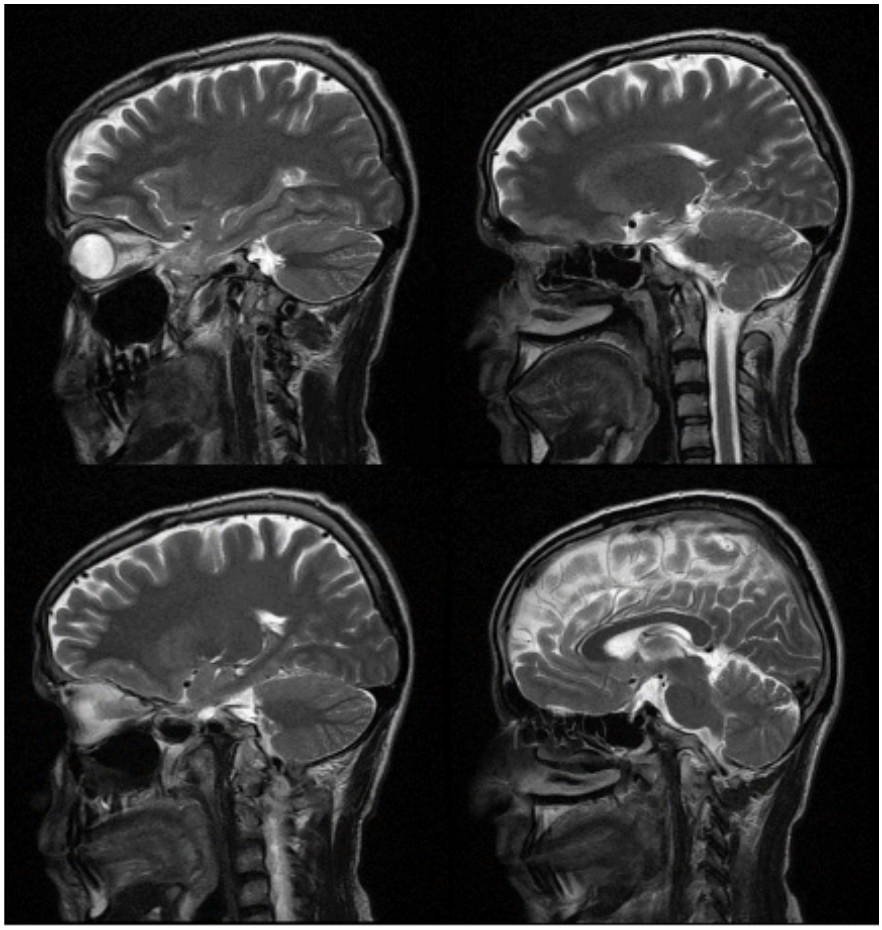

Picture 1. The cranial MR sections showed a ''4.9 mm displacement of C2 vertebra odontoid process towards the cranial, in sections passing through the skull base level (basilar invagination). Both cavernous segments are mildly dolichoectatic."

Case Report

A 25-year-old male patient, who had been followed up with the diagnosis of JIA for 14 years, described a complaint of dizziness during the control of the adult rheumatology outpatient clinic. The foreign national patient, who was diagnosed with JIA and given steroid, methotrexate and nonsteroidal anti-inflammatory drug (NSAID) treatment after being examined in his home country with a complaint of swelling in the knee and foot joints when he was 11 years old, was transferred to us by pediatric rheumatology at the age of 19. In the examinations performed in pediatric rheumatology, HLA B27 (+) and FMF gene test M694V and E148Q were found as (+). The patient, whose treatment was planned as an anti-TNF agent, had a history of irregular drug use due to social reasons. The patient had significant mobility restrictions. Findings of arthrosis were observed in both knees and hip joints. After the transfer to us, the patient, who was evaluated in the rheumatology council, was referred to orthopaedics because of arthrosis in both hip joints. Anti-TNF was planned to be started, and he was followed up. In the systemic and neurological examination of the patient who had been using etanercept for five years, no features were found except that he had 2/5 paraparesis (joint movements were completely limited due to bilateral frozen hip). Cranial magnetic magnetic resonance imaging (MRI) was performed on the patient. The MRI showed a ''4.9 mm displacement of C2 vertebra odontoid process towards the cranial, in sections passing through

the skull base level (basilar invagination). Both cavernous segments were mildly dolichoectatic." (*Picture 1*). The patient was consulted to the neurosurgery department with the preliminary diagnosis of atlantoaxial subluxation. Surgical intervention was not considered for the patient who had no neurological symptoms, and control was recommended six months later. The patient was followed up in our outpatient clinic with anti-TNF therapy, and periodic neurosurgery control was recommended for atlantoaxial subluxation.

Discussion

Cervical joint destruction in patients with rheumatoid arthritis (RA) and JIA may lead to vertebral malalignment (e.g., subluxation), causing pain, neurologic deficit, and deformity.[2-4] In one series, 159 consecutive patients with juvenile chronic arthritis had cervical spine radiographs taken at age 18.[5] In 62 per cent, some changes were noted, including 41 per cent with apophyseal ankylosis and 17 per cent with anterior atlantoaxial subluxation and 25 per cent with atlantoaxial impaction. In another study in one centre, all consecutive patients with JIA were followed into a transition program, and cervical spine radiographs were performed.[6] Of the 57 JIA patients, 65 per cent showed cervical spine lesions, and half had no symptoms.

In conclusion, it should not be forgotten that imaging patients can detect atlantoaxial subluxation findings without symptoms. The young age of the patients is essential in terms of being careful before the surgical procedures that may take place. Although routine imaging is not required in asymptomatic patients, cervical spine imaging is recommended before elective surgery that will require neck manipulation.

Acknowledgment

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: YC, BNC; Study Design: YC, BNC; Supervision: YC, BNC, ED, YP, NL, ZYB; Materials: YC, BNC, AE; Data Collection and/or Processing: YC, BNC; Statistical Analysis and/or Data Interpretation: YC, BNC, ED, YP; Literature Review: YC; Manuscript Preparation: YC, BNC, ; Critical Review: YC, BNC.

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Case Report

Nasal Cavity Neuroendocrine Carcinoma and Synchronous Breast Cancer: A Case Report

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ABSTRACT

Primary malignancies of the nasal cavity and paranasal sinuses are rare and diagnosed late. Herein, we presented a female patient with nasal cavity neuroendocrine carcinoma and synchronous breast cancer.

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Keywords: *Nonsteroidal anti-inflammatory drugs, adverse effect, indomethacin, liver damage, idiosyncratic toxic hepatitis, methylprednisolone treatment.*

Introduction

Primary malignancies of the nasal cavity and paranasal sinuses are rare among head and neck cancers. Most patients are diagnosed in the 6th decade or later. The most common nasal cavity tumours are squamous cell carcinoma and adenocarcinoma.[1] Neuroendocrine tumours and mucosal melanoma follow these. We presented a 44 year-old patient with synchronous primary malignant tumors, treated with multidisciplinary approach.

Case Report

A 44-year-old female patient was admitted to the department of otorhinolaryngology with the complaint of congestion and mass in the left nose. She was referred to us when the biopsy result from the nasal cavity was reported as neuroendocrine carcinoma (small cell type). In PET-CT of the patient, there was a 53 mm diameter mass lesion filling the left nasal cavity, extending to the maxillary sinus, posteromedial of the orbital cavity and superiorly to the ethmoid cells (*Image 1*). Large and small lymph nodes were observed in the left parapharyngeal left upper cervical 2A and 2B. There was a nodule with a long diameter of approximately 11 mm in the upper outer quadrant of the right breast (*Image 2*). After three cycles of chemotherapy, surgery was planned for the

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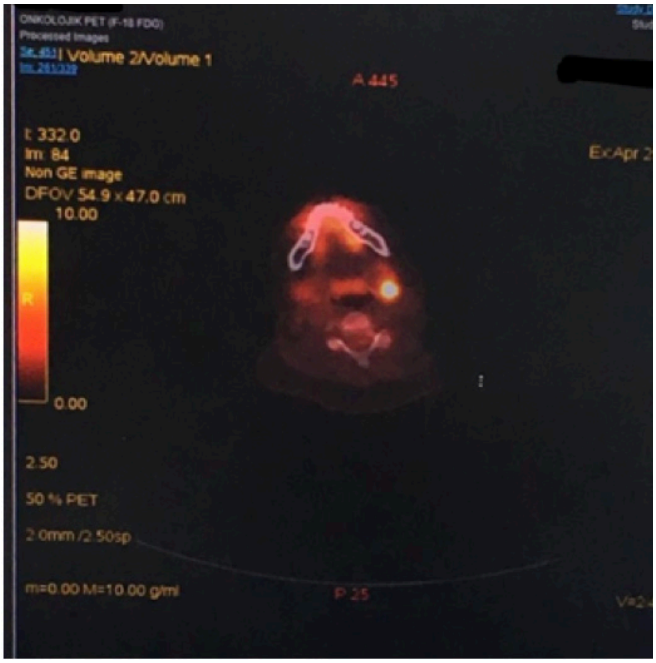

Image 1. Mass lesion with increased FDG uptake in the left nasal cavity.

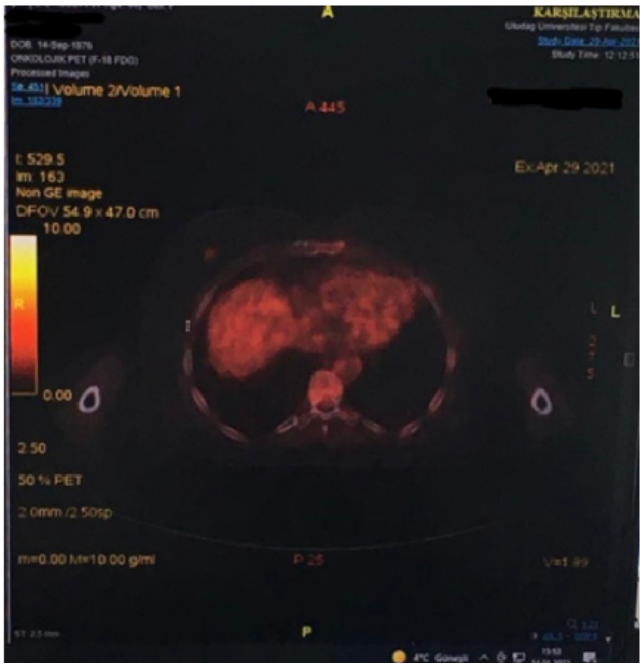

Image 2. 11 mm nodule in the right breast.

patient who was diagnosed with neuroendocrine carcinoma.

Meanwhile, the biopsy was planned for the lesion in the right breast. Control PET-CT showed regression in the activity of the mass lesion located in the left maxillary sinus, left nasal cavity and posterior orbit, reduction in the size and metabolic activity of the hypermetabolic lymph nodes in the left parapharyngeal area and level 2A. The nodule observed in the upper outer quadrant of the right breast was similar in size, and there was a decrease in metabolic activity. The breast biopsy resulted in invasive breast carcinoma (C-ERBB2: negative, ER/PR: strongly positive). Breast-conserving surgery and sentinel lymph node dissection were planned for the patient with synchronous breast cancer. Endoscopic excisional debulking biopsy was planned for the mass in the left nasal cavity. Nasal biopsy revealed hyalinized fibrotic tissue fragments and inflammatory granulation tissue. Additional surgical intervention was not considered for the patient who had a good response to chemotherapy. The right breast operation material was reported as invasive breast carcinoma. The lymph node was positive Adjuvant breast cancer treatment was planned for the patient after the end of neuroendocrine carcinoma treatment since it primarily affects survival. After chemotherapy, radiotherapy was mainly planned for the nasal region and breast cancer. Tamoxifen was started because the patient had hormone receptor-positive breast carcinoma. The patient still continues radiotherapy.

Discussion

Billroth introduced the definition of 'Multiple Primary Malignant Tumor' in 1889. According to this definition, tumours must first be histologically different and must have arisen in various organs. The possibility of metastasis between these two tumours should be excluded. Multiple primary malignant tumours are divided into synchronous and metachronous tumours.[2] Synchronous tumours detect the second primary cancer within six months of the first cancer diagnosis. In metachronous tumours, the diagnosis period between the second and the first is diagnosed longer than six months.[2,3]

Nasal neuroendocrine small cell carcinoma and synchronous breast cancer were detected in the patient in our case. T1N1miM0 and Stage 1B breast cancer were detected in the patient. According to the American Joint Committee on Cancer (AJCC), the 5-year survival rate is 98% for stage 1 disease. The disease-specific 5-year survival rate for T3N1M0 and Stage 3, small cell neuroendocrine carcinoma in the nasal cavity is 54-81%.[3,4]

In this case, the treatment of nasal cavity cancer was planned primarily because primary cancer affecting survival was neuroendocrine carcinoma in the nasal cavity. After the end of treatment, she was referred to radiotherapy for neuroendocrine carcinoma of the nasal cavity before adjuvant breast cancer treatment.

Acknowledgment

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Authors' Contribution

Study Conception: ASH, AD; Study Design: ASH, AD; Supervision: ASH, AD; Data Collection and/or Processing: ASH, AD; Literature Review: ASH; Manuscript Preparation: ASH; Critical Review: ASH, HD.

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Case Report

Pembrolizumab Induced Hypothyroidism: A Case Report

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ABSTRACT

Immune checkpoint inhibitors inhibit the inhibitory mechanism on the immune system, their side effects may be autoimmune diseases that occur due to excessive immune response. Pembrolizumab is an immune checkpoint inhibitor targeting PD-1. The most common clinical presentations of thyroid injury induced by pembrolizumab are destructive thyroiditis and overt hypothyroidism. Herein, we presented a case of pembrolizumab induced hypothyroidism.

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Keywords: *Pembrolizumab, immune checkpoint inhibitors, lung cancer, hypothyroidism, PD-1, non-small cell lung.*

Introduction

There are two main forms of lung cancer: non-small cell lung cancer (NSCLC) (85% of patients) and small cell lung cancer (SCLC) (15%). WHO has classified NSCLC into 3 main types: adenocarcinoma, squamous cell carcinoma and large cell.[1,2] The median overall survival and 5-year median survival rates for patients with non-small cell lung cancer were not promising until recently. The discovery of new agents and predictive biomarkers has played a role in improving prognosis in patients with advanced metastatic NSCLC.[3,4] Immune checkpoint inhibitors are one of these agents.

The importance of monoclonal antibodies as immune checkpoint inhibitors, in the field of oncology is increasing day by day. Since these drugs inhibit the inhibitory mechanism on the immune system, their side effects may also be autoimmune diseases that occur due to excessive immune response. When these side effects occur, it is important to discontinue the drug and start steroids. In checkpoint inhibition, programmed cell death 1 (PD-1), PD-1 ligand (PD-L1) receptors and cytotoxic T lymphocyte associated protein 4 (CTLA-4) are among the targets. Pembrolizumab and nivolumab targeting PD-1, atezolizumab,

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avelumumab and durvalumab targeting PDL-1 are used in many malignancies in various indications.[5] The most common clinical presentations of thyroid injury induced by pembrolizumab are destructive thyroiditis and overt hypothyroidism. In this case, we wanted to present a case of pembrolizumab induced hypothyroidism.

Case Report

A 64-year-old male patient with a known diagnosis of metastatic non-small cell lung cancer was admitted to the general internal medicine outpatient clinic with complaints of swelling in the legs, weakness, enlarged tongue, constipation, slowing of speech and dyspnea. He had no history of thyroid disease. Gemcitabine, cisplatin and pembrolizumab were started for the patient, who was diagnosed six months ago, for combined chemotherapy and immunotherapy. The patient received 7 cycles of pembrolizumab treatment. On physical examination, temperature was 36.3 °C and heart rate was 89 beats/min. He was conscious, oriented and cooperative. The patient had no hair and nail changes, and his skin looked pale yellow. Macroglossia was present. There were no rales or rhonchi on auscultation of the lungs. In the abdominal examination, the abdomen was slightly distended, there was no defense or rebound. Bilateral pretibial edema +++/+++ was present. The thyroid stimulating hormone (TSH) value measured before the patient's pembrolizumab use was 2.96 uIU/mL. In the laboratory tests of the patient at admission, TSH was 122 uIU/mL (reference values: 0.25-4.55 uIU/mL), free T3 <0.3 pmol/L, and free T4 1.86 pmol/L. Pembrolizumab was discontinued and chemotherapy was continued. The patient was started on 100 mcg of levothyron. Later, the dose of levothyron was gradually increased to 125 mcg. Simultaneously, 20 mg methylprednisolone was started and the patient was discharged with levothyron treatment. Seven weeks later, the patient's TSH value was found to be 20 uIU/mL.

Discussion

With the use of immune checkpoint inhibitors such as pembrolizumab, non-specific side effects such as weakness and fatigue often occur. In a meta-analysis of 38 studies and 2,551 patients, it was reported that the frequency of endocrinopathy induced by immune checkpoint inhibitors was 10% and hypothyroidism was the most common endocrinopathy.[6] Pembrolizumab induced autoimmune thyroid disease may present as primary hypothyroidism due to thyroiditis or hyperthyroidism due to Graves' disease.[7] In the phase 3 pembrolizumab study performed in advanced non-small cell cancer, hypothyroidism was observed in 8% of cases and hyperthyroidism was observed in 2-4% of cases.[8] Pembrolizumab can be given for up to 2 years, as the optimal duration of treatment has not been defined. Therefore, immune-related side effects may occur late in therapy or even after discontinuation of therapy.[9]

In mild cases of symptomatic thyroiditis, symptomatic treatment can be used, but in more severe cases, hospitalization and immunosuppressant treatment may be required. In this context, it should be considered that immune side effects such as hypophysitis, adrenalitis, and thyroiditis may occur in malignancy patients using immune checkpoint inhibitors, and patients should be followed closely in terms of these side effects.

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: SEY, IBG; Study Design: SEY, IBG; Supervision: YO; Materials: IBG, YO; Data Collection and/or Processing: SEY; Statistical Analysis and/or Data Interpretation: SEY, YO; Literature Review: IBG, SEY; Manuscript Preparation: SEY; Critical Review: YO.

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Case Report

Pityriasis Rosea After Pfizer-Biontech COVID-19 Vaccine: A Case Report

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ABSTRACT

After the pandemic started, vaccines against SARS-CoV-2 were developed and applied in a short time. Later, various side effects were reported during the use of these vaccines. Among the skin side effects, besides local skin reactions at the injection site, urticaria, maculopapular rash and pityriasis rosea-like reactions were observed. We presented a female case who developed pityriasis rosea after administering the 3rd dose of the Pfizer-BioNTech COVID-19 vaccine.

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Keywords: *COVID-19 vaccines, pityriasis rosea, Pfizer COVID-19 vaccine, drug-related side effects, adverse reactions.*

Introduction

SARS COV-2 is a virus that started in Wuhan, China in 2019 and caused the COVID-19 pandemic by affecting the whole world in a short time.[1,2] Although it can cause diseases in many systems, skin side effects are also observed (0.2%).[3] The most common skin lesions seen after COVID-19 infection are maculopapular, erythematous and urticarial lesions.[4,5] In the literature, there are a few cases developing pityriasis rosea after COVID-19 infection.[5-7] Herein, we presented a case of pityriasis rosea developing after Pfizer-BioNTech COVID-19 vaccine.

Case Report

The case is a 31-year-old woman with no known comorbidity and regular medications. The patient, five days after the administration of the 3rd dose of Pfizer-BioNTech mRNA COVID-19 vaccine, describes the lesions on her back as 2x3 cm in diameter, oval, sharply limited, pale erythematous, in the form of a herald patch with pitriasic scales observed in the periphery (*Picture 1*) and began to spread rapidly within two days from smaller sizes to the entire body (*Picture 2*). The patient stated that the rash was mildly itchy and there were no other symptoms accompanying itching. In the skin examination, it was observed that the rash was

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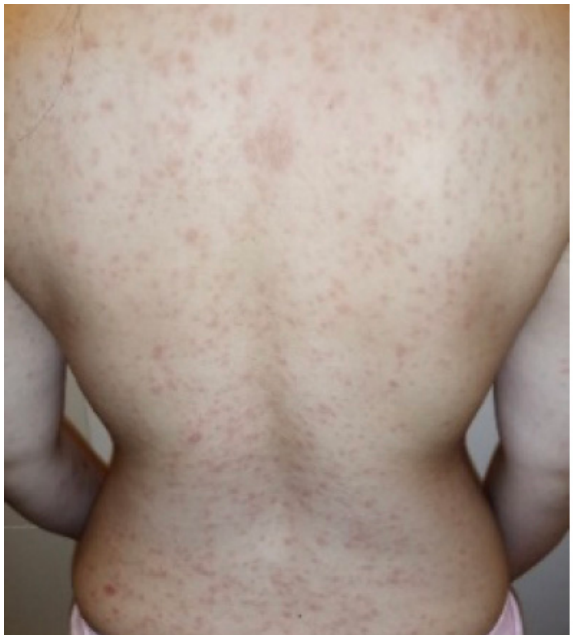
widespread throughout the body, including the face and the lesions were observed parallel to the skin lines. The patient was evaluated to have pityriasis rosea due to the medallion plaque presence, rash and the distribution character of the rash, and the absence of symptoms other than itching, therefore the patient was given topical steroid therapy. The topical steroids did not do any good for the patient, and systemic steroid treatment was started and it was seen that all lesions regressed in two weeks.

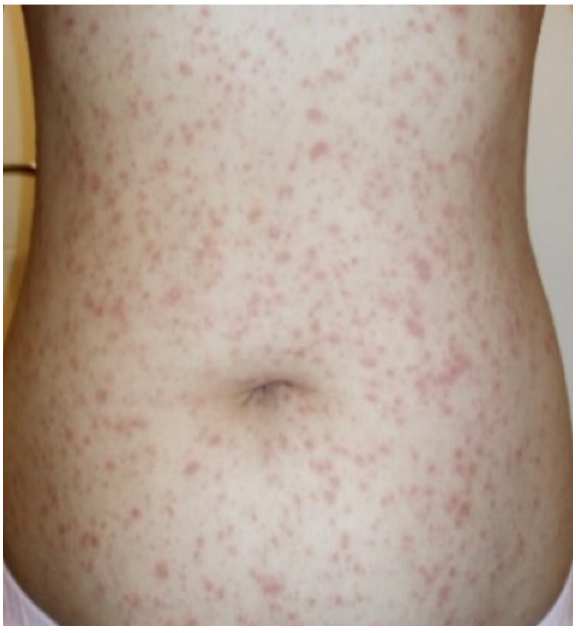
Discussion

Vaccines against SARS-CoV-2 are being developed and implemented at a rapid pace. With COVID-19 vaccine applications; in addition to common side effects such as pain at the injection site, weakness, headache, myalgia, and fever, skin side effects can also be seen. Examples of these are local skin reactions at the injection site, urticaria, maculopapular rash, and pityriasis rosea-like reactions.[8,9] Pityriasis rosea is a self-limiting acute rash disease in which viruses such as HHV-6 or HHV-7 play a role in the etiology.[10] Pityriasis rosea-like eruptions (PR-LE) may be seen after vaccination or as a drug reaction. Pityriasis rosea can be distinguished from pityriasis rosea-like rashes by the presence of prodromal signs and a herald patch.[11] Although pityriasis rosea can rarely be seen due to chickenpox, tuberculosis, influenza, HPV, poliomyelitis, diphtheria, pneumococcus, tetanus, hepatitis B vaccines, there are also cases of pityriasis rosea after COVID-19 vaccine.[12-16] It is believed that the cases developing pitriasis rosea associated with COVID-19 vaccine (mRNA) is similar to the herpes zoster virus reactivation mechanism after inactivated COVID-19 vaccine, since the effects of vaccine-specific particles on immunity may cause the development of pityriasis rosea.[16,17] In addition, it is argued that vaccines may cause delayed-type hypersensitivity with a drug-induced PR-LE-like mechanism.[15]

As a result, we presented a case with pityriasis rosea development after the third dose of Pfizer-BioNTech mRNA COVID-19 vaccine. Today, like with many vaccines, there are also cases of pityriasis rosea developing after COVID-19 vaccines. Further studies on tissue and serological examination are needed to establish a causal link between pityriasis rosea or PR-LE and COVID-19 vaccines.



Picture 1. Medallion plaque that first appears on the back and erythematous plaques that spread to smaller sizes over time.



Picture 2. Erythematous plaques located parallel to the skin lines in and around the abdomen.

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Conflict of interest

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Authors' Contribution

Study Conception: SHA, YG; Study Design: SHA, YG; Supervision: SHA, YG; Materials: SHA, YG; Data Collection and/or Processing: SHA; Statistical Analysis and/or Data Interpretation: YG; Literature Review: SHA; Manuscript Preparation: SHA, YG; Critical Review: SHA, YG.

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TURKISH JOURNAL OF INTERNAL MEDICINE
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Case Report

Primary Mediastinal Large B-Cell Lymphoma: Case Report

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ABSTRACT

Primary mediastinal large B-cell lymphoma is a rare tumour. Patients present with dyspnea, cough, dysphagia and superior vena cava syndrome. Thus, most patients are diagnosed early in stages 1-2. We reported a 19-year-old male patient diagnosed with primary mediastinal large B-cell lymphoma.

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Keywords: *Primary mediastinal large B-cell lymphoma, diffuse large B-cell lymphomas, non-Hodgkin lymphomas.*

Introduction

Primary mediastinal large B-cell lymphoma (PMLBCL) is a rare tumour globally.[1] Non-Hodgkin lymphomas (NHL) 2-3% diffuse large B-cell lymphomas (DLBCL) 6-10% constitutes.[2] It is more common in young white women (3:1) and occurs in the mediastinal region. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) therapy are widely used. Herein, we presented a 19-year-old male patient diagnosed with primary mediastinal large B-cell lymphoma.

Case Report

19-year-old male patient with no known disease, night sweats that started for about one month, weight loss (25 kilograms in 1 month), cough, and a palpable mass in the neck on thoracic tomography performed with packed lymph filling the anterior mediastinum and reaching both cervical subzones. When nodules (bulky mass) were detected (*Image 1*), the thoracic surgeon performed a tru-cut biopsy, and the patient was referred to us when PMLBCL was received as a result of the material sent to us pathology.

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PET-CT was taken for staging and bone marrow biopsy was performed on the patient. The patient, who was accepted as stage 2B, was started on R-CHOP treatment. Inadequate response after four cycles of R-CHOP was considered as refractory disease and the patient was given 2 cycles of R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) as salvage therapy. During these treatments, a tracheal stent was inserted by the thoracic surgeon due to tracheal compression (*Image 2*). When the cervical lymph nodes progressed 72 hours after the end of the treatment, the patient was consulted to the radiation oncology department and 4 sessions of radiotherapy were given. The patient was started on a targeted PD-1 blocker, nivolumumab, together with brentuximab, an anti-CD30 monoclonal antibody, for at least 4 cycles, once every 3 weeks. Three courses of treatment were given. It was learned that the patient died due to sudden respiratory arrest while he was at home in the seventh month of his illness.

Discussion

In PMLBCL, 5-years survival rate is 85%, and there is a difference between whites and blacks. The prognosis is worse with advancing age and the survival rate is less. Among other prognostic factors include socioeconomic status, advanced stage.[3] Risk factors for the white race, female gender, genetic predisposition, environmental factors, diet, occupational exposures, and socioeconomic status can be said to factors such as autoimmune diseases.[4]

Clinically patients with dyspnea, cough, dysphagia and superior vena cava syndrome (VCSS) is close to the findings of the symptoms (facial edema, konjonktival and arm edema). This may result in early diagnosis, and thus the diagnosis in most of the patients (around 80%) is determined as Grade 1 or 2.[5] The disease is a rare, aggressive lymphoma with good prognostic features, which is usually seen at a young age and present with the presence of mass disease.

First-line therapy in PMLBCL is still controversial.[6] Also radiotherapy consolidation treatment is controversial. R-CHOP treatment is the most commonly used chemotherapy protocol and it has been reported that radiotherapy has a positive effect on the prognosis in selected cases. In resistant patients, autologous stem cell transplantation can be progressed after R-DHAP or R-ICE (rituximab, ifosfamide, carboplatin, etoposide). PD-1 blockers emerge as an important treatment alternative. The cause of early death in our patient was not clearly understood. Although the five-years survival rate is 85%, early death occurs due to complications caused by aggressive lymphoma.

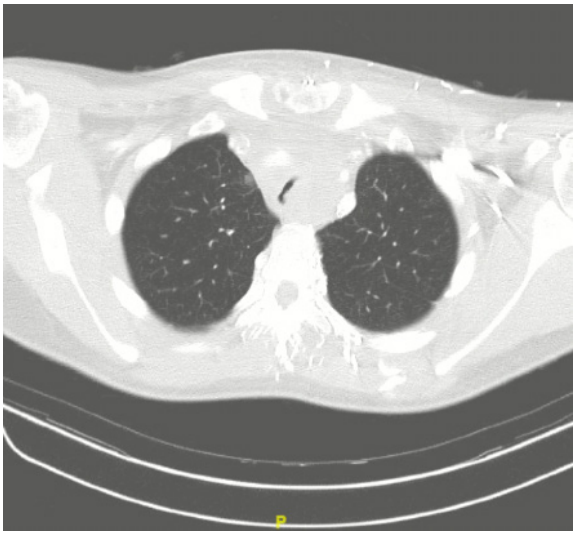

Image 1. Mediastinal mass and compression of the trachea. .

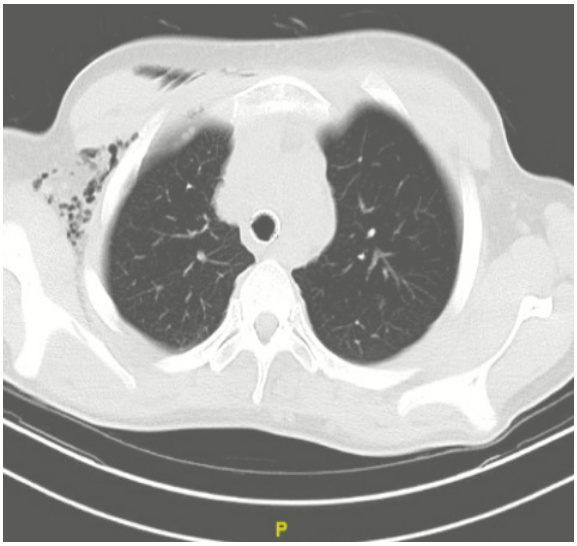

Image 2. Tracheal stent view

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: OC, FO; Study Design: OC, VO; Supervision: OC, VO; Funding: OC, TE; Materials: OC, SC; Data Collection and/or Processing: OC, FO; Statistical Analysis and/or Data Interpretation: YG; Literature Review: OC, VO; Manuscript Preparation: OC, FO; Critical Review: OC, FO.

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Case Report

Post-transplant Lymphoproliferative Disorder Following Kidney Transplantation: A Case Report

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ABSTRACT

Posttransplant lymphoproliferative diseases are complications that develop after solid organ transplantation. Primary EBV infection is one of the most important risk factors. After deceased kidney transplantation, we presented a young male patient diagnosed with diffuse large B-cell lymphoma.

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Keywords: *Chronic kidney disease, kidney transplantation, immunosuppression, complication, lymphoproliferative diseases.*

Introduction

Post-transplant lymphoproliferative disease (PTLD) is a severe complication of solid organ transplantations (SOT) associated with immunity changes. Risk factors are the degree of immunosuppression, recipients age, allograft type, and the most important is post-transplant primary EBV infections (i.e. recipient is EBV-seronegative before transplantation).[1] Herein, we presented a kidney transplant recipient diagnosed with diffuse large B-cell lymphoma.

Case Report

A 26-year-old male patient with a 5-year history of hemodialysis treatment for chronic kidney failure due to polycystic kidney disease had a kidney transplant from a deceased donor in June 2020. After transplantation, his nephrologist has started azathioprine (1x50 mg) and tacrolimus (2x4.5 mg) treatments to prevent rejection. In the tenth month of transplantation, he presented to the gastroenterology department with abdominal pain and loss of weight. After examination with gastroscopy and colonoscopy (with a sigmoid colonic biopsy), he was diagnosed with diffuse large B-cell lymphoma (DLBCL) and he was also EBV-positive. Then, the patient was admitted to the haematology department. A PET-CT scan demonstrated increased metabolic activities at the thyroid gland, neck (zone-II), right lung (lower zone), and right lobe of the liver, sigmoid colon, and caecum. He was evaluated as stage 4B-disease. We did not prefer chemotherapy at the first line. The nephrologist adjusted the immunosuppressive treatment to prevent graft rejection, taking into account the DLBCL treatment. Azathioprine was

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discontinued, half-dose tacrolimus was continued, and the mTOR inhibitor everolimus 2x1.25 mg was started. After three months, serum creatinine levels were stable. His complaints regressed, and a newly performed PET-CT scan demonstrated near-complete regression, so the treatment has proceeded. Another PET-CT scan after seven months of treatment revision didn't reveal any malignancy-associated metabolic activity. We considered the patient with stable renal function and no clinical complaints to be in remission.

Discussion

PTLD incidence is a variable of the type of SOT. This ratio is 1-3% after kidney transplantation. Studies suggest that this difference may be due to more aggressive immunosuppression in some solid organ transplantations in the early period. PTLD following kidney transplantation is not frequent, but it is more upfront relative to other SOTs because kidney transplantation is more common.[2,3]

PTLD can present itself either as a focal lesion in an organ or involvement of the allograft directly. The symptomatology of PTLDs differs according to the involved organ. Constitutional symptoms, lymphadenomegaly and hepatomegaly can be seen in patients with all PTLDs. However, organ-specific symptoms may occur if the allograft is involved. In the current approach, the goal is to reduce the usage of immunosuppressive therapy as a first-line treatment.[3,4] Most of the PTLDs are originated from the B-cells. Therefore, monoclonal antibodies are chosen for second-line treatment. Conventional chemotherapy is also an option for the treatment of PTLD.[4] As in our case, it would be beneficial to treat and monitor these cases with a multidisciplinary approach.

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: TZT, OC; Study Design: TZT, OC; Supervision: TZT, FO; Materials: TZT; Data Collection and/or Processing: TZT, OC, FO; Statistical Analysis and/or Data Interpretation: TZT, OC; Literature Review: TZT, VO; Manuscript Preparation: TZT, YG; Critical Review: TZT, TE.

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Case Report

Pulmonary Embolism Developing Despite the Use of Anticoagulants in COVID-19 Pneumonia: A Case Report

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ABSTRACT

COVID-19 pneumonia is one of the diseases that can cause hypercoagulability. It is not uncommon to encounter arterial or venous thromboembolic events during COVID-19 infection. In this case, we wanted to discuss a case of a pulmonary embolism due to COVID-19 infection, which developed despite the usage of therapeutic dosage of anticoagulants. A 41-year-old male patient with a known diabetes mellitus was admitted to our clinic with complaints of cough and headache. The patient was found to be COVID-19 positive. Along with steroid treatment, 2x6,000 IU enoxaparin treatment was initiated for the patient. He developed sudden respiratory distress and showed an increase in oxygen demand. D-dimer value increased abruptly to 35.2 mg/L. Pulmonary CT angiography showed multiple bilateral subsegmental pulmonary embolisms. Since COVID-19 infection can cause arterial and venous thromboembolic events in patients following up with COVID-19 pneumonia, prophylactic anticoagulation should be initiated in hospitalized patients. Attention should be paid to signs of bleeding, and dose adjustment should be made by monitoring coagulation parameters.

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Keywords: *COVID-19, pneumonia, hypercoagulability, thromboembolic events, pulmonary embolism.*

Introduction

COVID-19 pneumonia is one of the diseases that can cause hypercoagulability. It is not uncommon to encounter arterial or venous thromboembolic events during COVID-19 infection. Many changes in circulating prothrombotic factors have been reported or proposed in patients with severe COVID-19, such as elevated levels of factor VIII, fibrinogen, circulating prothrombotic microparticles, neutrophil extracellular traps (NETs) and hyperviscosity.[1,2] Venous thromboembolism (VTE), including extensive deep vein thrombosis (DVT) and pulmonary embolism (PE), was very common in acutely ill patients with COVID-19 during the early

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stages of the pandemic. Even when prophylactic anticoagulation was used, it is seen in up to one-third of patients in the intensive care unit (ICU).[3,4] Therefore, the importance of the usage of anticoagulant therapy and the follow-up of coagulation parameters, especially in inpatients, is obvious. In this case, we wanted to discuss an issue of a pulmonary embolism due to COVID-19 infection, which developed despite the usage of therapeutic dosage of anticoagulants.

Case Report

A 41-year-old male patient with no comorbidities other than a diagnosis of diabetes mellitus was admitted to our clinic with complaints of cough and headache lasting for seven days. The patient's saturation was 95% at room air. Heart rate was 95 beats/min, arterial blood pressure was 155/87 mmHg, and respiratory rate was 19 per minute. There were widespread bilateral crackles in all zones on auscultation of the lungs. The abdomen was not defensive to palpation, and there was no rebound tenderness. There were bilateral ground-glass consolidations on obtained thorax computed tomography (CT). The patient was not vaccinated against COVID-19. The patient was found to have a positive COVID-19 PCR test with a nasal and throat swab was admitted to our clinic for treatment and supportive care. In the laboratory tests performed on the first day of his hospitalization, D-dimer was found to be 1.03 mg/L. CRP was determined as 10.87 mg/dL, INR 0.9, and fibrinogen as 731 mg/dL. Along with steroid treatment, inhaler interferon and supportive treatment, 2x6,000 IU enoxaparin treatment was initiated to the patient who weighed 78 kilograms.

Since the patient developed hemoptysis on the 3rd day of follow-up, enoxaparin was started to be administered as a single dose of 6,000 IU and was used as a single dose for two days. On the 5th day of follow-up, the patient, who was supported with 4 L/min nasal oxygen support, developed sudden respiratory distress and increased oxygen demand. The patient was then supported with an 8 L/min reservoir oxygen mask. The patient's D-dimer value increased abruptly to 35.2 mg/L (*Figure 1*). With the current clinical and laboratory findings and a preliminary diagnosis of pulmonary embolism, the dose of enoxaparin was increased to 2x8,000 IU and pulmonary CT angiography was performed. Pulmonary CT angiography

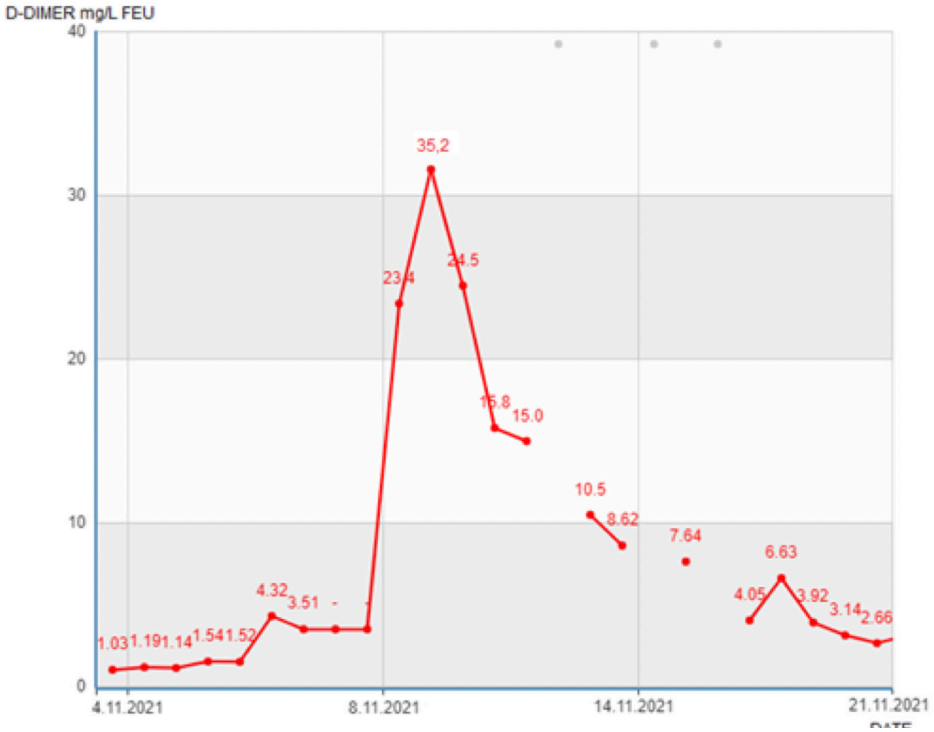

Figure 1. Daily D-dimer values.

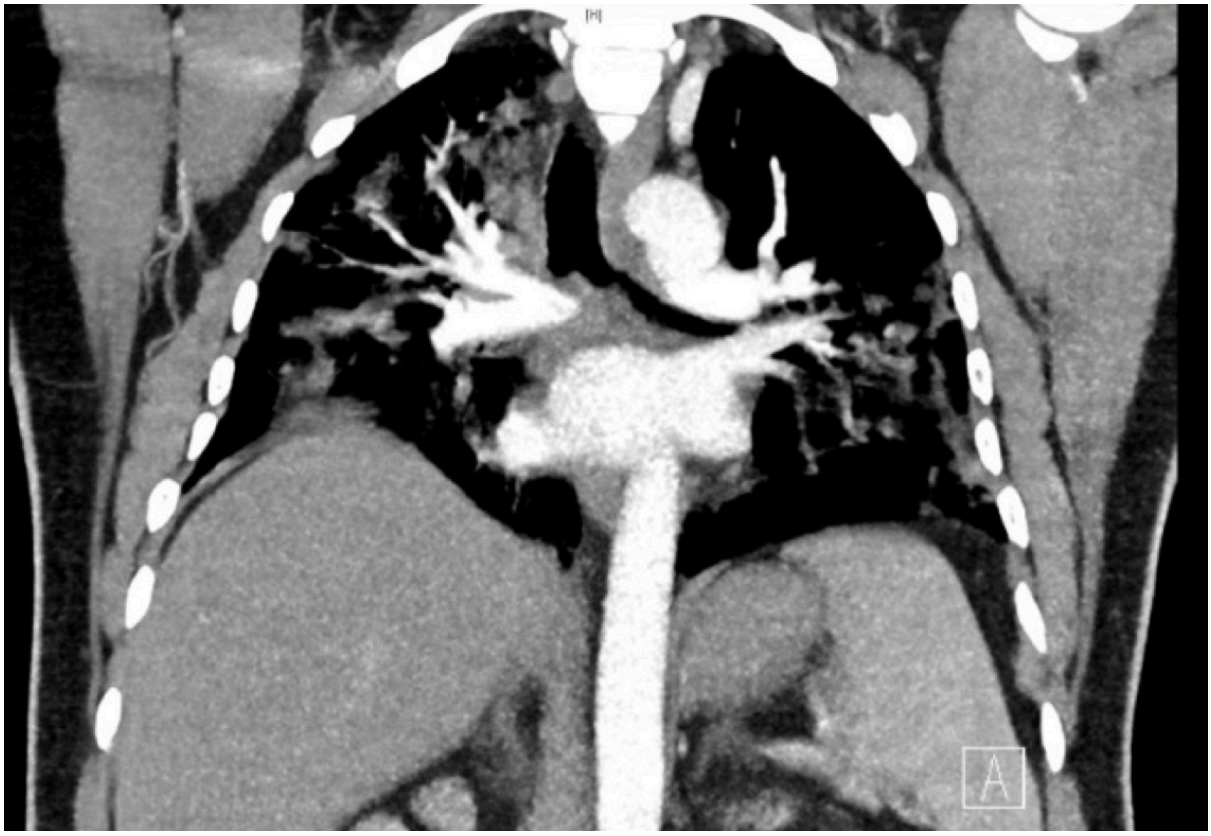

Image 1. Bilateral partial filling defects in subsegmental pulmonary arteries consistent with pulmonary embolism.

showed multiple bilateral partial filling defects in subsegmental pulmonary arteries, mainly in the posteroinferior segment of the left lung compatible with pulmonary embolism (*Image 1*). The patient showed no signs of discolouration, temperature increase, tenderness, swelling or pain in his lower extremities. There was no finding of deep vein thrombosis in the lower extremity venous doppler ultrasonography. The patient continued to use 2x8,000 IU enoxaparin, and the D-dimer value gradually decreased to 4.05 mg/L in the follow-ups. The treatment of the patient who did not have deep vein thrombosis and had pulmonary embolism foci in the subsegmental areas were arranged in consultation with the department of cardiovascular surgery and chest diseases. The patient was discharged after his clinical condition improved. There was no desaturation at room air on the 14th day with supportive, steroid and anticoagulant treatment, and he continued his prescribed medicine to be later seen at office visits.

Discussion

This systematic review of the evidence suggests that hospitalized patients with COVID-19, screened or assessed for VTE, present a pooled prevalence of DVT and PE at about 30% each, despite thromboprophylaxis in most cases. The VTE risk appears to be considerably higher than in patients without COVID-19 admitted in the same ICU's.[4] A meta-analysis of a total of 91 studies reporting on 35,017 patients with COVID-19 showed the overall frequency of VTE in all patients, ICU and non-ICU, was 12.8%, 24.1%, and 7.7%, respectively.[5]

Cytokine storm induced by the COVID-19 profoundly activates the coagulation cascade causing venous thromboembolism.[5] The risk of developing venous thromboembolism continues even if prophylactic anticoagulants are used in COVID-19 cases who are hospitalized and followed up especially in the ICU.

Keeping in mind that COVID-19 infection can cause arterial and venous thromboembolic events in patients followed up with COVID-19 pneumonia, increase in oxygen demand, sudden dyspnea, deterioration in general condition or in patients with a significant increase in serial D-dimer follow-ups as in our case, diagnoses such as pulmonary embolism, obstructive cerebral disease and myocardial infarction should also be considered in differential diagnosis. Therefore, prophylactic anticoagulation should be initiated in hospitalized patients, attention should be paid to signs of bleeding, and dose adjustment should be made by monitorization of coagulation parameters.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: IBG, SEY, YO; Study Design: YO, SEY, IK; Supervision: YO, IK, SEY; Materials: IBG, SEY; Data Collection and/or Processing: IBG, SEY; Statistical Analysis and/or Data Interpretation: IBG, SEY; Literature Review: IBG, SEY, YO; Manuscript Preparation: IBG, SEY, YO, IK; Critical Review: YO, IK, SEY, IBG.

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Case Report

Thrombocytopenic Thrombotic Pupura Presenting with Neurological Symptoms: A Case Report

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ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is thrombotic microangiopathy caused by decreased activity of ADAMTS13, a von Willebrand factor-degrading metalloprotease. Here, we present a male patient with neurological symptoms, diagnosed with TTP and successfully treated with plasmapheresis.

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Keywords: *Thrombotic microangiopathy, thrombocytopenic thrombotic pupura, ADAMTS13, neurological symptoms, plasmapheresis.*

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy (TMA) caused by severely reduced activity of the von Willebrand factor-cleaving protease ADAMTS13.[1] Complete pentad includes thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fever, neurological findings and renal failure.[2] However, the complete pentad may not be detected in most patients. In this article, we aimed to present a case of TTP presenting with neurological symptoms.

Case Report

A 53-year-old male patient was admitted to the emergency service with the complaints of slurring of the tongue, headache and weakness. The patient's temperature was 36.2 °C at the time of admission. Cranial computed tomography (CT) or magnetic resonance imaging (MRI) was found to be normal in the patient whose neurological and systemic examination did not reveal any obvious pathology. Complete blood count (CBC) revealed anemia and thrombocytopenia (leukocyte 6,070/mm^3, neutrophil 4,220/mm^3, hemoglobin 8.9

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g/dL, platelet 20,300/mm^3), and features of hemolysis (lactate dehydrogenase [LDH] 821 U/l, total bilirubin 2.9 mg/dL) was detected. In biochemical parameters, creatinine was 1.17 mg/dL and urea was 35 mg/dL. In the peripheral blood smear; schistocytes were seen in 3-4 high power fields and also one orthochromatophilic cell. The platelet count and frequency were consistent with the hemogram. Evaluated with these findings, the patient was admitted to the hematology clinic with a preliminary diagnosis of TTP. The blood sample was stored at -80 °C for the ADAMTS13 test at the patient's admission. Therapeutic plasma exchange (TPE) and 1 mg/kg methylprednisolone were initiated. After 15 sessions of TPE, the platelet count increased to 154,400/mm^3, and LDH levels decreased to 207 U/l. The complaints of slurring of the tongue and headache disappeared. After the patient received 19 sessions of TPE, the platelet count were 183,500/mm^3 and the LDH levels were within the normal range, so it was decided to open the intervals between the TPE sessions. The diagnosis of TTP was confirmed after ADAMTS13 activity was reported as 6.84% (low), ADAMTS13 antigen 0.096 (low), and ADAMTS13 inhibitor 16.07 (high). TPE was performed 2 days a week for 3 weeks. Afterwards, he was discharged with stable vitals and hemodynamics. After discharge, TPE was performed once a week for a total of 5 weeks. Methylprednisolone treatment was tapered and discontinued. The patient is being followed up.

Discussion

Deficiency of the ADAMTS13 is seen in 90-95% of TTP cases. Microangiopathic hemolytic anemia (MAHA) and thrombocytopenia are hallmarks of TTP.[1-3] Neurological symptoms are seen in 39-80% of cases, fever in 27-42%, renal failure in 10-75% of cases, while the complete pentad is seen in only 7%. According to a review of 78 patients with acquired TTP from Oklahoma, published by Page et al.[4] in 2017, 41 (53%) had neurological symptoms, 8 (10%) had fever, 11 (14%) creatinine level ≥2.5 mg. /dL, 4 (5%) had acute kidney injury.[4]

In the first presentation of our patient, neurological findings, microangiopathy and thrombocytopenia were present, but there was no fever and elevated creatinine. In conclusion, considering that complete pentad is seen in only 7% of patients, possibility of TTP should be suspected in any patient presenting with MAHA findings and thrombocytopenia with or without symptoms of organ involvement and without an alternative explanation.

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This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: YC, VO; Study Design: YC, BO, VO; Supervision: YC, VO, FO; Materials: YC, BO, VO; Data Collection and/or Processing: YC, BO, FO; Statistical Analysis and/or Data Interpretation: YC, BO, FO; Literature Review: YC, BO, VO; Manuscript Preparation: YC, BO, VO; Critical Review: YC, BO, VO.

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Case Report

Thyroid Storm Associated with Diabetic Ketoacidosis: A Case Report

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ABSTRACT

Various autoimmune diseases may accompany type 1 diabetes. Autoimmune thyroid diseases are common in these patients. Herein, we presented a type 1 diabetic female patient with diabetic ketoacidosis accompanied by a thyroid storm.

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Keywords: *Autoimmune diseases, type 1 diabetes mellitus, thyroid diseases, hyperthyroidism, diabetic ketoacidosis, thyroid storm.*

Introduction

Type 1 diabetes is an autoimmune disease in which genetic and immunological factors play a role. 5-10% of diabetes in adult patients is type 1 diabetes.[1] It is caused by insulin deficiency due to immune-mediated destruction of pancreatic beta cells. It constitutes approximately 80% of newly diagnosed diabetes cases in patients under 19.[2] While non-acidosis hyperglycemia is typically the initial symptom in children, they are diagnosed with diabetic ketoacidosis with the second frequency.[3] Type 1 diabetes may be accompanied by autoimmune diseases such as Graves disease, celiac disease, and primary adrenal insufficiency.[4] Autoimmune thyroid diseases are the most common immunological disease in these patients. Hyperthyroidism is observed in approximately 1-2% of patients. We aimed to present a case with graves who had type 1 diabetes and was diagnosed with thyroid storm.

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Case Report

A 22-year-old female patient presented to the emergency department with complaints of nausea, vomiting, palpitations, and shortness of breath. She had a known diagnosis of type 1 diabetes mellitus (DM) since nine, uses an insulin pump, and has no comorbidities. At presentation, the patient was conscious, oriented, and cooperative. The respiratory sounds were bilaterally equal and natural, the abdomen was relaxed (no defense and rebound), no pretibial edema, peripheral pulses were palpable and equal. In her neurological examination, muscle strength was 5/5, cerebellar and cranial nerve examinations were regular, and she did not find neck rigidity. She had a history of diabetic ketoacidosis four years ago. Her mother had a thyroid nodule and thyrotoxicosis in her four aunts.

Sinus tachycardia was present in the patient's electrocardiography (ECG) (beats 156/min). In her laboratory, capillary blood glucose was 308 mg/dL, no electrolyte imbalance, and standard kidney function tests. There were elevated liver function tests in ALT dominance (ALT: 86 U/L, AST: 53 U/L). We detected bilirubin elevation in indirect bilirubin dominance. (total bilirubin: 2.4 mg/dL, direct bilirubin: 0.33 mg/dL). There was neutrophilic leukocytosis in the hemogram (leukocyte: 14,100/mm^3, neutrophil: 9,470/mm^3), and CRP was negative. There was decompensated metabolic acidosis in the arterial blood gas of the patient. (pH: 7.19, pCO_2: 34, pO_2: 78, SpO_2: 91%, HCO_3: 13.5 mmol/L). In the complete urinalysis, the pH was 5, protein negative, glucose 4+, ketone 2+, erythrocyte/leukocyte/bacteria negative. We detected pulmonary edema in the thorax computed tomography.

The patient, whose complaints increased and acidosis worsened during the emergency follow-up, was followed up in the intensive care unit (ICU). The patient, who developed respiratory distress during her follow-up in the ICU, was followed up with elective intubation. As the acute phase reactants increased, we started broad-spectrum antibiotic treatment (piperacillin/tazobactam, teicoplanin, oseltamivir) and methylprednisolone. We performed drainage was due to pleural fluid. We detected in the thyroid function tests (TFT) sent during the patient's hospitalization, TSH: 0 mIU/mL, free T4: 5 ng/dL, free T3: 20 ng/L, and sent control TFT one week later. We observed TSH: 0.01 mIU/mL, free T4: 2.22 ng/dL, free T3: 10.78 ng/L. In the neck ultrasonography, the thyroid parenchyma had a heterogeneous hypoechoic appearance. The gland vascularization increased, and it was evaluated as subacute thyroiditis consistent with the elevation of thyroid hormone. Considering thyroid storm, we started propylthiouracil (PTU) and hydrocortisone 4x50 mg and stopped methylprednisolone. Cardiology performed transthoracic echocardiography because of bilateral pleural effusion; ejection fraction was expected, and pulmonary artery pressure was found to be high. On the other hand, in the lower extremity doppler ultrasonography was taken due to the increase in diameter in the bilateral lower extremities of the patient, a thrombus in the deep venous system, which may be compatible with the acute or chronic period, was observed.

During follow-up, ALT increased 10-fold, so we discontinued PTU and steroid therapy. We planned thyroid apheresis, and a dialysis catheter was inserted through the right femoral vein. Fresh frozen plasma was prepared, and the patient started apheresis treatment. We added propranolol because of tachycardia and applied apheresis for a total of eight doses. We planned a total thyroidectomy for the patient, who was evaluated in the endocrinology, and ear, nose, and throat diseases committee because she could not take anti-thyroid medication and be diagnosed with Graves' disease. The committee deemed it appropriate to make the patient euthyroid by applying high-dose iodine treatment and re-plasmapheresis before the operation. ENT on the patient performed total thyroidectomy.

We started calcium D3 and levothyroxine due to transient hypoparathyroidism in the post-operative period (TSH: 0.01 mIU/mL, free T4: 1.37 ng/dL, free T3: 2.28 ng/L, parathormone: 10 ng/L). Thyroidectomy pathology, diffuse hyperplasia, benign lymph node, and parathyroid tissue were reported. The council deemed it appropriate to make the patient euthyroid by applying high-dose iodine treatment and re-plasmapheresis before the operation. We discharged the patient without complications after the operation. Calcium was

discontinued during outpatient follow-ups, and the levothyroxine dose was increased to 125 mcg. We turned off the insulin pump, we started long, and short-acting insulin therapy.

Discussion

It is common for individuals diagnosed with an autoimmune disease to be accompanied by another autoimmune disease. In the follow-up of diagnosed patients, it may be necessary to closely follow up and examine other possible conditions in line with their complaints. Type 1 DM is the most common autoimmune disease highly related to thyroid diseases.[5] For this reason, the controls of type 1 DM patients or seeing TFT at the first application are among the situations that should be careful. Hypothyroidism is the most common disease with type 1 DM, and the diagnosis of thyroid disease is usually made before diabetes.[6]

In our case, in a patient with a known diagnosis of type 1 DM, diabetic ketoacidosis and thyroid storm were observed simultaneously. We wanted to present it because the patient underwent surgery later in the clinical process.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: NGA; Study Design: CA; Supervision: EH; Materials: EA; Data Collection and/or Processing: YC, BO, FO; Statistical Analysis and/or Data Interpretation: CE; Literature Review: OOG; Manuscript Preparation: SC.

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Case Report

Thyrotoxic Hypokalemic Periodic Paralysis: A Case Report

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ABSTRACT

Thyrotoxic hypokalemic periodic paralysis is a rare and fatal complication of hyperthyroidism and is associated with low serum potassium levels and muscle weakness. Herein, we presented a young male patient who did not use the antithyroid drugs given for Graves' disease and was admitted with the complaint of weakness in the extremities and diagnosed with thyrotoxic hypokalemic periodic paralysis.

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Keywords: *Thyrotoxicosis, treatment, complication, hypokalemia, paralysis, outcomes.*

Introduction

Thyrotoxic hypokalemic periodic paralysis (THPP) is a rare complication of hyperthyroidism, characterized by low serum potassium levels and acute muscle weakness without any sensory deficit or confusion.[1] We presented a Graves' disease patient who developed weakness in the extremities after stopping the antithyroid medication and was diagnosed as thyrotoxic hypokalemic periodic paralysis.

Case Report

A 22-year-old male patient diagnosed with Graves' disease three years ago was admitted to the emergency department with complaints of weakness in his upper and lower limbs. At the time of diagnosis, his symptoms were hand tremors and irritability. In his thyroid function tests, thyroid-stimulating hormone (TSH) was <0.0025 mU/L (normal range [NR]: 0.35-4.94), free thyroxine (fT4) was 1.43 ng/dL (NR: 0.7-1.47), free tri-iodothyronine (fT3) was 4.96 ng/L (NR: 1.71-

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3.71), TSH-receptor antibody was 9.25 IU/L, which was highly positive (NR <1.5 IU/L). His thyroid scintigraphy showed diffuse enlargement of both thyroid lobes with uniform isotope uptake. After diagnosing Graves' disease, methimazole 10 mg twice a day, propranolol 40 mg daily, and potassium citrate tablets once daily was started. However, the patient stated that he did not use his medications for the last eight months.

On physical examination, the patient was conscious, oriented, afebrile. His pulse rate was 110/min regular, and blood pressure was 100/80 mmHg. His electrocardiogram (ECG) showed sinus tachycardia. Neurologic examination revealed his upper and lower limb power as grade 1/5 with intact sensation. Higher mental function, including speech, cranial nerves and autonomic nervous system examination revealed no abnormality. Complete blood count showed total leukocyte count 13,110 K/mcl, neutrophils 10,960 K/mcL, hemoglobin 15.7 g/dL, platelet 269,000 K/mcL and venous blood gas analysis showed pH of 7.34, pCO_2 46 mmHg, HCO□ 21 mmol/L. Random blood sugar was 112 mg/dL, blood urea 34 mg/dL, serum creatinine 0.67 mg/dL, sodium (Na) 143 mmol/L, potassium (K) 2.2 mmol/L, total calcium 9.8 mg/dL and all liver enzymes were within normal limits (Table 1).

Based on the neurological examinations and the biochemical results, THPP was diagnosed. 30 mEq intravenous potassium chloride in %0.9 sodium chloride solution was started immediately, and the patient was treated with 40 mg oral propranolol per six hours and 30 mg methimazole daily. Serum potassium levels increased to 4.2 mmol/L after five hours of treatment, and neurologic examination revealed upper and lower limbs power was grade 5/5. The patient was examined in the endocrinology clinic the day after. Complete clinical recovery was seen. Thyroid function tests revealed TSH <0.01 mU/L, fT4 2.92 ng/dL, fT3 14.31 ng/dL, potassium was 4.91 mmol/L and the other parameters were within normal limits. The patient was educated to take his medications regularly, avoid strenuous exercise, alcohol use and a high-carbohydrate diet.

Discussion

The incidence of THPP, which is commonly identified in East Asian men, is also increasing in other parts of the world. In THPP, □ncreased beta-adrenergic stimulation and overactive Na-K-ATPase channels cause potassium leak into muscle cells, and muscle cells can not be stimulated due to hyperpolarization. Factors such as a high

Table 1. Laboratory findings at diagnosis, at admission to emergency department and at discharge.

Parameters	At the time of diagnosis of Graves	At the admission to emergency department	At discharges
Leukocyte count (K/mcL)	8,730	13,110	6,730
Hemoglobin (g/dL)	15.5	15.7	14.8
Urea (mg/dL)	25	34	21
Creatinine (mg/dL)	0.82	0.68	10
Sodium (mmol/L)	137	143	139
Potassium (mmol/L)	4.52	2.2	4.4
Thyroid-stimulating hormone (mU/L)	<0.0025	<0.01	<0.01
Thyroxine (ng/dL)	1.43	2.92	0.61
Free triiodothyronine (ng/L)	4.96	14.31	2.49
TSH-receptor antibody (IU/L)	9.25	14.1	

carbohydrate diet, strenuous exercise, emotional stress can precipitate an attack of THPP.[2] The ion channel defect in familial periodic paralysis is not found in the thyrotoxic form. Some genetic mutations on proteins called "kir 2.6", regulated by thyroid hormones and responsible for membrane potassium transitions, can cause THPP.[3]

Thyrotoxicosis is the most common cause of acquired periodic paralysis.[4] In the absence of a family history of paralysis, renal tubular acidosis should also be considered.[5] Symptoms of hyperthyroidism may not always be evident in patients, or muscle paralysis could be the first manifestation of thyrotoxicosis. THPP can be complicated with ventricular fibrillation or hypercapnic respiratory failure if not diagnosed and treated promptly.[6]

In summary, THPP is an infrequent complication of hyperthyroidism that can be mortal. The most critical step in preventing THPP is to achieve euthyroidism.

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Conflict of interest

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Authors' Contribution

Study Conception: SE, EA; Study Design: SE; Supervision: SE, EA, CE; Materials: SE, EA, CE; Data Collection and/or Processing: SE, EA, CE; Statistical Analysis and/or Data Interpretation: SE, CE; Manuscript Preparation: SE; Critical Review: SE, EA, CE.

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Case Report

Use of SGLT-2 Inhibitor in Decompensated Heart Failure Presenting with Bilateral Resistant Pleural Effusion

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ABSTRACT

Chronic diseases concomitantly decrease quality of life and lifespan expectancy. Novel medications, including Sodium-glucose-co-transporter-2 inhibitors (SGLT-2i), affect both diabetes, heart failure, and diabetic kidney disease. These multisystemic effects give patients with mono systemic and multisystemic diseases new treatment options. Recent studies have shown that SGLT2i may benefit heart failure patients without diabetes. In this case report, we presented a 65-years old patient who was admitted to the emergency room with shortness of breath. Bilateral pleural effusion was observed in the chest X-ray. After etiological studies, empagliflozin was initiated for pleural effusion, which is thought to be related to heart failure. The patient's symptoms declined on the fourth day of the treatment, and the control lung X-ray revealed that the effusions declined.

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Keywords: *Pleural effusion, heart failure, SGLT-2 inhibitors.*

Introduction

Chronic diseases constitute a significant group that reduces the quality of life, especially in the middle-advanced age group. New treatment options provide a better quality of life in hypertension, diabetes, kidney, and heart failure. Multiple chronic diseases result in a higher risk of cardiovascular events and death.[1] Treatment options, particularly in low ejection fraction heart failure, include improving health status (symptoms, physical function, and quality of life) reducing the rate of hospitalization and mortality. Sodium-glucose-co-transporter-2 inhibitors (SGLT-2i), introduced as an oral antidiabetic, have been shown to reduce hospitalization rate and improve quality of life regardless of diabetes in patients with heart failure.[2] SGLT-2 inhibitors have proven to be very effective for glycemic control and have adjunctive effects in managing heart failure, hypertension, diabetic nephropathy, and even weight loss.

SGLT2i are effective osmotic diuretics on proximal tubules that maintain heart function by reducing volume load and blood pressure. It affects partly by reducing atrial-natriuretic-peptide and diuretic resistance and inhibiting Na-H modifiers and sympathetic tone.[2] It has also been reported that SGLT2i have anti-inflammatory and anti-fibrotic effects and reduce oxidative stress. Herein, we reported the management of a 65-year old female patient with decompensated heart failure.

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Case Report

A 65-year-old female patient with a history of diabetes, hypertension, chronic renal disease, and tuberculosis was admitted to the emergency room with shortness of breath. She had no fever (36.8 °C), tachycardia (75 beat/min), hypertension (130/80 mmHg), or hypoxemia (SaO_2: 88%). Respiratory sounds were decreased in bilateral middle and lower zones. Chest X-ray shows bilateral pleural effusion extending to the middle zones (*Image 1A*). Computed tomography reports pleural effusion up to fissure level in the right and left lungs. Pleural fluid studies, including; cell count, total protein albumin, glucose, lactate dehydrogenase (LDH), adenosine deaminase (ADA), acid-fast bacilli (AFB), and cytology is, consisted of a transudate. The cytology was reported as reactive inflammatory effusion. Bilateral chest tube drainage was applied for the management of massive effusion.

Repeated AFB and ADA results were negative for tuberculosis. The echocardiographic evaluation of the patient was compatible with heart failure (left heart cavities were dilated, left ventricular global hypokinesis, mild mitral insufficiency, and ejection fraction calculated as 30%). Since the patient's pleural effusion did not regress with diuretic therapy, SGLT2i (empagliflozin 10 mg/day) was started. Pleural effusions decreased, and symptoms were declined in the control lung x-ray of the patient on the fourth day of the treatment. After room air sPO2 was determined as 95%, the patient was discharged with empagliflozin treatment. The outpatient control chest X-ray shows significant regression in pleural effusion (*Image 1B*).

Discussion

SGLT2i in heart failure has been shown to reduce hospitalizations in the acute condition and the chronic period. Ipragliflozin, the first SGLT-2 inhibitor approved in Japan, treatment was started for a patient who had a history of hospitalization at least four times in the last five years. For two years, no hospitalization for heart failure was required during the ipragliflozin treatment.[3] As in our case, signs, and symptoms were regressed with empagliflozin treatment. Bilateral pleural effusion was resolved entirely within three weeks under empagliflozin treatment.

In the analysis of the EMPA-REG study, involving 7020 patients with a high risk of cardiovascular disease, which compared the placebo with empagliflozin (10 mg and 25 mg) groups, it was reported that the need for furosemide was significantly decreased in patients using empagliflozin.[4] Our patient's diuretic requirement was finished entirely after the sixth week of empagliflozin treatment.

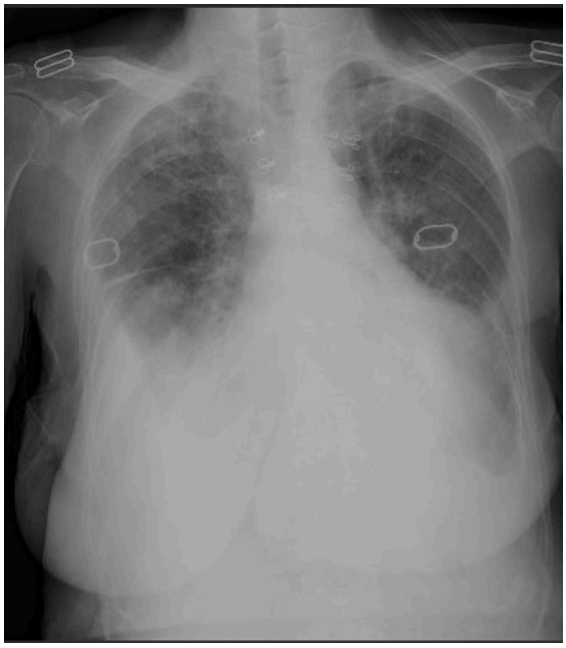

Image 1A. Before the use of SGLT-2 inhibitors.

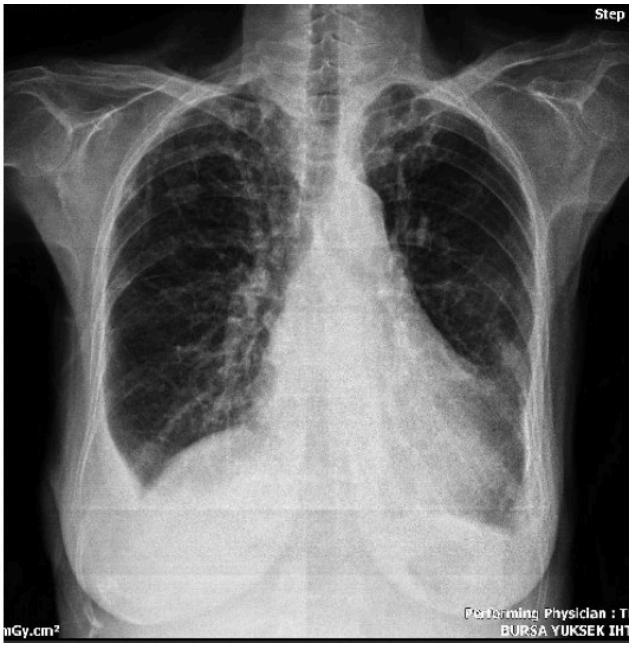

Image 1B. After the use of SGLT-2 inhibitor.

In the RECEDE CHF study conducted with 23 participants, a significant increase in 24-hour urine volume was found on the third and sixth weeks when the empagliflozin group was compared with the placebo group. Empagliflozin with a loop diuretic treatment results in a significant increase in 24-hour urine volume without increasing urinary sodium.[5] Our patient did not require the addition of loop diuretics six weeks after treatment. Since a minimal glomerular filtration rate (GFR) decrease was experienced in the first week, the GFR turned back to the expected value within two weeks.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

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Authors' Contribution

Study Conception: NK, BT, EK, UA; Study Design: NK, BT, EK, UA; Supervision: NK; Funding: NK; Materials: NK, BT, EK, UA; Data Collection and/or Processing: NK, BT, EK, UA; Statistical Analysis and/or Data Interpretation: NK, BT, EK, UA; Literature Review: NK, BT, EK, UA; Manuscript Preparation: NK, BT, EK, UA; Critical Review: NK.

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Case Report

Low-Dose Methotrexate Toxicity in a Hemodialysis Patient: A Case Report

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ABSTRACT

Methotrexate (MTX) is an effective drug used to treat various diseases, especially rheumatological diseases. However, myelosuppression is a severe side effect, the frequency of which increases in patients with renal insufficiency. Here, we presented a chronic hemodialysis patient who developed pancytopenia and mucositis after using low-dose MTX to treat psoriasis.

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Keywords: *Methotrexate, adverse effect, myelosuppression, renal insufficiency, dialysis, pancytopenia, mucositis.*

Introduction

Methotrexate (MTX) is widely used to treat various malignancies and chronic inflammatory diseases. This antimetabolite agent impairs DNA synthesis by competitively inhibiting the dihydrofolate reductase enzyme. MTX may cause side effects such as nausea, stomatitis, myelosuppression, hepatic, renal and pulmonary toxicity due to usage in its high doses, decreased elimination and polypharmacy. Since the primary excretion site is the kidneys (90%), MTX may accumulate in cases with impaired renal function. Herein, we presented a subject in the hemodialysis (HD) program and developed pancytopenia and mucositis due to using low-dose MTX to treat psoriasis.

Case Report

A 30-year-old female patient with psoriasis and hypertension was treated with intermittent HD for end-stage renal disease secondary to membranoproliferative glomerulonephritis. The patient was using ramipril, amlodipine, carvedilol, doxazosin and moxonidine. Two weeks ago, a dermatologist started subcutaneous 7.5 mg/week MTX treatment for psoriasis. Four days after the first dose, the patient developed diarrhoea and increased after the second MTX administration. Two days later, severe widespread abdominal pain developed. There were plaques on the oral mucosa, crusty ulcerations on the lips, widespread erythematous plaques in the body, widespread abdominal tenderness, voluntary defence, and rebound in his

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physical examination. Other system examinations were normal. Abdominal CT angiography performed with the preliminary diagnosis of the acute abdomen revealed diffuse edematous wall thickening, increased mucosal staining, and marked valarectasis in the colon loops, ascending colon, and cecum. In the laboratory examination, leukocyte 1.910/mm³, neutrophil 1360/mm³, hemoglobin 8.7 g/dL, platelet 76,000/mm³, CRP 207 mg/L, vitamin B12 level 125 ng/L in peripheral blood. His blood MTX level was 0.03 mcmol/L. Blood CMV-DNA PCR was negative. There were no parasites in the stool.

A bone marrow biopsy was performed because atypical cells were seen in the peripheral smear. The bone marrow imprint material revealed an increase and paused in early myeloid elements. Although the serum MTX level was low due to the 6-8 hour serum half-life of MTX, we considered MTX toxicity due to pancytopenia and mucositis after the last MTX treatment, and she was hospitalized. We started folinic acid 3x50 mg, granulocyte colony-stimulating factor 5 mcg/kg/day, vitamin B12 replacement and total parenteral nutrition for oral intake insufficiency due to mucositis. Upon the deepening of pancytopenia, we replaced erythrocyte and thrombocyte suspensions. She recovered from neutropenia on the 8th day of his hospitalization. The patient continued the routine HD program. She received ciprofloxacin and metronidazole treatment for ten days. After 15 days of hospitalization, the patient's clinical condition improved, and she was discharged.

Discussion

Methotrexate is a folic acid analogue, and it binds to dihydrofolate reductase, reducing thymidylate, purine synthesis and cell proliferation. And also, methotrexate is a disease-modifying, anti-rheumatic drug used in treatment schemes of different diseases; however, long-term use may cause side effects in 61% of patients and may lead to discontinuation of the drug in 20% of patients.[1] High-dose MTX is defined as a dose greater than 500 mg/m^2 given intravenously and is mainly used to treat diverse malignancies.[2] Low-dose treatment (5 mg to 25 mg once weekly) has been widely and safely used to treat rheumatoid arthritis and psoriasis, and many other rheumatologic diseases.

The kidneys excrete more than 90% of MTX and its metabolites through both glomerular filtration and tubular secretion; therefore, renal failure is a limiting risk factor for side effects that may occur for MTX treatment. Myelosuppression is one of the most feared side effects.[3,4] In our case, oral mucositis and gastrointestinal mucositis developed as side effects besides pancytopenia. According to an analysis of 11 clinical studies of 496 patients, patients using MTX to treat rheumatoid arthritis were found to have a fourfold increased probability of excessive toxicity in patients with reduced kidney function compared to those with average creatinine clearance.[5] As in our case, cases of pancytopenia associated with the use of low-dose MTX have been reported in HD patients.[6-8] Deaths have been reported as a result of the use of 2.5 mg MTX in HD patients.[9,10]

On the other hand, Mori et al.[11] retrospectively analyzed 40 cases of low-dose MTX induced myelosuppression. They stated that serum albumin levels and folic acid supplementation were the most critical risk factors affecting the severity of pancytopenia. In our case, the serum albumin level was not very low and timely, and the appropriate dosage of folic acid replacement perhaps caused pancytopenia to last shorter than expected.

Boey et al.[12] strongly recommended that MTX toxicity be carefully monitored in patients with stage 3 or stage 4 kidney disease, and MTX should not be used in patients with stage 5 kidney disease. Diskin et al. [13] reported that the amounts of MTX in the dialysate were completely equal in the first hour of both HD and peritoneal dialysis, but not after the first hour. Indeed, HD is superior because of the constantly renewed dialysate. But neither method could prevent the patient's death.[13] Alzate et al.[14] prevented MTX-related toxicity in peritoneal dialysis patients by switching to multiple exchange peritoneal dialysis without transferring the patient to HD. In another study, researchers reported that acute intermittent HD with a high-flux dialyzer was effective in MTX clearance in 6 patients.[15]

In 2012, the US FDA approved glucarpidase, a recombinant form of carboxypeptidase G2, a bacterial enzyme that splits MTX into two catabolites for intravenous use in MTX toxicity in renal failure. Currently, data on the use of glucarpidase in low-dose MTX toxicity are lacking.[16] In conclusion, management of MTX toxicity is directed towards increasing MTX elimination in conjunction with folinic acid rescue therapy.

Conclusion

One of the reasons why MTX is not sufficiently removed by dialysis is the tight binding to plasma proteins and accumulation of metabolites in the cell. Under normal conditions, MTX treatment is not recommended in HD patients. However, it can be applied by reducing the dose, especially in malignant diseases with no alternative option. In this case, MTX was prescribed because there was no response to secukinumab in the treatment of psoriasis. It should be kept in mind that toxicity may develop even with low-dose MTX use in HD patients, and the patients should be followed closely.

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: TY; Study Design: MS; Supervision: KA; Materials: FA; Data Collection and/or Processing: TY, MRG; Statistical Analysis and/or Data Interpretation: TY, MRG; Literature Review: MS; Manuscript Preparation: MS, AE; Critical Review: AE.

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Case Report

Development of AA Amyloidosis in a Patient with Psoriasis: A Case Report

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ABSTRACT

Psoriasis is a chronic, recurrent, inflammatory and common skin disease of unknown aetiology. Amyloidosis is defined as a heterogeneous group of diseases in which generally soluble plasma proteins accumulate in the extracellular space as insoluble abnormal fibrils. Type AA amyloidosis is a late and severe complication of chronic inflammatory disorders and some chronic infections. Although psoriasis is a common inflammatory skin disease, the development of amyloidosis is rare. Herein, we presented a case of psoriasis who developed AA-type amyloidosis.

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Keywords: *AA amyloidosis, secondary, reactive, complication, chronic inflammation, psoriasis.*

Introduction

Amyloidosis is a heterogeneous group of diseases and is recognized by showing the accumulation of insoluble abnormal fibrillar forms of soluble proteins in the extracellular space in a tissue sample. The accumulation in primary amyloidosis is associated with a systemic or generalized type of monoclonal plasma cell proliferation. In secondary (reactive) amyloidosis, the accumulation is caused by an underlying chronic disease. Approximately 45% of amyloidoses are reactive amyloidosis. The leading causes of reactive amyloidosis are chronic infections, inflammatory diseases and malignancies. Although psoriasis is a common inflammatory skin disease, the development of amyloidosis is rare. Here, we presented a psoriatic case of secondary type amyloidosis.

Case Report

A 64-year-old female patient was followed for two years to diagnose plaque psoriasis on the scalp and joint extensor faces. There was no regular treatment for psoriasis. The patient had a history of swelling, pain and redness in the right ankle six weeks ago, and she used non-steroidal anti-inflammatory drugs and antibiotics. Her swelling and redness regressed, but the pain continued. She was admitted to the emergency service with a complaint of weakness and dry mouth. On the physical examination: there were no signs of swelling, hyperemia, temperature increase, or oedema in the right ankle. A lesion suggestive of psoriatic plaque was observed in the sacral region of the patient. Pretibial oedema was a bilateral positive. In the laboratory examination:

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leukocyte 16,300/mm^3, hemoglobin 8.9 g/dL, platelet 372,000/mm^3, CRP 204.6 mg/L, serum albumin 2.6 g/L, creatinine 6.4 mg/dL, urea 195 mg/dL, potassium 7.2 mmol/L. Her arterial blood gas analysis showed metabolic acidosis (pH 7.24 and HCO_3 16.1 mmol/L). Urinalysis showed microscopic hematuria and protein positivity (+). There was no dilatation in bilateral pelvicalyceal structures in the urinary system ultrasonography (USG), and we excluded from post-renal kidney injury. We hospitalized her and started the patient dialysis treatment for acute renal dysfunction. On the 2nd day, the patient had macroscopic hematuria. We performed a kidney biopsy considering rapidly progressive glomerulonephritis due to restriction of urine output, detection of 3,360 mg/day proteinuria in 24-hour urine and macroscopic hematuria. After the biopsy, we applied 250 mg of methylprednisolone for three days and then 40 mg of methylprednisolone. A full immune evaluation revealed negative anti-nuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), anti-double-stranded DNA (anti-dsDNA), anti-Sm, anti-Ro, anti-La, rheumatoid factor (RF), and anti-cyclic sitrüline peptide antibody (anti-CCP). Protein electrophoresis, serum immunoglobulin, C3 and C4 serum levels were normal. The pathological result was compatible with AA-type amyloidosis.

Urinary system USG was performed in the patient whose hematuria continued to increase. In the cystoscopy of the patient with bladder floor irregularity, an organized hematoma filling the inside of the bladder was observed. The hematoma was partially cleared with cystoscopy. B-51 and B-13 allele genes were detected to determine the patient's HLA-B groups. Both sacroiliac joints were observed in normal width in the sacroiliac joint radiography, but periarticular sclerosis was noted on both sides (bilateral grade 2 according to New York criteria). No uveitis was detected in the eye examination. The patient did not need HD after six sessions. Her urine output increased. We planned to gradually decrease the corticosteroid treatment dose and discontinue the corticosteroid treatment, and started colchicine 0.5 mg twice a day.

Discussion

Causes of AA amyloidosis include rheumatic diseases (ankylosing spondylitis, rheumatoid arthritis, juvenile arthritis), idiopathic diseases (sarcoidosis, Crohn's disease, ulcerative colitis, Rosai-Dorfman disease), hereditary diseases (familial Mediterranean fever [FMF], tumour necrosis factor-associated periodic fever syndrome), infectious diseases (tuberculosis and leprosy), and malignant tumours (mesothelioma and Hodgkin's disease).[1] Few cases of coexistence of psoriasis and amyloidosis have been reported to date.[2] The first case of psoriasis-associated amyloidosis was described in 1965.[2-4] Therefore, we tried to exclude other diagnoses accompanying amyloidosis in our patient, who did not have any other known comorbidities other than the diagnosis of psoriasis.

In Turkey, a Mediterranean country, the most common cause of reactive amyloidosis is FMF disease, a hereditary familial disease.[5] Our patient was born in Azerbaijan. We avoided the diagnosis of FMF because she did not describe abdominal pain and fever attacks in his childhood, and she did not have a family history of FMF. Since rheumatoid arthritis is one of the most common causes of reactive amyloidosis, RF and anti-CCP were requested for diagnosis. The results were negative, and the diagnosis of rheumatoid arthritis was excluded because the patient did not have a history of morning stiffness or involvement in small joints.

The patient, who was evaluated for another cause, ankylosing spondylitis (AS), had no symptoms that would meet the diagnostic criteria and no findings suggestive of inflammatory bowel disease. She has no enthesopathy. No uveitis was detected in the eye examination. In the sacroiliac joint X-ray, both sacroiliac joints were found to be of normal width, but periarticular sclerosis was noted on both sides (bilateral grade 2 according to New York criteria). For the presence of sacroiliitis or axial spondyloarthritis or AS, the presence of bilateral stage 2 or unilateral at least stage 3 sacroiliitis is required.[6] However, considering the clinical symptoms, the diagnosis of AS was dismissed. Distal interphalangeal involvement, asymmetric sacroiliitis or spondylitis, dactylitis

and enthesitis can be seen in psoriatic arthritis.[7] In a patient diagnosed with psoriasis, this involvement may be associated with psoriatic spondyloarthritis.

Systemic lupus erythematosus (SLE), Behçet's disease and Takayasu's arteritis are rare causes of reactive amyloidosis.[5] In our patient, malar rash, photosensitivity; Since ANA, anti-dsDNA, Anti-Sm, Anti-Ro, Anti-La antibodies were not positive, the diagnosis of SLE was ruled out. Our patient had good peripheral pulses. She had no findings to suspect Takayasu's arteritis. HLA B51 alone was not found to be significant in a patient with female gender, but HLA B51 single allele positivity, who did not describe oral aphthae, genital ulcer, pustular rash, or uveitis attack. Although the HLA-B51 antigen differs between ethnic groups, it is present in approximately 20% healthy individuals.[8]

Gregory et al.[4] reported psoriasis-associated amyloidosis in 18 patients in their 1950-1992 Mayo Clinic screening. Twelve of them had psoriatic arthritis, and four had pustular psoriasis.[4] Psoriatic arthritis is chronic inflammatory arthritis associated with psoriasis involving the peripheral joint, spine, and enthesis area.[7] It can be thought that this situation facilitates the development of amyloidosis in psoriatic patients.[2] It can be considered a psoriatic arthritis attack in our patient who had arthritis symptoms six weeks before hospitalization. In amyloidosis accompanying psoriasis, amyloid deposition is frequently seen in the kidneys, gastrointestinal tract, or both systems. When amyloidosis is detected in most cases, the diagnosis of psoriasis is an average of 14.4 years.[2] In our case, the diagnosis of psoriasis was made two years ago, which is a very early period for the detection of amyloidosis, according to the literature.

Considering the patient's recent high-dose NSAID, the nephrotic syndrome may be thought to be due to NSAID use. The association of NSAIDs and the nephrotic syndrome has been recognized for a long time, and minimal change disease and membranous nephropathy were the most common findings in kidney biopsies of these patients.[9] Considering that minimal change disease does not show any results on light microscopy, a biopsy may have enabled us to diagnose amyloidosis incidentally. The patient's current nephrotic syndrome may be due to NSAID use, amyloid deposition, or both. Arthropathy is also present in 85% of patients with amyloidosis accompanying psoriasis.[2,3] In the study of Gregory et al.[4], most of the patients had psoriatic arthritis or pustular psoriasis. In other words, it is seen that amyloidosis can develop in patients with more severe psoriasis. Amyloid deposition accompanying psoriasis is a rare complication detected later than other diseases accompanied by amyloidosis. However, in our case, it was observed that this situation was not always late, but amyloid deposition could be observed earlier.

Conclusion

Colchicine treatment is mandatory to prevent AA amyloidosis in FMF, which is one of the important diseases that cause amyloid deposition.[10] Suppose the amyloid deposition is detected in such a short time in psoriasis. Would it be a correct approach to give colchicine prophylaxis to every patient, as in FMF, to prevent amyloidosis? Other similar observations are needed to answer this question.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: MS; Study Design: MS; Supervision: AY, AO, MY, MG, KD; Materials: MS, SEGB; Data Collection and/or Processing: MS, SEGB; Statistical Analysis and/or Data Interpretation: MS, SEGB; Literature Review: MS; Manuscript Preparation: MS, AE; Critical Review: AE.

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Case Report

Post-COVID ANCA-associated Vasculitis: A Case Report

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ABSTRACT

Although it has been reported rarely in the literature in patients who develop acute kidney injury after COVID-19 disease, ANCA-related vasculitis should also be kept in mind. Thus, it is possible to reduce mortality and morbidity. We presented a middle-aged male patient who was diagnosed with post-COVID ANCA-associated vasculitis.

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Introduction

The new coronavirus disease 2019 (COVID-19), which severe acute respiratory syndrome coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) is responsible for, is a highly contagious respiratory infection disease. This viral syndrome affects many organs and systems, including the kidneys, apart from the lungs.[1] Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are life-threatening autoimmune diseases frequently accompanied by necrotizing rapidly progressive crescentic glomerulonephritis, which include findings of glomerulonephritis in mononuclear cell infiltration of small and medium-sized vessels and kidney biopsy. In the literature, various complications and symptoms that spread over a long period of time have been described in cases with a history of COVID-19 disease.[2] Anti-glomerular basement membrane disease, de novo ANCA-associated vasculitis with glomerulonephritis and IgA vasculitis with nephritis (Henoch-Schönlein purpura) have been reported in cases with COVID-19 infection.[3-5] We presented a case of ANCA-associated vasculitis after COVID-19.

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Case Report

A 51-year-old male patient diagnosed with chronic obstructive pulmonary disease and diabetes mellitus was followed up in the chest diseases clinic after the diagnosis of post-COVID pneumonia with the complaint of shortness of breath about one month after the COVID-19 treatment was completed. In the patient's physical examination, there was ral in the bilateral bases in the lungs. There was no feature in the cardiovascular system and abdominal examination. Pretibial oedema was negative. There was no history kidney disease (previous laboratory results showed a serum creatinine of 0.90 mg/dL 3 months before). When he was consulted to the nephrology department due to high creatinine (5.4 mg/dL) and urea (134 mg/dL) levels during his hospitalization, he was intermittently taken to hemodialysis considering acute kidney injury (AKI). Other blood tests were: leukocytes $17.2x10^9$/L, hemoglobin 8.3 g/dL, platelets $271x10^3$/L, potassium 4.4 mmol/L, sodium 135 mmol/L, albumin 2.9 g/dL, and CRP 132 mg/L. In arterial blood gas analysis, pH was 7.32, HCO_3 was 15.3 mmol/L, lactate was normal, and anion gap was 10, consistent with metabolic acidosis. There was microscopic hematuria and protein positivity (++) in the urinalysis. Daily protein loss in urine was 2 g.

Anti-nuclear antibodies (ANA), ANA profile, proteinase-3 (PR3), anti-glomerular basement membrane (anti-GBM) and hepatitis markers were negative. Cytoplasmic-antineutrophil cytoplasmic antibodies (C-ANCA), perinuclear-antineutrophil cytoplasmic antibodies (P-ANCA) and myeloperoxidase (MPO) were positive at 1/10 titer (end-point). Serum protein electrophoresis complements C3 and C4, immunoglobin G, A, and M were within normal limits. Chest computed tomography revealed bilateral pulmonary infiltration and nodular cavitary lesions (Image 1). We diagnosed the patient with ANCA-associated vasculitis, administered 500 mg of cyclophosphamide treatment, and continued methylprednisolone at a continuous dose of 0.5 mg/kg. A permanent jugular venous dialysis catheter was inserted because the patient's need for hemodialysis continued. We discharged the patient with two sessions of dialysis per week.

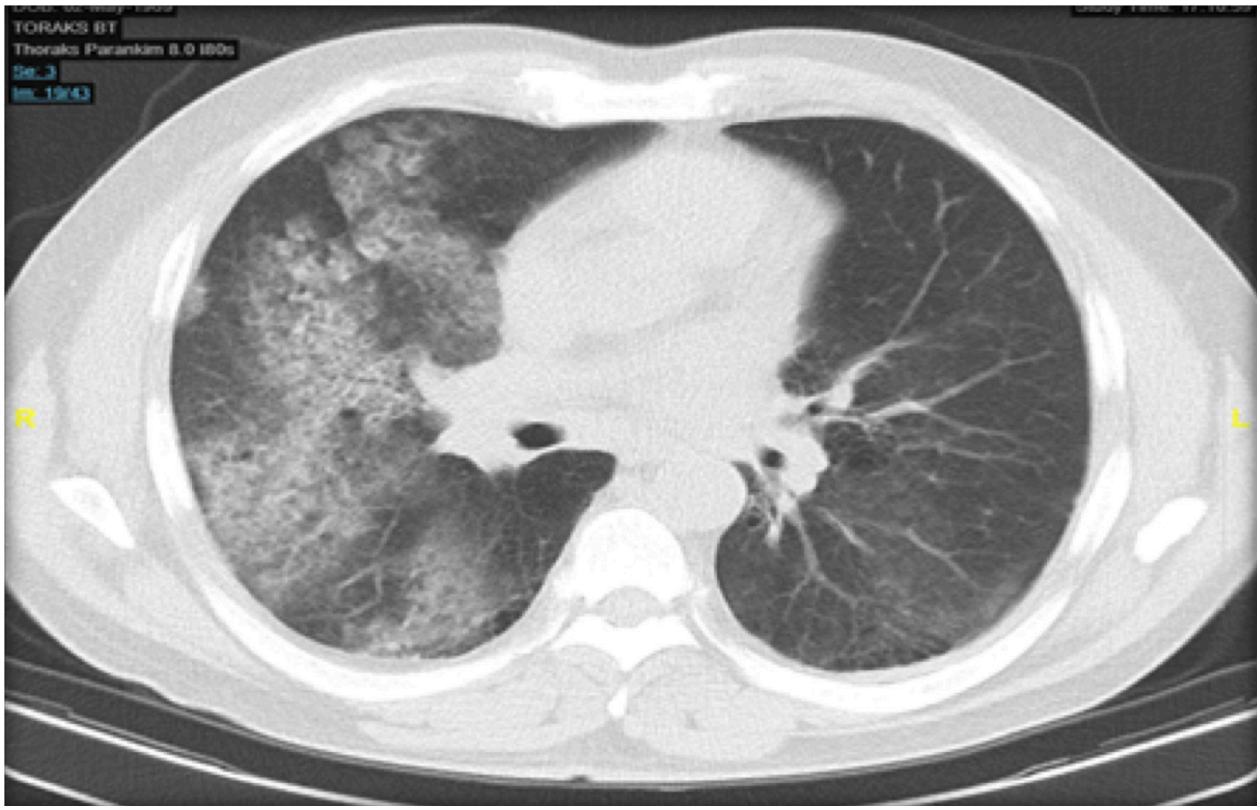

Image 1. The appearance of the lesions in the chest computed tomography of the case.

Discussion

COVID-19 has been a significant global economic and health burden. COVID-19 primarily affects the respiratory system, but kidney involvement is not uncommon. The relationship between COVID-19 disease and acute kidney injury is well known, but the number of cases in which COVID-19 and ANCA-associated vasculitis coexist is rare in the literature. In a systematic review, Wong et al.[2] analyzed the relationship between COVID-19 and vasculitis. Among 9 cases of vasculitis, 4 had Kawasaki disease, 3 had leukocytoclastic vasculitis, and 2 had IgA vasculitis. One of the cases did not respond to treatment and died.[2]

Morris et al.[6] reported that a patient who developed ANCA-associated vasculitis after COVID-19 had lung involvement due to vasculitis and the need for hemodialysis. Because of the worsening of the coagulopathy, they diagnosed vasculitis without performing a kidney biopsy. After the clinical condition of our patient stabilized, we continued intermittent dialysis. We also diagnosed ANCA-associated vasculitis in our case without renal biopsy based on clinical and laboratory findings and radiological imaging, and applied immunosuppressive treatment. One required hemodialysis in the other two COVID-19-related cases, and the other did not.[5] In some instances of ANCA-associated vasculitis developed after COVID-19, renal replacement therapy was not required, although severe kidney damage was present at the time of diagnosis.[7,8]

Duran et al.[9] applied glucocorticoid and cyclophosphamide treatment in patients with ANCA-associated vasculitis developing after COVID-19. Unlike our case, Uppal et al.[5] preferred to use rituximab with glucocorticoids to treat ANCA-associated vasculitis after COVID-19.

Conclusion

ANCA-associated vasculitis should also be considered in the differential diagnosis of COVID-19 cases presenting acute kidney injury. Diagnostic kidney biopsy may not always be possible in patients with COVID-19 who have renal involvement due to the risk of hypercoagulation and venous thromboembolism. Therefore, in selected cases, anamnesis, physical examination, laboratory and imaging findings should be evaluated together, and treatment should not be delayed. In conclusion, the possibility of ANCA-related vasculitis should be considered in the aetiology of acute kidney injury.

Acknowledgment

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: KO, MS; Study Design: MS; Supervision: AY, AO, MY, MG, KD; Materials: KO, MS, SEGB; Data Collection and/or Processing: KO, MS, SEGB; Statistical Analysis and/or Data Interpretation: KO, MS, SEGB; Literature Review: KO, MS; Manuscript Preparation: KO, MS, AE; Critical Review: AE.

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Oral Communications

OC001

Gamma Glutamyl Transferase (GGT) Levels in Individuals with Vitamin D Deficiency

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Background Low serum 25-hydroxy-vitamin D levels have been associated with dyslipidemia and also cardiovascular diseases but the mechanism underlying these associations is not clear. Epidemiological studies suggests that, there is a relationship between high gamma glutamyl transferase (GGT) activity levels and coronary heart disease (CHD) or death risk due to CHD. High GGT activity level is associated with cardiovascular risk factors, metabolic syndrome, systemic inflammation, oxidative stress ; multiple cardio-metabolic risk factors including several comorbidities that have negative effect on the patient's risk profile and prognosis. In this study, we aimed to compare the GGT levels of the individuals with vitamin D deficiency and normal vitamin D levels.
Material and Methods In this cross-sectional study, data collected routinely in a general hospital laboratory database from 2020 to 2021 were used. 25-hydroxy-vitamin D and GGT levels of the patients were registered. Exclusion criteria were: <18 years, hypertension, diabetes mellitus, chronical kidney failure, alcohol users and liver function levels of more than 3 times normal. Furthermore, patients who recieved vitamin D defficiency diagnosis and took a treatment excluded from the study. Patients were evaluated as group 1 with vitamin D deficiency and group 2 with normal vitamin D levels as the control group. Group 1 was consisted of total 322 patients with low vitamin D levels (average age 54.4±12.2 years, 120 male %37.2); group 2 was the control group with total of 343 patients with normal vitamin D levels (average age 49±11.3, 125 males 36.4%). Clinical treshold levels of 25(OH)D was evaluated as deficient (<20 ng/mL), moderately deficient (≥20–30 ng/mL), and optimal (≥30 ng/mL). GGT ≥73 U/L levels was accepted as high.
Results Total 322 patients with vitamin D deficiency included in the study, 109 of the 322 patients were deficient, remaining 213 patients were detected as moderately defficient. GGT levels were significantly higher in patients with low vitamin D levels compared to the control group. (Group 1 average GGT 81±11 U/L, Group 2 average GGT 43±18 U/L) (p<0.002). GGT levels were significantly different between the patients with deficient and moderately defficient Vitamin D.(GGT levels in vitamin D deficient group: 85±13 U/L; GGT levels in vitamin D moderately deficient group: 75±12 U/L) (p<0.05).
Conclusions The relationship between Vitamin D deficiency and cardiovascular diseases has been shown previously. In the recent study; it's demonstrated that the GGT level is higher in people with vitamin D deficiency, and also this elevation increases as the vitamin D decreases. The fact that the mechanism of cardiovascular risk and vitamin D deficency is unclear suggests that increased GGT levels have a place in this mechanism. GGT may be used as a cardiovascular predictor in individuals with vitamin D deficiency due to oxidative stress and systemic inflammation. Randomized, controlled, large prospective studies are needed for this.

OC002

The Comparison of Target Variables for Secondary Prevention of Coronary Artery Disease between Smoker and Non-Smoker Patients

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Background Secondary prevention of coronary artery disease (CAD) involves both control of risk factors and therapeutic options for protecting the coronary arteries from plaque eruption. We think that people who continues smoking after coronary events are more resistance to accept advices for modifying their life styles or using drugs regularly. Thus, we hypothesized in this study that reaching optimal goal of secondary prevention in patients who continued smoking might be more difficult than those who gave-up smoking after coronary events.
Material and Methods We retrospectively collected 150 patients, who had coronary artery events in this observational study. Patients were divided into three groups, as continued smoking (CS) (n=34), gave-up smoking (GS) (n=91), and smoking again after gave-up (SAG) (n=25). The variables for secondary prevention of CAD were compared between groups.
Results SAG patients were older than CS group (p=0.036). Regularly drug use was lower in CS patients than in GS patients (p=0.009). CS patients had more frequent regularly fitness than SAG patients (p=0.009).

There were no statistically significant differences between groups with respect to weight loss, rates of diet, blood cholesterol and triglyceride levels, and HbA1c levels. In the follow-up, CS and SAG patients had more frequent coronary events than GS patients (p<0.0001).

Conclusions Patients continuing cigarette smoking were worse for regularly drug use after cardiac events. Morover, this group had more frequent cardiac events as expected. But there were no statistically significant differences between groups for other target variables of secondary prevention of CAD.

Table 1. The comparion of demographic, clinical, and laboratory characteristics between groups.

Variables	Smoking group (N=34)	Non-smoking group (N=91)	Re-smoking group (N=25)	p value
Age, years	58.7(13.3)[a]	63.2(11.7)	66.9(11.4)[b]	**0.036**
Gender male, n(%)	6(17.7)	27(29.7)	6(24)	0.382
Hypertension, n (%)	28(82.4)	73(80.2)	23(92)	0.386
Diabetes mellitus, n (%)	14(41.2)	42(46.2)	13(52)	0.711
Cerebrovascular events, n (%)	0(0)	0(0)	0(0)	NA
Thyroid dysfunction, n (%)	0(0)	5(5.5)	0(0)	0.340
Peripheral arterial disease, n (%)	1(2.9)	0(0)	0(0)	0.393
Chronic kidney disease, n (%)	0(0)	1(1.1)	0(0)	1.000
Cigarette status				
When stopped smoking?	-			0.583
in-hospital	-	60(65.9)	15(60)	
after discharge	-	31(34.1)	10(40)	
Why stopped smoking?	-			0.461
Doctors advice	-	39(42.9)	13(52)	
Family force	-	18(19.7)	6(24)	
Death fear due to MI	-	34(37.4)	6(24)	
MI type				0.133
Anterior STEMI	8(23.5)	19(20.1)	8(32)	
Inferior STEMI	16(47)	25(27.5)	7(28)	
Non-STEMI	10(29.4)	47(51.6)	10(40)	
Regularly drug use, n (%)	9(26.5)[b]	51(56)[a]	10(40)	**0.009**
Fitness regularly, n (%)	15(44)[a]	25(27)	2(8)[b]	**0.009**
Weight loss, n (%)	19(55.9)	46(59.1)	7(28)	0.078
Weight loss in kg	2.5(0-5)	2(0-5)	2.5(0-3)	0.091
Regular diet, n (%)	22(64.7)	52(57.1)	9(36)	0.077
Regular out-patient clinic control, n(%)	16(47)[a]	69(76)[b]	15(60)	**0.007**
Total cholesterol, mg/dL	165.7(56)	179.4(42)	170.4(50.5)	0.307
Triglyceride, mg/dL	100.3(72-162.6)	119.8(88.2-210.6)	101.7(84.9-124.8)	0.175
LDL cholesterol, mg/dL	102.8(69.2-129.2)	107.6(81.9-127.4)	99.8(68.7-116.1)	0.566
HDL cholesterol, mg/dL	38.9(9.2)	39.9(9.5)	41(8.6)	0.692
HbA1c, before	5.4(5-7.1)	5.6(5-7.6)	6.3(5-7.7)	0.604
HbA1c, after	5.4(5.1-6.7)	5.6(5.1-6.9)	6.1(5.3-7.9)	0.374
Events, n(%)				**<0.001**
No event	11(32)	62(68)	12(48)	
PCI, CABG, arrhythmia	23(68)	29(32)	15(60)	

MI: myocardial infarction, STEMI: ST-segment elevation MI, LDL: low-density lipoprotein, HDL: high-density lipoprotein, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, HbA1c: glycated hemoglobin.

OC003

Investigation of Primary Care and Diabetes Attitudes of Type 2 Diabetes Patients towards the Disease

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Background Type 2 diabetes mellitus (DM) is a common chronic metabolic disease that can be seen at any age, characterized by insufficient insulin production, insulin resistance, or hyperglycemia resulting from both, and causes significant morbidity and mortality. DM is one of the leading causes of death from non-communicable diseases. Patients should be informed about complications due to diabetes and diabetic foot. At the same time, they must comply with the follow-up schedules defined in their outpatient clinics for compliance with medical treatment. For this purpose, it is necessary to evaluate patients' primary care and treatment behaviours for the disease. Thus, the control and management of the disease are facilitated. This study examined patients' self-care and attitudes towards type 2 diabetes disease.

Material and Methods In this descriptive and cross-sectional study, a questionnaire consisting of 13 questions was applied to 300 diabetic patients, which was developed according to the purpose of the research and based on the literature. The study included type 2 diabetes patients aged between 18 and 90 who had no hearing or comprehension problems and agreed to participate in the study.

Results Our study included 138 (46%) male and 162 (54%) female patients. The mean age was 58.9±13.5 years (58.8±12.6 in men and 59±14.3 in women). Age distributions according to gender did not differ (p=0.8). While 26 (8.7%) of the patients were illiterate; 41 (13.7%) were literate, 100 (33.3%) primary school, 35 (11.7%) secondary school, 49 (16.3%) high school, 49 (16.3%) university graduate. Again, 225 (75%) of the patients were married, and 75 (25%) were single. In the assessment of the income status of the patients, 46 (15.3%) stated that their economic status was poor, 168 (56%) moderate, and 86 (28.6%) good. The least disease duration was one year, the longest disease

duration was 50 years (mean duration 11.9±8.3). Of the participants, 164 (50%) had diabetes less than ten years, and 95 (86%) had diabetes between 10-20 years. There was no significant difference between the duration of diabetes according to gender (p=0.11). Only 110 (36.6%) of the patients were receiving insulin therapy. Of the patients, 144 (48%) received insulin administration training and 85 (28.3%) foot/pulse training. 141 (47%) patients stated that they had knowledge about vaccination and 131 (43.7%) patients about diabetes-related complications. Fifty (16.7%) patients applied to the examination every three months as recommended, and 183 (61%) less frequently than once a year. 182 (60.7%) patients had never had an eye examination. The examinations of the participants revealed that 125 (41.7%) had proteinuria screening, and 214 (72%) had electrocardiography (ECG).

Conclusions Since diabetes is a lifelong disease, diabetes education is an essential part of the disease's prevention, treatment, care, and follow-up. Primary care and awareness is the most critical part of the treatment in diabetic individuals. Considering the individual characteristics of the patients, we think that it is essential to determine the missing information and negative attitudes towards the disease, organize training to improve their knowledge and perspectives and carry out studies to increase their awareness in terms of morbidity and mortality.

OC004

The Role of Serum Magnesium Level in Metabolic Dysfunction-Associated Fatty Liver Disease

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Background Metabolic dysfunction-associated fatty liver disease (MAFLD) is a new disease pattern that has been discussed in recent years and is stated to occur as a result of the association of non-alcoholic fatty liver disease (AFLD) with metabolic dysfunction. In the current literature, although the role of serum magnesium (Mg) level in patients with LFS is not clear, few studies emphasize that Mg may be associated with steatosis and inflammation. However, there is no study examining the role of Mg in clinic of MAFLD. In this study, we aimed to examine the role of Mg in MAFLD.

Material and Methods This cross-sectional study retrospectively screened patients who applied to the Balikesir University Faculty of Medicine Internal Medicine Clinic. In the whole group, patients diagnosed with hepatosteatosis by ultrasonography (USG) and accompanied by metabolic disorder-related conditions [obesity, diabetes mellitus (DM), metabolic syndrome (MetS)] were considered as the MAFLD patient group, and those without any pathology were considered as the healthy control group. We compared the two groups' blood glucose, HOMA-IR, Mg levels, and fatty liver fibrosis scores and performed correlation analysis of Mg with other parameters.

Results Our study included 82 (48 females, 34 males) healthy individuals with a mean age of 38.10±12.25 years and 173 (104 females, 69 males) MAFLD patients with a mean age of 39.21±10.32 years. Weight, body mass index (BMI), insulin, HOMA-IR, Mg, NFS and FIB-4 score values were measured as 71.98±15.50 kg, 25.45±4.62 kg/m^2, 8.11±10.60 U/L, 2.33±4.33, 2.05±0.36 mg/dL, -3.28±1.06, and 0.70±0.33, and 85.96±16.12 kg, 31.11±4.57 kg/m^2, 11.71±9.04 U/L, 2.96±2.52, 1.99±0.15 mg/dL, -3.23±1.27 and 0.61±0.28 in the control and patient groups, respectively. After pairwise comparison, there was a statistically significant difference between patient and control groups in weight, BMI, insulin and HOMA-IR ($p<0.05$), but not statistically significant between Mg, NFS and FIB-4 scores ($p\geq0.05$). There was no statistically significant relationship between Mg and other parameters in the patient group ($p\geq0.05$).

Conclusions Our study found no significant difference in serum Mg levels between patients with and without MAFLD. In addition, in the correlation analysis, we did not find a significant relationship between serum Mg levels and insulin resistance and fatty liver fibrosis scores in the patient group. Non-alcoholic fatty liver disease (NAFLD) is a common chronic liver disease worldwide. In the terminology of NAFLD, which occurs due to increased triglyceride load in the liver and concomitant insulin resistance, both the lack of dual etiologies and the inadequacy of the definition of the metabolic disorder have led to the necessity to define this disease as MAFLD in recent years. Mg is an essential element that has a role in intracellular transmission pathways and enzyme systems and plays a role in many physiological events such as cellular energy metabolism, DNA transcription, protein synthesis and electrolyte balance. In addition, studies in the current literature have shown that Mg also plays a role in the pathogenesis of MetS-related diseases such as obesity and DM. However, clinical studies examining the role of Mg in NAFLD patients have had mixed results, and there is no study investigating its role in MAFLD patients. Few studies have emphasized that Mg may be

associated with hepatosteatosis in NAFLD patients. In conclusion, our pioneering research investigating the role of Mg in MAFLD has determined that Mg is not directly related to this disease.

OC005

Evaluation of Diabetic Patients with COVID-19 and Determination of the Contribution of the Severity of Diabetes to COVID-19

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Background The coronavirus disease (COVID-19) continues its impact as a pandemic that threatens public health worldwide. The coexistence of COVID-19 with diabetes mellitus (DM), another global epidemic characterized by chronic hyperglycemia, systemic complications and multi-organ dysfunctions, is known to increase the severity of the disease. This study aimed to analyze the demographic and laboratory findings of diabetic patients followed and treated for COVID-19 and evaluate the severity of diabetes to laboratory findings reflecting the seriousness of COVID-19.
Material and Methods This study was carried out by retrospectively scanning the data of 122 patients with DM who were followed up with the diagnosis of COVID-19 in the internal medicine clinic. Patients with a history of acute or chronic inflammatory, autoimmune or infectious disease, haematological disease, malignancy, renal and hepatic injury, documented cardiovascular disease, and a history of major surgery or trauma excluded in the study. Clinical outcomes were recorded by grouping them as discharge from the hospital, transfer to the intensive care unit, and death. We grouped diabetic patients according to their HbA1c values (≤7.5%, 7.5-9%, and ≥9%) and calculated diabetes age (years) from the time elapsed since the first diagnosis of DM.
Results Our study was conducted with a total of 122 COVID-19 patients, 75 (61.5%) male and 47 (38.5%) female. Of the patients, 5 (4.1%) died, 9 (7.4%) were transferred to the intensive care unit, and 108 (88.5%) were discharged with good recovery. In the patient group with a discharge rate of 88.5%, 50% had HbA1c ≤7.5%, 26.2% had 7.5-9.0% and 23.8% had ≥9%. There was a statistically significant difference in age, ferritin, D-dimer, CRP, LDH and HbA1c variables between death, intensive care transfer and discharge groups ($p<0.05$). Age and LDL-cholesterol were significantly higher in the death group than in the discharge group. While ferritin, D-dimer and CRP were significantly higher in the death and intensive care unit transfer group than in the discharged group, the HbA1c value was significantly higher in the intensive care unit transfer group than in the discharged group. When HbA1c values are grouped, there is a significant difference between these three groups only in glucose ($p<0.05$). Glucose values of the ≤7.5% group were significantly lower than ≥7.5% of all groups, while the glucose values of the 7.5-9.0% group were lower than the ≥9% group. In Spearman's correlation analysis, there was a negative low-level significant relationship between HbA1c and leukocyte values (r: -0.20, $p<0.05$) and a positive high-level association with glucose values (r: 0.77, $p<0.05$). Also, there was a positive low-level relationship between diabetes age and age values (r: 0.36, $p<0.05$) and a negative low-level significant association with lymphocyte values (r: -0.20, $p<0.05$).
Conclusions DM is one of the main comorbidities that affect the course and severity of COVID-19. Our study confirms the severe course of COVID-19, especially in elderly and diabetic patients with high acute phase reactants. In addition, it shows that the severity of diabetes does not have an additional contribution to the course of the disease. More research is needed to reveal the relationship between DM and COVID-19 severity to improve clinical outcomes.

OC006

A Case of Chronic Autoimmune Atrophic Gastritis Accompanying Primary Hyperparathyroidism

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Background Although most cases of primary hyperparathyroidism (PHPT) are sporadic, it may also be a component of the MEN-1 syndrome. In addition, there is a non-hereditary and unexplained association between PHPT and chronic autoimmune atrophic gastritis (COAG). This case is presented to emphasize that COAG can develop in a patient with PHPT without the familial syndrome.
Case Report A 54-year-old female patient with known diagnoses of Hashimoto's thyroiditis and

left nephrolithiasis applied to us with complaints of weakness and widespread bone pain. The patient had a serum ionized calcium (Ca) level of 11.2 mg/dL and an inorganic phosphorus level of 3.3 mg/dL. There was no known liver or renal failure or a history of drug use affecting Ca metabolism. 25(OH)-vitamin D level was 32 ng/mL. While the Ca in 24-hour urine was 225 mg/day, the Ca/creatinine clearance was 0.06. The plasma PTH level was 115.7 mg/dL. Parathyroid scintigraphy revealed that a diagnosis of primary hyperparathyroidism was made based on parathyroid adenoma. In the bone densitometry performed on the patient, the T-score was L1-L4: -3.08. We referred the patient to general surgery for parathyroidectomy. Concurrently, we requested anti-intrinsic factor and anti-parietal antibody tests due to the patient's chronic vitamin B12 deficiency, and both antibodies were positive. After an upper gastrointestinal system endoscopy, multiple gastroscopic biopsies showed chronic atrophic gastritis, achlorhydria and intestinal metaplasia. Control gastroscopy was recommended to the patient one year later.

Conclusions There is a significant association between PHPT and COAG, and it should be kept in mind that these two clinical manifestations can coexist without MEN-1 syndrome. Although the pathological mechanisms underlying this relationship have not been fully elucidated, autoimmunity can be considered a possible cause. We may recommend screening patients with PHPT for COAG and patients with COAG for PHPT.

OC007

Investigation of Compliance with COVID-19 Hygiene Measures in Patients Undergoing Hemodialysis in a University Hospital

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Background The World Health Organization declared the COVID-19 infection as a pandemic on March 11, 2020. Infection is transmitted through the respiratory tract and close contact. For this reason, personal hygiene and social distance-mask measures are important for protection. This study aimed to investigate the compliance of patients undergoing dialysis treatment in the hemodialysis unit with COVID-19 hygiene measures during the pandemic.

Material and Methods The study included 100 (60% male, 67.8% married, 57.8% 56 years and older) patients who underwent routine hemodialysis treatment in our unit and examined the patients' compliance to the hygiene measures with the "COVID-19 Hygiene scale". We scored these categories; hygiene (H), changing hygiene behaviours (CHB), home hygiene (HomeH), social distance mask (SDM), shopping hygiene (SH), hand hygiene (HandH), and hygiene when coming home from outside (CHH) categories.

Results From the epidemic's beginning until 15.07.2021, 12 of our 65 dialysis patients had COVID-19 infection. Mean scores were high in all categories (H 85.7±18.3, CHB 18.5±4.3, HomeH 11.9±3.2, SDM 16.1±2.7, SH 12.7±4.9, HomeH 16.3±4.3, and CHH 9.3±2.9). The scores were similar between the groups when the patients were compared according to marital status, gender, and family structure. HomeH and SH scores were significantly lower in the advanced age group. Total H, SH, HomeH, CHH scores were significantly higher for those with a high education level. Total (82.4±18.6 vs 96.7±12.2, p=0.001) and other H scores (CHB 17.8±5 vs 20.9±3.7, HomeH 11.4±3.2 vs 13.8±2.4, SDM 15.7±2.9 vs 17.2±1.7, SH 11.9±5 vs 15.3±3.7, HandH 15.±4.2 vs 18.6±3.7, CHH 8.9±2.9 vs 10.8±2.1, $p<0.05$) in those with a history of COVID-19 in themselves or a relative were significantly higher.

Conclusions COVID-19 infection in dialysis patients has high morbidity and mortality. This study aimed to determine individuals' personal and general hygiene behaviours according to their socio-demographic characteristics during the COVID-19 epidemic process. Our investigation determined that dialysis patients showed a high level of compliance with individual hygiene measures. The fact that the patient or one of his relatives had a COVID-19 infection positively affected hygiene compliance. Continuing education on patients' compliance with mask, distance and hygiene rules during the pandemic will be beneficial in protecting from COVID-19 infection.

OC008

Does Megaloblastic Anemia Affect Glycated Hemoglobin?

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Background Glycated haemoglobin (HbA1c) is used as a clinical indicator of an individual's blood sugar level in the previous three months. Vitamin B12 deficiency anaemia may cause falsely high HbA1c values due to prolonging erythrocyte (RBC) survival time. In this study, we investigated whether vitamin B12 deficiency anaemia affects HbA1c.
Material and Methods We included a total of 37 patients with a diagnosis of vitamin B12 deficiency anaemia with erythrocyte volume (MCV) >100 fL and vitamin B12 <126 ng/L in the study. The patients had not been diagnosed with diabetes before and were not using any antidiabetic drugs. Fasting plasma glucose (ABG) was <100 mg/dL, HbA1c <6.5%, and hemoglobin (Hgb) <12 g/dL (female) and 13 g/dL (male) in the patients. Patients were given 1 mg/day cyanocobalamin (vitamin B12) orally for three months to treat vitamin B12 deficiency. Hgb, MCV, FPG, HbA1c, vitamin B12 and body mass index (BMI) values of the patients were measured at the beginning and the end of the 3rd month and were compared.
Results A total of 37 patients included in the study consisted of 27 women (72.98%) and ten men (27.02%). The mean age was 38.12±7.71 years in females and 46.62±8.52 in males. While the initial HbA1c value was 6.02±0.37%, the HbA1c value at three months was 5.61±0.46% and was statistically significantly lower ($p<0.001$). While initial vitamin B12 was 112.43±7.18 ng/L and Hgb 11.31±0.28 g/dL, vitamin B12 and Hgb levels at 3rd month were 408.48±119.61 ng/L and 12.26±0.33 g/dL, and the increase was statistically significantly ($p<0.001$ and $p<0.001$, respectively). MCV values statistically significantly decreased from the baseline 104.05±4.03 fL to 93.24±3.98 at three months ($p<0.001$). There was no significant difference between baseline and 3rd-month FPG and BMI values ($p=0.887$, $p=0.839$, respectively).
Conclusions Correction of vitamin B12 deficiency anaemia before any diagnosis or treatment decision is made according to the HbA1c level will prevent patients from being misdiagnosed as diabetes and prevent additional unnecessary intervention in the diabetes treatment of diabetic patients. Giving further treatment to diabetic patients with vitamin B12 deficiency according to high HbA1c will increase the risk of hypoglycemia in patients and bring additional drug costs to the state economies. Early diagnosis and treatment of vitamin B12 deficiency anaemia in diabetic patients can improve glycemic control and prevent or delay complications.

OC009

Retrospective Evaluation of Patients with Acute Leukemia

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Background Acute leukemia (AL) results from malignant transformation of myeloid or lymphoid hemopoietic progenitor cells. In this retrospective study, we aimed to examine the cases of AL over a 10-year period and to compare the obtained findings with the literature.
Material and Methods In our study, age, gender, clinical findings from the file records of 130 AL cases between 1987-1997 in Osmangazi University Faculty of Medicine, department of Hematology. Laboratory characteristics, treatment modalities, response and survival data were evaluated.
Results 130 adult AL cases were studied; 98 (75.4%) had acute myeloid leukemia (AML) 28 (21.5%), acute lymphoblastic leukemia (ALL), 4 (3.3%), acute undifferrentiated leukemia (AUL). The mean age was 43±1.7 years in AML and 30±2.6 years in ALL. 55 (56.1%) male, 43 (43.9%) female of 98 AML patients, 17 (60.7%) male of 28 ALL patients, 11 (39.3%) was a woman. The most common complaint in cases with AML and ALL was fatigue 93.6-92.9%. Sternal tenderness, lymphadenomegaly (LAM) and splenomegaly were significantly higher in patients with ALL. Extramedullary involvement (lymphadenomegaly, hepatomegaly, splenomegaly, gingival hypertrophy) was most frequently detected in the M5 subtype. The leukocyte (WBC) count was 99.303±19.990/µl in the ALL group and 47.843±6.609/µl in AML, with a significant difference ($p<0.01$). Anemia and thrombocytopenia were present in both groups, and the mean hemoglobin value was 7.45±0.21g/dL in AML and 8.8±0.47 g/dL in ALL. Thrombocytopenia was found to be 95.7% in AML and 96.4% in ALL. In AML and ALL, subgroups were recorded from the files. In AML, M5 (23.4%) followed by M3 and M2. In ALL, L2 (85.7%) followed by L1 and L3 subtypes were seen the most. Generally, it was

found that the cases entered remission with one cure. The mean time to stay in remission is 7.6±1.58 months in AML and 9.31±2.35 months in ALL. The most common site of relapse is the bone marrow. The most common cause of death in both groups, respectively sepsis and cerebrovascular accident.

Conclusions In our study, the incidence of ALL, AML, gender distribution, infection rate, weight loss, LAM, splenomegaly, hepatomegaly, central nervous system (CNS) involvement (high in ALL) were found to be compatible with the literature. Complete remission rates, duration of stay in remission and relapse site (boneity) were the same as in the literature, but survival times were found to be shorter than in the literature.

OC010

Evaluation of Relationship between Thyroid Volume and Impaired Glucose Metabolism

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Background Functional and morphological alterations of the thyroid gland generated by insulin resistance and related metabolic disturbances constitute the hot agenda of the endocrine research recently. Impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus (DM) are basic disorders of glucose metabolism in which insulin resistance plays a prominent role. The present case-control study aimed to investigate the changes in thyroid volume and nodule prevalence in patients with disturbed glucose metabolism.

Material and Methods Patients with IFG and IGT were grouped as prediabetes (n=250). The other two groups were type 2 DM (n=141) and a control group (n=261) which consisted of cases with no known glucose metabolism disturbance. All of the patients were recently diagnosed. Body weight, waist circumference, serum TSH levels of all cases were measured. A single operator performed thyroid ultrasonography to all participants.

Results The mean TSH value was found to be significantly higher in DM group than the other two groups (mean TSH of DM group was 1.87±0.9 mIU/ml; that of prediabetes group was 1.49±0.8 mIU/ml and that of the control group was 1.47±0.8 mIU/ml; p<0.001). Mean thyroid volume was significantly different from each other in all groups. It was significantly higher in prediabetics than the control group (18.8±9.0 and 12.8±4.2 ml, respectively), in DM group than the prediabetic group (20.6±8.7 and 18.8±9.0 mL, respectively) (p<0.001). The prevalence of thyroid nodule was significantly higher in DM group than the prediabetic and the control groups, in the prediabetic group than the control group (61.0%, 44.4%, and 17.2%, respectively, p<0.001*)*. Among patients with nodular goiters, the evaluation according to the mean of maximum nodule diameter revealed significantly lower values in the control group (mean value*:* 8.1±3.8 mm*)* than the other two groups (p<0.001). The mean values were higher in DM group than the prediabetics, though not significantly (12.2±7.7 and 11.2±7.2 mm, respectively).

Conclusions: The results demonstrate that patients with DM and prediabetes have significantly increased thyroid volume and nodule prevalence according to the control group. Our findings are probably the first evidence showing prospectively morphological and functional alterations in the thyroid gland caused by a pathological course of disturbed glucose metabolism in which insulin resistance plays a basic role.

OC011

Angina Bullosa Haemorrhagica: A Case Report

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Background Angina bullosa haemorrhagica (ABH); It is characterized by recurrent hemorrhagic bullae in the oral mucosa, it is rare and the cause is unknown. It has been reported in the literature that no concomitant systemic disease has been found. The pathogenesis of the disease is unknown; intraoral local traumas are thought to be the trigger. Spontaneous resolution has been reported within 7 to 10 days. Those located close to the root of the tongue are particular importance as they may cause obstructive respiratory distress with irritation and bleeding. Herein, we presented a patient with recurrent hemorrhagic bullae secondary to local trauma in the oral mucosa.

Case Report 47-year-old female patient was admitted to our clinic with the complaint of recurrent, painless, hemorrhagic bullae in the mouth for 7 years. The lesions usually started suddenly on the floor of the mouth and under the tongue after eating lavash bread and some foods and healed spontaneously within a few days. It was learned that the patient had a history of chronic gastritis and hyperlipidemia, and had rashes on the skin due to eating strawberries and UV exposure. She had been using combined oral contraceptives and intermittent nonsteroid antienflamatuary drugs for headache complaints for a long time. Intraoral examination revealed hemorrhagic bullae on the floor of the mouth and under the tongue. In the examinations performed: IgE 151 IU/mL, CRP, INR and PT normal, aPTT 20.2 sec, fibrinogen 510 mg/dL, sedimentation rate 40/h, hemoglobin 8.4 g/dL, glucose 106 mg/dL, total iron binding capacity 543 ug/dl, ferritin 3.8 ng/mL, iron 14 ug/dL, ANA and RF (-). Thyroid function tests and vitamin B 12 was normal. Folate was 2.1 ng/mL. Anti-TPO and C4 were normal. The food prick tests and food-specific IgE tests were negative. Bullous diseases and bleeding dyscrasias were excluded by clinical picture and laboratory tests, and the patient was diagnosed with angina bullosa hemorrhagica. For treatment, the clinical course was explained to the patient, and intraoral trauma was recommended to be avoided. Oropharyngeal bulla and the possibility of airway obstruction were explained. Chlorhexidine mouthwash was recommended.

Conclusions Angina bullosa hemorrhagica is not accompanied by coagulation disorders or vesiculobullous diseases such as pemphigus. Local traumas and vascular fragility have been implicated in its pathogenesis. There are publications reporting that it is associated with long-term inhaled steroid use, glucose metabolism disorder and hypertension. In differential diagnosis; thrombocytopenia, amyloidosis, Osler-Weber-Rendu disease, fixed drug eruptions, cicatricial or bullous pemphigoid, bullous lichen planus, dermatitis herpetiformis and linear IgA disease should be considere. The bullae rupture in a short time and heal spontaneously within a week or two without leaving a trace.

OC012

Investigation of Baseline Characteristics of Rheumatology Patients Receiving Nintedanib: A Single Center Study

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Background Nintedanib is an intracellular tyrosine kinase inhibitor used in the lung involvement of idiopathic pulmonary fibrosis (IPF), systemic sclerosis, Sjögren's syndrome (SjS) and rheumatoid arthritis (RA). In our study, we aimed to examine the admission characteristics of patients with pulmonary involvement due to rheumatological diagnosis,who received follow-up nintedanib treatment from our clinic.

Material and Methods The clinical, laboratory and radiological features of 12 patients who had a rheumatological disease and lung involvement due to this disease and were started on nintedanib between January 2009 and December 2021 were examined.

Results 9 of our patients(75%) were female, mean age was 62.9±11.7 (median 66.5) years; mean age at diagnosis was 55.8±12.5 (median 57.5) years. Radiologic patterns of lung involvement was in UIP (usual interstitial pneumonia) pattern in 7 patients. There were 3 patients who developed lung involvement after the diagnosis of rheumatologic disease, and 2 patients who were diagnosed with rheumatologic disease after lung involvement. One of these two patients was diagnosed with scleroderma and the other with SjS. There was the highest number of patients with a diagnosis of scleroderma. In the final high resolution lung tomography (HRCT) before nintedanib, there were 7 patients with ground glass areas and 8 patients with honeycomb appearance. All patients had signs of fibrosis in lung. Of the two patients with negative ANA, one was diagnosed as undiferenced connective tissue disease (UCTD)+SjS and the other was diagnosed as SjS. Scl 70, Sm, nRNP/Sm antibodies of the patient diagnosed with UCTD+SjS were positive. There were 7 (58.3%) patients with pulmonary artery pressure ≥25 mmHg on echocardiography.There was no active smoker, one of our patients was ex-smoker. The percentile mean of FEV1 value was 80.0±24.4% (median 75.5%), the percentile mean of FVC value was 79.3±27.6% (median 71%), DLCO adj 43.0±17.7% (median 40%). Four of the patients with a diagnosis of scleroderma were using iliomedin treatment for

digital ulcer. The mean of cyclophosphamide used at least once in all patients was 6.0±3.2 g (median 4.5). The number of immunosuppressives used was 2.5±0.6 (median 3). Concomitant nintedanib and immunosuppressive therapy was present in 11 (91.6%) patients.There were 6 (50%) patients receiving mycophenolate mofetil (MMF)+nintedanib, 3 (25%) patients receiving rituximab+MMF+nintedanib, and 2 (16.6%) patients receiving azathioprine+nintedanib. The mean of comorbid disease was 2.5±1.3 (median 2). The mean erythrocyte sedimentation rate before nintedanib was 18.6±11.8 mm/h (median 15); The mean of C-reactive protein (CRP) was 5.5±6.7 mg/L (median 2.6). There were 2 (16.6%) patients who discontinued the drug due to side effects. The drug was discontinued due to elevated liver function tests in one patient and intolerable nausea and vomiting in the other patient. Medication side effects were observed in five patients, and the most common side effect was nausea. Vomiting, fatigue and abdominal pain were other side effects.

Conclusions Nintedanib is also used in interstitial lung diseases due to scleroderma, SjS and RA, as in IPF. In the INBULID study, regardless of the fibrotic pattern in HRCT, the rate of progression of interstitial lung disease was slower in patients receiving nintedanib than in those receiving placebo. Our observations will contribute to other studies that will use nintedanib.

OC013

A case of sinus bradycardia in a patient treated with pulse steroids for adult-onset Still's Disease

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Background Adult-onset Still's Disease (AOSD) is a rare systemic inflammatory disorder characterized by fever, transient salmon-pink maculopapular rash, inflammatory polyarthritis, lymphadenopathy and sore throat. Aetiology of AOSD is currently unknown. Non-specific clinical presentation, lack of diagnostic biomarkers and rarity of AOSD often results in significant delay in diagnosis and treatment. Steroids are the basis of treatment. In this case of a patient who was diagnosed with AOSD, we investigated clinical findings, treatment and the sudden bradycardia that occurred after patient underwent pulse steroid therapy.

Case Report In November 2021, a 30 year old woman applied with transient whole-body maculopapular rash, sore throat and joint pain. Patient underwent empiric antibiotic therapy as an infection couldn't be excluded, however complaints of patient didn't regress. Rheumatological workup demonstrated normal renal and hepatic parameters, negative autoantibodies, ESR: 63 mm/h, CRP: 262 mg/L, ferritin 4,214 µg/L, fibrinogen 890 mg/dL. Preliminary findings were compatible with AOSD; thus, methylprednisolone treatment was initiated. Arthralgia and rash regressed after pulse steroid treatment, supporting AOSD diagnosis. The patient was discharged with methotrexate and prednisolone however the patient applied to hospital again with attack after 5 days and was admitted. A pulse steroid of 1 g/day methylprednisolone was planned for 3 consecutive days. After 2 days of pulse steroid treatment, patient's laboratory parameters and clinical signs didn't regress, thus Anakinra was initiated. The patient, whose pulse was within the normal range in the previous follow-ups, developed asymptomatic sinus bradycardia after 3 doses of pulse steroid therapy without deterioration of other vital parameters. The patient was monitored with Holter, however a cardiac pathology that explains bradycardia was not found and the case has been evaluated as isolated sinus bradycardia. Bradycardia of unknown etiology was considered secondary to pulse steroid therapy. The patient, whose clinical and laboratory parameters improved with pulse steroid and anakinra treatment, was discharged.

Conclusions In the literature, many cases of sinus bradycardia that developed after steroid infusion and were usually asymptomatic and resolved spontaneously after stopping the infusion were reported. Sinus bradycardia is a side effect that may occur following steroid infusion. Its etiopathogenesis has not been fully elucidated. While the blood pressure of our case was within normal limits, sinus bradycardia developed after pulse steroid therapy and spontaneously returned to sinus rhythm at normal rate within days. Although not in our patient, there are data indicating that steroid infusion rate, electrolyte imbalance or underlying cardiac pathology increase the risk of bradycardia. It is important to consider the side effects such as tachyarrhythmia and bradyarrhythmia that may develop secondary to pulse steroid therapy, monitor the patient during the infusion and administer prolonged infusion, especially in cases with underlying cardiac pathology.

OC014

Malnutrition Status at Admission May Predict Post-Discharge Short Term Mortality in Palliative Care Unit

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***Background*:** Malnutrition is an immense problem and highly prevalent in patients admitted to palliative care units. We aimed to determine the impact of nutritional status at admission and the risk factors for short-term (90-day) mortality after discharge.
Material and Methods This study included patients admitted to and discharged from the palliative care unit (PCU). Totally 118 patients were classified into two groups: patients who died within 3-month after hospital discharge and patients who survived in the same period. The nutrition status of the patients was retrospectively assessed with NRS-2002.
Results The mean age of the patients was 70.9±13.4 years. The overall post-discharge 90-day mortality was 40% (n=47). Twenty (16.9%) patients were transferred from other clinics, 17 (14.4%) from home, and 81 (68.6%) from intensive care units to PCU. Age, gender, and length of stay in PCU were similar between the two groups. With regards to chronic illnesses, chronic obstructive pulmonary disease and malignity were found to be higher in the group with 90-day mortality [9 (19.1%) vs. 5 (7%), p=0.046 and 19 (40.4%) vs. 9 (12.7%), p=0.001, respectively]. NRS 2002 (Nutritional Risk Score) and decubitus ulcer rate on admission were higher in patients with 90-day mortality [4 (3-6) vs. 3 (2-5), p=<0.001 and 36 (76.6%) vs. 34 (47.9%), p=0.002, respectively]. Seventy-six patients (64%) were discharged with enteral nutrition (percutaneous endoscopic gastrostomy/nasogastric tube), and the rest were on oral nutrition. In addition, patients had lower both systolic and diastolic blood pressure measurements on admission in the mortality group [108±12.8 vs. 118.6±14.2 mmHg, p=<0.001 and 67.2±9.5 vs. 72.8±9.5 mmHg, p=0.002, respectively].
Conclusions In addition to comorbid diseases, hemodynamic findings and nutritional status on admission may be associated with early post-discharge mortality in patients hospitalized in PCU.

Table 1. The results of the study regarding ninety day post-discharge mortality

	Ninety day post-discharge mortality		
	No (n=71)	Yes (n=47)	p
Age ± SD	70.8 ± 13.9	71 ± 12.8	0.954
Gender, female, n (%)	36 (50.7)	19 (40.4)	0.273
Length of Hospitalization in Palliative Care Unit	23 (3-75)	23 (2-107)	0.766
Length of Hospitalization in Intensive Care Unit*	42.5 (7-526)	74 (17-400)	0.007
Body Mass Index	24.5 ± 3.2	24.6 ± 2.8	0.770
Nutrition type at discharge Oral, n (%) Enteral, n (%)	 24 (33.8) 47 (66.2)	 18 (38.3) 29 (61.7)	0.618
Diabetes Mellitus, n (%)	21 (29.6)	13 (27.7)	0.822
Hypertension, n (%)	33 (46.5)	19 (40.4)	0.517
Chronic Obstructive Pulmonary Disease, n (%)	5 (7)	9 (19.1)	**0.046**
Coronary Artery Disease, n (%)	12 (16.9)	10 (21.3)	0.550
Heart Failure, n (%)	6 (8.5)	3 (6.4)	0.679
Dementia, n (%)	16 (22.5)	9 (19.1)	0.659
Atrial Fibrillation, n (%)	14 (19.7)	12 (25.5)	0.456
Parkinson Disease, n (%)			
Malignity, n (%)	9 (12.7)	19 (40.4)	**0.001**
Metastatic Cancer, n (%)	1 (10)	13 (68.4)	**0.005**
Cerebrovascular Disease, n (%)	34 (47.9)	15 (32.6)	0.102
Percutaneous endoscopic gastrostomy (*PEG*), n (%)	36 (50.7)	17 (36.2)	0.120
Decubitus Ulcer, n (%)	34 (47.9)	36 (76.6)	**0.002**
NRS 2002, median (min-max)	3 (2-5)	4 (3-6)	**<0.001**
Systolic blood pressure ± SD	118.6 ± 14.2	108 ± 12.8	**<0.001**
Diastolic blood pressure ± SD	72.8 ± 9.5	67.2 ± 9.5	**0.002**

*n:78, NRS 2002: Nutritional Risk Screening

OC015

Diabetic Rethinopathy Patients with HFpEF Left Atrial Strain Echocardiography Functions

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Background Diabetic retinophaty in which patients may have symptoms and signs of heart failure but preserved ejection fraction. Left atrial (LA) volume and function may impaired in these patients. Two-dimensional speckle-tracking echocardiography (2D-STE) has recently enabled the quantification of LA deformation dynamics. In this study, we evaluated the use of 2D-STE for the diagnosis of HFpEF.
Material and Methods The study included patients with suspected HFpEF. Patients were divided into two groups after HFpEF had been diagnosed according to current guidelines. Parameters of diastolic dysfunction were evaluated, including left ventricular mass index (LVMI), LA volume index (LAVI), E/A ratio, deceleration time (DT), E/E', and STE parameters such as global longitudinal LA strain during ventricular systole (GLAs-res) and strain during late diastole (GLAs-pump).
Results The values of BNP, LVMI, DT, LAVI, and

GLAs-res were significantly different between the two groups. In univariate analysis, a strong negative correlation was seen between GLAs-res and BNP (r: -0.567, p<0.001) as well as between GLAs-res and DT (r: -0.665, p<0.001), while a moderate negative correlation was found between GLAs-res and LVMI (r: -0.458, p<0.001) and GLAs-res and LAVI (r: -0.316, p=0.004). In logistic regression analysis, GLAs-res (p=0.049, OR=0.71, 95% CI: 0.451-0.99), BNP (p=0.025, OR=1.08, 95% CI: 1.01-1.14), and LAVI (p=0.042, OR=1.59, 95% CI: 1.02-2.48) were found to be independent predictors of HFpEF.

Conclusions LA function as assessed by 2D-STE is impaired in patients with HFpEF. A GLAs-res value of <17.5% can be useful for the diagnosis of HFpEF.

Table 1 demographic properties of patient group

	Overall	Group 1	Group 2	Group 3	P Value (between 3 group)
N	170	54	62	54	
Systolic BP	129±22.1	126±17.5	126±28	130±19.8	**0.011**
Heart Rate	86.3±11.7	82.3±12.7	86.1±12	91.2±10.4	**<0.001**
Age	54.5±10	52.6±9.3	54.7±9.1	56.2±11.5	0.197
HBa1c	8.0±0.43	8.0±0.43	8.2±0.48	8.2±0.48	**<0.035**
BMI	29.4±4.7	31.5±5.3	28.3±4.3	28.5±3.5	**<0.001**
TSH	1.44±0.8	1.47±0.7	1.48±1.1	1.39±0.6	**0.748**
EF-Biplan simpson	66.9±8.4	67.5±7.5	67.4±9.6	65.5±7.6	0.351
Tapse	2.3±0.3	2.3±0.2	2.2±0.3	2.3±0.4	**0.007**
Mapse	1.2±0.2	1.3±0.2	1.1±0.2	1.2±0.3	**<0.001**
e/a	0.8±0.3	0.9±0.2	0.8±0.2	0.8±0.4	**<0.001**
e/e'	9.8±4.2	9.2±3.8	10.2±5	10.1±3.5	0.315
torsion	2.8±1	2.9±1.2	2.7±0.9	2.8±0.8	0.401
LV Global Strain	-18.2±2.8	-19.3±2.1	-18.2±2.7	-16.9±3.3	**<0.001**
LAVI	46.3±17.6	40.5±13.2	46±13.3	53±23.4	**0.003**
LA-reservoir	23.9±6.7	28.6±6.2	22.1±6.1	21.2±5.1	**<0.001**
LA-Conduit	14.4±4.2	16.2±3.4	14.2±4.6	12.7±3.9	**<0.001**
LA-SRs	1.3±0.4	1.6±0.4	1.3±0.3	1.1±0.3	**<0.001**
LA-SRe	-0.99±0.6	-1.2±0.6	-0.9±0.5	-0.9±0.5	**0.028**
LA-SRa	-1.6±0.6	-1.7±0.6	-1.5±0.6	-1.7±0.6	0.167

Group 1 normal retina
Group 2 nonproligerative retina
Group 3 proliferatif retina
Basal karateristikleri yapıldıktan sonra anova ile gnup içi karşılaştırma yapıldı(p değerleri)

Table 2 statistiscal significant result chescked by post hoc by tukey test

variables	Between 1-2	Between 1-3	Between 2-3
Systolic BP	p=0.568	p=0.088	P=0.013
Heart Rate	P=0.233	p<0.001	P=0.041
HBa1c	P=0.063	p=0.067	p=0.999
BMI	p<0.001	p=0.002	p=0.935
Tapse	p=0.005	p=0.341	p=0.714
Mapse	P<0.001	p=0.067	p=0.428
e/a	P<0.030	p=0.067	p=0.428
e/e'	p=0.030	p=0.030	p=0.030
Torsion	p=0.409	p=0.914	p=0.637
LV Global Strain	p=0.034	P<0.001	p=0.061
LAVI	p=0.067	P=0.004	p=0.151
LA-reservoir	p<0.001	p<0.001	p=0.639
LA-Conduit	P=0.020	p<0.001	p=0.169
LA-SRs	p<0.001	p<0.001	p=0.004
LA-SRe	p=0.045	p=0.040	p=0.962
LA-SRa	p=0.063	p=0.067	p=0.999

Table 3 ordinal logistic regression

Variables	OR, 95% CI	P value
Systolic blood pressure	1.028 (1.004, 1.054)	0.022
Heart rate	1.01 (0.976, 1.055)	0.497
age	1.006 (0.966, 1.049)	0.765
Cinsiyet	1.364 (0.587, 3.173)	0.469
HBa1c	3.196 (1.464, 7.211)	0.004
EF (Biplan Simpson)	1.034 (0.984, 1.089)	0.193
e/e'	1.027 (0.924, 1.146)	0.614
Torsion	0.906 (-0.664, 0.438)	0.725
LV-Global Strain	1.099 (0.933, 1.300)	0.259
LAVI	1.034 (1.009, 1.064)	0.011
LA-Reservoir	0.854 (0.786, 0.924)	<0.001
LA-Conduit	0.978 (0.885, 1.081)	0.665
LA-SRs	0.088 (0.025, 0.280)	<0.001
LA-SRe	0.484 (0.200, 1.157)	0.104
LA-SRa	3.196 (1.464, 7.211)	0.004

OC016

Are the Treatment Efficacies of Domestic and Foreign Colchicine Preparations Used in Familial Mediterranean Fever Different?

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Background Familial Mediterranean fever (FMF) is the most common inherited autoinflammatory disease with acute episodes of fever and serosal inflammation. Colchicine is the drug of first choice in the treatment of FMF. In this study, we aimed to investigate the benefit of changing the drug in terms of frequency and duration of attack in patients who are resistant to the domestic colchicine preparation used in the treatment of FMF.

Material and Methods Seventy-five patients who were diagnosed with FMF, used a domestic colchicine preparation in their treatment and were switched to an foreign colchicine preparation due to resistance or side effects were included in the study. The files of the patients were reviewed retrospectively. Demographic, clinical, genetic characteristics and response rates to treatment were evaluated.

Results 21 (28%) of the patients were male and 54 (72%) were female. The mean age of the patients was 39.0±11.71 years, the mean age at diagnosis was 24.0±14.58 years, and the mean time to diagnosis was 11.0±9.02 years. In patients, exon 10 mutations were detected in 45.3%, exon 2 mutations in 9.3%, exon2 and 10 mutations together in 17.3%. Renal amyloidosis was 5.3%. Preparation change due to unresponsiveness to treatment was found to be 84%. It was observed that the frequency of attacks of 7 or more per year in patients who switched from a domestic preparation to a

foreign preparation in treatment decreased from 78.7% to 30.7%, and the rate of 4-6 attacks decreased from 14.7% to 9.3%. The rate of no attack increased from 4% to 28%, the frequency of 1-3 attacks increased from 2.7% to 32.0% (p<0.001). The ratio of patients with an attack duration of 4 or more days decreased from 52% to 10.7% after switching to foreign colchicine. It was determined that the mean attack duration decreased from 4.02 days to 1.8 days (p<0.001).

Conclusions In patients who could not use domestic colchicine preparations due to colchicine resistance or side effects, there was a significant decrease in the annual mean frequency and duration of attacks with the use of foreign colchicine preparations before switching to biological treatment. For this reason, the use of different pharmaceutical preparations of colchicine is seen as an alternative and effective treatment option before switching to biological treatments which are more costly and have patient's adapting difficulties.

Table 1. Demographic and clinical characteristics of patients with familial Mediterranean fever (n=75)

Appendectomy history Family history of FMF Family history of hemodialysis	49.3% 58.7% 14.7%
Stomach ache Myalgia Fever Arthralgia Arthritis Pleuritis Erythepelas-like rash Pericarditis Orchitis	89.3% 76% 72% 70.7% 62.7% 60% 33.3% 18.7% 4%
Comorbidity	34.7%
Used foreign colchicine preparations	Italian colchicine 46.7% Spanish colchicine 14.7% French colchicine 54.7%
Reasons for switching to foreign colchicine preparation	Resistance 84% Diarrhea 21.3% Myopathy 2.7% LFT elevation 6.7% Other 10.7%
The rate of switching to biological treatment after foreign colchicine treatment	Anakinra 22.7% Canakinumab 4%

OC017

Cardiac MRI and Corrected QT Interval in Young Patients with Myocarditis

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Background Myocarditis is an inflammatory myocardial disease that can affect systolic functions and pose a life-threatening risk due to ventricular arrhythmias. In this study, we examined the relationship between cardiac MRI defined left ventricle ejection fraction (MR_LVEF) and corrected QT interval (QTc) in soldiers hospitalized and followed up with the diagnosis of myocarditis.

Material and Methods This cross-sectional study included 41 patients with myocarditis. The clinical features, comorbidities and electrocardiogram (ECG) findings of the patients were recorded. QTc was recorded from the automatic measurements of the 12-lead ECG device. The correlation between cardiac MR_LVEF and QTc was examined.

Results The mean age was 27.2±6.9 years and all patients were male. Echocardiographic mean LVEF was 58.58 ± 8.24% and cardiac MR_LVEF 56.30 ± 5.67%. Levels of cardiac biomarkers were high due to the active infection and myocardial injury. QRS_duration was 97.43 ± 12.67 ms, QTc 405.09 ± 29.45 ms, Frontal QRS-T angle 53.95 ± 43.69 respectively. Mean CK_MB was negatively correlated with LVEF (r: -0.345, p: 0.027). Mean QTc was negatively correlated with MR_LVEF (r: -0.311, p: 0.047).

Conclusions: Cardiac MRI is the gold standard test in the evaluation of cardiac functions and for diagnosis of myocarditis. The decrease in cardiac MR_LVEF and the prolongation of the QTc show a significant correlation. Decrease in cardiac systolic functions may predict cardiac electrical instability indicated by prolonged QTc interval.

Variable	Myocarditis Group
Age	27.29 ± 6.92
LVEF(%)	58.58 ± 8.24%
MR_LVEF (%)	56.30 ± 5.67%
MR_EDV (ml)	132.66 ± 28.27
MR_ESV (ml)	57.91 ± 14.41
QRS_duration (ms)	97.43 ± 12.67
QTc (ms)	405.09 ± 29.45
Frontal QRS-T angle	53.95 ± 43.69
CK_MB	51.35 ± 69.47
Trop I	4.95 ± 8.40
WBC	11.11 ± 4.29

WBC: White blood cell, EDV: End-diastolic volume, ESV: End-systolic volume

OC018

General Characteristics of Our Paradoxical Cases of Psoriasis: Single Center Experience

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Background Paradoxical psoriasis (PPs) is the occurrence of psoriatic skin lesions or worsening of psoriatic skin lesions in the presence of existing psoriasis after initiation of treatment with biologic agents, especially Anti-tumour necrosis factor (TNF). In this study, we aimed to reveal the characteristics and treatment choices of our patients who developed PPs and used biologic agents in their treatment.
Material and Methods 29 patients who developed paradoxical psoriasis while being followed up in our center and receiving biologic agent treatment were included in our study. The files of the patients were reviewed retrospectively. Demographic characteristics of the patients, age at diagnosis, time between diagnosis and paradoxical event, and selection of biological agents used in the treatment during the event were recorded.
Results Twenty-three patients (79.3%) were female and 6 patients (20.7%) were male. The mean age of the patients was 47.7 (25-80) years. Eleven patients (37.9%) were diagnosed with rheumatoid arthritis, 10 patients (34.4%) with axial spondyloarthritis, 3 patients with peripheral spondyloarthritis, 2 patients with psoriatic arthritis, 1 patient with enteropathic arthritis, 1 patient with vasculitis, 1 patient with adult-onset Still's disease. There was no family history of psoriasis in 7 patients whose family history could be reached. Of the 15 patients whose smoking characteristics could be reached, 10 were active smokers. The mean age at diagnosis of the patients was 33.1 (16-65) years. Disease duration of the patients was 153.6 (14-348) months. The time between disease onset and event was 122 (4-348) months. The time between starting the biological agent and the time of the paradoxical event was 19.4 (1-77) months. During the event, 9 (31%) patients were using adalimumab, 6 (20.6%) patients were using infliximab, 7 (24.1%) patients were using etanercept, 3 (10.3%) patients were using certolizumab, 2 (6.8%) patients were using abatacept, 2 (6.8%) patients were using rituximab.
Conclusions PPs may develop in all diseases for which anti-TNF is used and during the treatment of all anti-TNF agents. It can be seen in 5% of patients receiving treatment. It usually presents as palmoplantar pustular psoriasis. Although it can be seen in both sexes, it is more common in women. It may occur days or years after the start of treatment. In its treatment, the anti-TNF agent can be discontinued, switched to another biological agent, or adjuvant therapy can be added to the existing treatment and continued. Of 104 patients screened in a literature review, 53% were using infliximab, 29% were using etanercept, and 18% were using adalimumab. PPs related to adalimumab were most common in our patients. It should be kept in mind that a paradoxical event may have developed when a rash develops during the commonly used biological treatments.

OC019

Use of Thoracic Computed Tomography for COVID-19 Pandemic - Is It Early or Delayed Diagnosis of Malignancy? A Case Report and Literature Review

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Background Coronavirus disease 2019 (COVID-19) was first reported as an unidentified viral pneumonia type in Wuhan, China and spread all over the world over time.Real-time reverse transcription polymerase chain

reaction (RT-PCR) test and thoracic imaging methods are used for diagnosis.Thoracic computed tomography (CT) has been reported as an important tool in the early diagnosis and evaluation of COVID-19 disease. CT findings are especially helpful for diagnosis when there is any limitations with RT-PCR assay. Herein a case in which a mass was detected as a result of thoracic CT imaging due to COVID-19 pandemic and the malignancy follow-up process during pandemic will be presented. The use of thoracic CT in diagnosis and follow-up and its possible advantages and disadvantages will be emphasized.

Case Report A 73-year-old male patient was admitted to the hospital with complaint of shortness of breath. He had known diagnoses of Parkinson's disease, diabetes mellitus, primary hypertension, chronic kidney disease (atrophic left kidney), benign prostatic hyperplasia. Pacemaker was inserted due to symptomatic bradycardia. He was vaccinated with two doses of inactivated vaccine (Sinovac) in February and March 2021 and one dose of mRNA vaccine (BNT162b2 , Pfizer-BioNTech) in August 2021. After detecting SARS-CoV-2 PCR positivity in the oropharyngeal-nasopharyngeal swab sample made upon his complaints, he was isolated at home. After that he presented to the emergency department of our hospital with complaints of deterioration in general condition, weakness and sudden blurred vision. In the thoracic CT performed for the purpose of screening and follow-up of suspected patients due to the COVID-19 outbreak, ground glass opacities admixed with patchy areas of consolidation were observed in the lung parenchyma starting from the upper lobes and this appearance was compatible with multifocal infiltration of early-mid period of COVID-19 pneumonia. In the right axillary and deep pectoral region conglomerate lymph node masses reaching 36x23 mm in size in the widest part and in the mediastinum and both hilar localizations lymph nodes some of which are calcified and do not exceed 1 cm in short axes are observed. The patient admitted to covid department for follow-up. However, the application for further examination of the suspicious mass was 6 months later to the internal medicine and geriatrics clinic of our hospital with complaint of palpable lump in the right armpit.On physical examination the mass in the right axilla was painless and had a rubbery consistency.Ultrasonography of the right axillary region showed a spherical shaped, 63 mm sized mass lesion with insufficient blood flow and smooth sharp contours, that lost its ovoid structure. In the inferior posterior part of this lesion 33 mm. sized second hypoechoic lesion with smooth sharp contours and insufficient blood flow was observed.This appearance was primarily evaluated in favor of benign lesions or lymph node whereas physical examination of the mass was consistent with a malignant lesion. Biopsy of the mass was reported as diffuse large B-cell lymphoma originating from the germinal center.Positron emission tomography was performed and during hematology follow-up chemotherapy was planned.

Conclusions The radiation effective dose of thoracic CT imaging varies between 1-10 mSv. This dose is 10-100 times higher than a chest radiography. Thoracic CT imaging is frequently used for the diagnosis and follow-up during COVID-19 pandemic. In order to reduce radiation exposure, it would be appropriate to perform tomography imaging using high-resolution low-dose radiation protocols. Increase in the number of thoracic CT performed due to COVID-19 pneumonia may be important in the early diagnosis of mass and related malignancies.However the decrease in services for advanced diagnosis such as biopsy delays the diagnosis and treatment of cancer.Due to this reason, cancer screening and diagnosis services should be adapted to the pandemic period and new protocols should be established accordingly.

OC020

A Rare Cause of Hypokalemia: Ectopic ACTH Syndrome

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Background Ectopic adrenocorticotropic hormone (ACTH) secretion is a rare paraneoplastic syndrome associated with a large group of tumours, the majority of which are neuroendocrine cell origin. It is most commonly associated with small cell carcinoma of the lung (SCLC). Although this syndrome is associated with severe hypercortisolemia findings, some findings of Cushing's syndrome such as central obesity may not be observed due to underlying malignant diseases. Especially in the presence of hypokalemia accompanying hypertension and proximal muscle weakness, if weight loss accompanies the picture, it should be kept in mind in the differential diagnosis. In this case, we aimed to present a case who developed

ectopic ACTH syndrome due to small cell lung cancer. ***Case Report*** A 66-year-old male patient with known hypertension and coronary artery disease was admitted to our outpatient clinic with complaints of weakness, fatigue, proximal muscle weakness, hoarseness and weight loss for the last 2 weeks. There was no pathological finding in his physical examination, and it was detected that he had a 40 pack/year smoking history. The patient, who was found to have hypokalemia (2.34 mEq/L) and metabolic alkalosis (pH 7.51, HCO_3 34.7 mmol/L) in the examinations, was admitted to our service to investigate the etiology. Oral and intravenous potassium replacement was started to the patient in order to correct his hypokalemia. 1 mg dexamethasone suppression (DST) was planned for the patient whose basal cortisol level was 55 mcg/dL in the tests requested for the etiology. Hypercortisolism was confirmed in the patient whose cortisol level was 45 mcg/dL as a result of DST. ACTH-dependent Cushing's was considered in the patient whose ACTH level was high, and pituitary MRI was requested to rule out pituitary causes. Ectopic ACTH syndrome was considered in the patient because adenoma was not detected in the pituitary MRI and there was no suppression of cortisol level in the high-dose DST test. On thorax HRCT imaging, a mass lesion measuring 4 cm and a soft tissue thickening of approximately 35 mm in the right hilar region were observed. The pathological examination of the biopsy taken from the mass was compatible with SCLC and the patient was referred to the oncology service for further examination and treatment.

Conclusions Ectopic ACTH syndrome is a rare paraneoplastic syndrome caused by ACTH secreting tumour. While Cushing's disease is more common in women aged 30-40 years, ectopic ACTH syndrome is mostly found in men and women at same ratio aged 45-50 years. In addition to the classical symptoms of hypercortisolemia such as fatigue, proximal myopathy, and striae, findings related to high ACTH levels such as severe hypokalemia and hyperpigmentation may be observed. Weight gain is not as prominent in ectopic ACTH syndrome as in Cushing's patients because of the accompanying malignancy. Resection of the tumour causing ectopic ACTH release is the optimal treatment method. However, chemotherapy treatment is at the forefront because SCLCs have a low resectability rate and respond well to systemic treatment. In this case, we tried to emphasize that ectopic ACTH syndrome due to malignant causes should be kept in mind in the differential diagnosis of patients presenting with resistant hypokalemia.

OC021

What is the main reason of erectile dysfunction in lymphoma patients: Chemotherapy or Depression?

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Background Erectile dysfunction (ED) may be associated with both chemotherapy and depression in lymphoma patients. The role of depression in erectile dysfunction during chemotherapy in lymphoma patients may be more important than chemotherapy. This study aimed to determine the factor which plays a more important role in ED.

Material and Methods This study included 20 patients aged under 60 years who were admitted to the Hematology Outpatient Clinic between March 2015 and March 2016 and diagnosed with lymphoma. While the Beck Depression Inventory (BDI) was used to assess depression severity before (T1), during (T2) and after (T3) chemotherapy, the International Index of Erectile Function (IIEF) was used to assess sexual function. The Mann-Whitney U and Wilcoxon Signed-Rank tests were used for statistical analysis. A p-value of <0.05 was considered statistically significant.

Results Twenty male lymphoma patients (14 [70%] patients with non-Hodgkin's lymphoma and 6 [30%] patients with Hodgkin's lymphoma) were included in the study. The mean BDI score was 11.75±1.44 at T1, 6.60±3.61 at T2, and 3.25±2.12 at T3, respectively ($p<0.01$). The mean IIEF score was 15.25±6.12 at T1, 12.95±6.03 at T2, and 20.40±8.59 at T3, respectively ($p<0.01$). There was a significant decrease in both the mean BDI and IIEF scores between T1 and T2. However, the mean BDI score continued to decrease between T2 and T3, while the mean IIEF score tended to increase.

Conclusions It is not possible to suggest a single cause when considering the multifactorial etiology of ED in lymphoma patients. However, our study clearly showed that depression and related psychological factors are the main cause of ED in lymphoma patients.

OC022

Ground Glass Appearance During the Pandemic Period: Everolimus Induced Interstitial Pneumonia

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Background The mammalian target of rapamycin (mTOR) plays a regulatory role in cell proliferation and growth. mTOR activity is frequently found to be increased in cancers. Since mTOR inhibitors cause tumour cell apoptosis, cell division cycle arrest, signal transduction inhibition, mTOR becomes a therapeutic target in diseases where cell regulation is impaired such as cancer. Everolimus inhibits mTOR functional complex 1 as an allosteric mTOR inhibitor and is used in ER+ breast cancers. The ground glass appearance is a nonspecific finding that can be seen in COVID-19 lung involvement, which we see the most today, in etiologies such as chronic interstitial disease, acute alveolar disease or infection. Here, we wanted to present one of the etiologies that can be confused with the ground glass appearance, which is one of the radiological findings of COVID-19 pneumonia.

Case Report: A 48-year-old female patient with known breast cancer and bone metastasis and using hormonal therapy and chemotherapy admitted to us with low saturation, dyspnea and worsening of general condition. The patient had fever, cough and sputum. On physical examination, her general condition was good, he was conscious, oriented, and cooperative. On lung auscultation, basal and midline fine rales were present. In the abdominal examination there were no tenderness, rigidity and rebound. Oxygen saturation was 97% with 3 liter/min oxygen support from nasal cannula and 85% at rest in room air. The patient was started on teicoplanin and ciprofloxacin as antibiotic therapy. Lung computed tomography (CT) on 23.06.2021 has been reported as "In addition to the covid-19 sequelae identified in the examination on 12.06.2021, ground-glass consolidations in the lung parenchyma from the apex to the basal and vascular-bronchial clarifications in these areas are compatible with the second COVID-19 infection and active inflammation and it appears to be progressive compared to the examination on 12.06.2021." The suspected COVID-19 infection in the patient and the previous COVID-19 infection could not be proven by PCR. All PCR results were negative. Previously, COVID-19 treatment was given, considering it was a CT-positive COVID-19 case. We ruled out COVID-19 when the SARS-COV-2 antibody test and PCR test were negative on 24.06.2021. She had been using everolimus for the past four months. The reason for the ground-glass appearance in low-dose thoracic CT was thought to be related to interstitial pneumonia and was investigated. The patient, who was evaluated together with the department of oncology, was considered as everolimus induced interstitial pneumonia. Interstitial lung involvement, occasional pneumonic consolidation, ground glass appearances and hyperaeration findings suggested bronchiolitis and interstitial pneumonia in the patient who was consulted with the department of lung and chest diseases. Bronchoscopy, transbronchial biopsy and/or bronchoalveolar lavage were recommended to the patient in order to detect the pathogen and also to understand whether there is a drug-related lung pathology. The patient refused. The patient was started on 100 mg of methylprednisolone. The patient was warned not to use everolimus. In the tests taken from the patient, CMV IgM was negative and IgG positive. Candida beta-glucan antigen was negative. Aspergillus Galactomannan antigen was negative. On the 4th day of the patient's use of 100 mg methylprednisolone the patient's room air saturation was 91% and there were no rales or rhonchi on lung auscultation. The patient's admission CRP was 33.05 mg/dL, and the CRP value, which decreased significantly after starting methylprednisolone, was 1.31 mg/dL at the patient's discharge. The patient was ordered 100 mg of prednol for 7 days on hospitalization, and the patient, who showed significant improvement and did not get desaturated at room air, was discharged with the recommendation to continue using 32 mg methylprednisolone for 15 days at home.

Conclusions: The patient was diagnosed with everolimus induced interstitial pneumonia because infectious causes were excluded, the clinical status of patient improved with steroid therapy, and the radiological and clinical findings were consistent with drug induced pneumonitis. It is important to consider other etiologies in the differential diagnosis, especially during the pandemic period, as the ground glass appearance leads clinicians to the diagnosis of COVID-19.

OC023

Anxiety and Sleep Problems in Intensive Care Patients

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Background Intensive care units are very comprehensive units where the vital functions of critically ill patients are monitored and maintained, special treatment.
Material and Methods The detailed and complex care applications are made.
Discussion For these reasons, these units are environments where patients encounter many physical and psychosocial stressors. Patients hospitalized in intensive care units experience psychosocial problems as a result of encountering many stressors such as being threatened, unusual medical devices, a strange environment, monotonous and frightening sounds, being away from their families and relatives, inability to meet their self-care needs and addiction, the seriousness of their illness and the feeling of being close to death. Anxiety and sleep problems are the leading ones. The presence of anxiety also delays recovery by causing sleep problems, reveals different physiological and psychological problems and increases the existing anxiety even more. In order for individuals to be in good physical, mental and psychological well-being, their sleep needs must be met regularly and in a balanced way. Many researchers examining the sleep of patients hospitalized in the intensive care unit have revealed that these patients' sleep is adversely affected in terms of duration and quality, their sleep structure is disrupted, and sleep problems are experienced frequently.
Conclusions For this reason, nurses should be able to identify patients' anxiety and sleep problems in the early period, reduce existing stressors, create a therapeutic environment for quality sleep and make necessary environmental arrangements and practices. In this way, possible problems that may arise due to anxiety and sleep disorders will be prevented.

OC024

Pulmonary Embolism Developing Despite the Use of Anticoagulants in COVID-19 Pneumonia: A case report

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Background COVID-19 pneumonia is one of the diseases that can cause hypercoagulability. It is not uncommon to encounter arterial or venous thromboembolic events during COVID-19 infection. Therefore, the importance of usage of anticoagulant therapy and the follow-up of coagulation parameters, especially in inpatients, is obvious. In this case, we wanted to present a case of pulmonary embolism due to COVID-19 infection, which developed despite the usage therapeutic dosage of anticoagulants.
Case Report A 41-year-old male patient with no comorbidities other than a diagnosis of diabetes mellitus admitted to our clinic with complaints of cough and headache lasting for 7 days. The patient 's saturation was 95% at room air. Heart rate was 95 beats/min, arterial blood pressure was 155/87 mmHg, and respiratory rate was 19 per minute. There were bilateral widespread crackles in all zones on auscultation of the lungs. The abdomen was not defensive to palpation and there was no rebound tenderness. There were bilateral ground glass consolidations on obtained thorax computed tomography (CT). The patient was not vaccinated against COVID-19. The patient, who was found to have a positive COVID-19 PCR test with a nasal and throat swab, was admitted to our clinic for treatment and supportive care. In the laboratory tests performed on the first day of his hospitalization, D-dimer was found to be 1.03 mg/L. CRP was determined as 10.87 mg/dL, INR 0.9, and fibrinogen as 731 mg/dL. Along with steroid treatment, inhaler interferon treatment and supportive treatment, 2x6,000 IU enoxaparin treatment was initiated to the patient who weighed 78 kilograms. Since the patient developed hemoptysis on the 3rd day of follow-up, enoxaparin was started to be administered as a single dose of 6,000 IU and was used as a single dose for 2 days. On the 5th

day of follow-up, the patient, who was being supported with 4 lt/min nasal oxygen support, developed sudden respiratory distress and showed an increase in oxygen demand. The patient was then started being supported with 8 lt/min reservoired oxygen mask. The patient's d-dimer value increased abruptly to 35.2 mg/L (Figure 1). With the current clinical and laboratory findings and a preliminary diagnosis of pulmonary embolism, the dose of enoxaparin was increased to 2x8,000 IU and pulmonary CT angiography was performed. Pulmonary CT Angiography showed multiple bilateral partial filling defects in subsegmental pulmonary arteries, mainly in posteroinferior segment of left lung compatible with pulmonary embolism (Figure 2). Patient showed no signs of discoloration, temperature increase, tenderness, swelling or pain in his lower extremities. There was no finding of deep vein thrombosis in the lower extremity venous doppler ultrasonography. The patient continued to use 2x8,000 IU enoxaparin, and the d-dimer value gradually decreased to 4.05 mg/L in the follow-ups. The treatment of the patient who did not have deep vein thrombosis and had pulmonary embolism foci in the subsegmental areas was arranged in consultation with the department of Cardiovascular Surgery and Chest Diseases. The patient was discharged after his clinical condition improved and there was no desaturation at room air on the 14th day with supportive, steroid and anticoagulant treatment and continiued his prescribed treatment to be later seen at office visits.

Conclusions Keeping in mind that COVID-19 infection can cause arterial and venous thromboembolic events in patients followed up with COVID-19 pneumonia, increase in oxygen demand, sudden dyspnea, deterioration in general condition or in patients with a significant increase in serial D-dimer follow-ups as in our case, diagnoses such as pulmonary embolism, obstructive cerebral disease and myocardial infarction should also be considered in differential diagnosis. Therefore, prophylactic anticoagulation should be initiated in hospitalized patients, attention should be paid to signs of bleeding, and dose adjustment should be made by monitorization of coagulation parameters.

OC025

COVID-19 Presenting with Diabetic Ketoacidosis: A case report

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Background Diabetic ketoacidosis (DKA) is one of the most common complications of diabetes with the highest mortality rate among hyperglycemic emergencies. Intervening infections, medication non-compliance, cerebrovascular events, and acute coronary syndromes can be counted as facilitating factors for DKA. DKA has been reported in COVID-19 infection as well as in other intercurrent serious infections. The expected DKA mortality in patients without COVID-19 with confirmed diagnosis is approximately 3% to 8%, with a 2020 small case series reporting a mortality rate as high as 50% in patients with COVID-19. In this case, a case of diabetic ketoacidosis caused by Covid-19 infection will be discussed.

Case Report A 71-year-old female patient with a known diagnosis of type 2 diabetes mellitus, whose blood sugar was not regulated, was admitted to the emergency service with weakness and general condition deterioration. On physical examination, she had clouding of consciousness. There were no rales and rhonchi on auscultation of the lung sounds. On abdominal palpation no rigidity or rebound tenderness was spotted. Oxygen saturation in room air was 97%. The patient had sinus tachycardia and was prone to hypertension. Arterial blood pressure was 140/75 mmHg, heart rate was 123 bpm. There was severe metabolic acidosis with increased anion gap in the obtained venous blood gas sample. The pH was 6.8, the bicarbonate was 5 mmol/L. There was leukocytosis in the laboratory examinations on arrival. D-dimer 4.12 mg/L FEU, blood glucose 740 mg/dL, creatinine 2.04 mg/dL, sodium 121 mmol/L, potassium 5.39 mmol/L, chlorine 88 mmol/L, C reactive protein (CRP) 1.60 mg/dL, and hemoglobin A1c were obtained as 15.4%. In the complete urinalysis, glucose was 3+ and ketone was 3+. After the patient's COVID-19 rapid antigen test was positive, polymerase chain reaction (PCR) test was taken and it was confirmed that the patient was positive for COVID-19. The patient was not vaccinated

against COVID-19. Low-dose thorax computed tomography (CT) revealed bilateral mild ground-glass infiltrates. Aggressive hydration, bicarbonate infusion and insulin infusion were started to the patient. Blood glucose, blood gases, electrolyte and kidney function tests were obtained with short intervals. During the close follow-ups, the metabolic acidosis of the patient, who was not desaturated in room air, was conscious and oriented, cooperative, and normouric, regressed, and the creatinine value decreased to 1.12 mg/dL. The patient, whose general condition and ketoacidosis improved, was followed up with COVID-19 supportive treatment and steroid treatment. Insulin infusion was stopped and quadruple subcutaneous insulin therapy was started. However, on the 9th day of the COVID-19 infection, the patient whose oxygen demand increased, was transferred to the intensive care unit and intubated. The patient, who was intubated for 23 days, was then transferred to the internal medicine ward and was discharged 52 days after her first hospitalization, due to her general condition improving.

Conclusions Diabetic patients are at severe risk for COVID-19 infection. DKA is one of the diabetic complications, and COVID-19 may present with DKA as the first symptom. Corticosteroids used to manage COVID-19 disease aggravate hyperglycemia and become difficult glycemic control in DKA. In our patient, we started 250 milligrams of methylprednisolone during COVID-19, which resulted in the patient becoming hyperglycemic again and DKA redeveloping. Therefore, close follow-up with frequent blood gas control should be provided in patients whose glycemic control can not be achieved.

OC026

Comparison of Clinical Progress of COVID-19 Patients Followed in the Hospital by Vaccination Status

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Background Although COVID-19 vaccines cannot prevent infection with SARS-CoV-2, they do allow infected people to have a milder illness. In unvaccinated people, the disease progresses more severely and the disease can be fatal. Both inactivated (Sinovac) and mRNA (BioNTech-Pfizer) vaccines are used in Turkey. In this retrospective study, clinical course, radiological involvement and some laboratory parameters that are important for COVID-19 were compared in unvaccinated and vaccinated patients who were infected and followed up in the hospital.

Material and Methods Patients between the ages of 17-95 who were hospitalized in the COVID-19 isolation wards between June 2021 and November 2021 were included in the study. Patients' symptoms, hematological and biochemical test *Results*, radiological findings, clinical course, length of hospital stay, and negative time for COVID-19 polymerase chain reaction (PCR) were scanned retrospectively from the hospital registry system.

Results 68 patients were included in the study. However, 14 patients with unknown vaccination status were excluded from the study. The female male ratio included in the study was 24/30. 55.6% of the patients were male, and the mean age of all patients was 50.76±16.82. The mean age was lower in male (47±18.39) patients than in female (55.46±13.58) patients (p=0.06). When the vaccination status of the patients was evaluated, 26 (48.1%) patients were unvaccinated, 5 (9.3%) patients were single Sinovac, 3 (5.6%) patients were single BioNTech, 11 (20.4%) patients were double or more Sinovac and 7 (13%) patients had double BioNTech, 2 (3.7%) patients had mixed vaccine protocol. 2 (3.7%) patients were exitus. One of these patients was unvaccinated and the other had a mixed vaccine protocol. Group 1 (34 patients) was determined as single vaccinated and unvaccinated, and Group 2 (20 patients) as double vaccinated or mixed vaccinated. The rate of women gender in Group 1 and Group 2 did not differ (44.1% vs 45%, respectively, p=0.950). There was no difference in the mean age, highest fibrinogen, D-dimer, ferritin, creatinine, interleukin-6 values, the time taken for the COVID-19 PCR test to turn negative and antibody levels between groups. The patients in Group 2 were discharged significantly earlier than Group 1 (7.8 vs 12.69 days, p=0.046). There was a significant difference in low-dose thoracic computed tomography (CT) findings between both groups (p= 0.023). Severe bilateral involvement of lungs was 58.8% in Group 1 and 25% in Group 2. 17 (50%) patients in Group 1 and 9 (45%) patients in Group 2 had comorbidities. (20.6% vs 20%, 8.8% vs 10%, 26.5% vs 15% type 2 diabetes mellitus, cancer, and hypertension, respectively). Other comorbidities

such as asthma, rheumatologic, neurologic, cardiac and thyroid diseases were seen at lower rates. When all comorbidities were compared, no significant difference was found between the two groups.

Conclusions Our results showed that regardless of the type of vaccine, vaccination against COVID-19 reduces hospitalization rates, length of stay and prevents serious involvement in the lungs.

OC027

Pembrolizumab Induced Hypothyroidism: A Case Report

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Background The importance of monoclonal antibodies as immune checkpoint inhibitors, in the field of oncology is increasing day by day. Since these drugs inhibit the inhibitory mechanism on the immune system, their side effects may also be autoimmune diseases that occur due to excessive immune response. When these side effects occur, it is important to discontinue the drug and start steroids. In checkpoint inhibition, Programmed Cell Death 1 (PD-1), PD-1 ligand (PD-L1) receptors and Cytotoxic T Lymphocyte Associated Protein 4 (CTLA-4) are among the targets. Pembrolizumab and Nivolumab targeting PD-1, atezolizumab, avelumumab and durvalumab targeting PDL-1 are used in many malignancies in various indications. The most common clinical presentations of thyroid injury induced by pembrolizumab are destructive thyroiditis and overt hypothyroidism. In this case, we wanted to present a case of pembrolizumab induced hypothyroidism.

Case Report A 64-year-old male patient with a known diagnosis of metastatic non-small cell lung cancer was admitted to the general internal medicine outpatient clinic with complaints of swelling in the legs, weakness, enlarged tongue, constipation, slowing of speech and dyspnea. He had no history of thyroid disease. Gemcitabine, cisplatin and pembrolizumab were started for the patient, who was diagnosed six months ago, for combined chemotherapy and immunotherapy. The patient received 7 cycles of pembrolizumab treatment. On physical examination, temperature was 36.3 degrees Celsius and heart rate was 89 beats/min. He was conscious, oriented and cooperative. The patient had no hair and nail changes, and his skin looked pale yellow. Macroglossia was present. There were no rales or rhonchi on auscultation of the lungs. In the abdominal examination, the abdomen was slightly distended, there was no defense or rebound. Bilateral pretibial edema +++/+++ was present. The thyroid stimulating hormone (TSH) value measured before the patient's pembrolizumab use was 2.96 uIU/mL. In the laboratory tests of the patient at admission, TSH was 122 uIU/mL (reference values: 0.25-4.55 uIU/mL), free T3 <0.3 pmol/L, free T4 1.86 pmol/L. Pembrolizumab was discontinued and chemotherapy was continued. The patient was started on 100 mcg of levothyron. Later, the dose of levothyron was gradually increased to 125 mcg. Simultaneously, 20 mg methylprednisolone was started and the patient was discharged with levothyron treatment. Seven weeks later, the patient's TSH value was found to be 20 uIU/mL.

Conclusions With the use of immune checkpoint inhibitors such as pembrolizumab, non-specific side effects such as weakness and fatigue often occur. In a meta-analysis of 38 studies and 2,551 patients, it was reported that the frequency of endocrinopathy induced by immune checkpoint inhibitors was 10% and hypothyroidism was the most common endocrinopathy. Pembrolizumab induced autoimmune thyroid disease may present as primary hypothyroidism due to thyroiditis or hyperthyroidism due to Graves' disease. In this context, it should be considered that these side effects may occur in malignancy patients using immune checkpoint inhibitors, and hypothyroidism should be included in the differential diagnosis.

OC028

Early Ophthalmological Findings in Type 2 Diabetes Mellitus Cases

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Background Type 2 diabetes mellitus (DM) is a chronic metabolic disease that is seen quite frequently nowadays. Retinal neurodegeneration, choroidal vascular changes and diabetic retinopathy (DR) are important complications of the disease. In this study, we compared the peripapillary retinal nerve fiber layer (pRNFL) and central macular thickness (CMT) of newly diagnosed patients with type 2 DM without DR finding and healthy individuals. Thus we aimed to detect CMT and pRNFL changes that are presumed to occur before the visible signs of DR occur in Type 2 DM patients and to reveal the early retinal involvement of the disease with the help of Optical coherence tomography (OCT).
Material and Methods 53 newly diagnosed patients with DM without DR and 54 healthy control groups admitted to Lütfi Kırdar Kartal City Hospital Ophthalmology Department between January 2021 and January 2022 were included in the study. The best corrected visual acuities of the cases were measured, and anterior and posterior segment biomicroscopic examinations were performed. Mean and four quadrants (superior, inferior, nasal, temporal) CMT and pRNFL thickness measurements were performed with a Spectral-Domain optical coherence tomography (spectralis OCT) device.
Results 53 eyes of 53 newly diagnosed DM patients without DR and 54 eyes of 54 control group were included in the study. Age, gender, spherical equivalent, best corrected visual acuity, intraocular pressure and axial length values were compared between the two groups. No significant difference was found between the two groups. There was no significant difference in the mean and four quadrants (superior, inferior, nasal, temporal) CMT measurements in the newly diagnosed DM group compared to the control group. (respectively, p=0.327, p=0.276, p=0.217, p=0.605, p=0.916). In the pRNFL analysis, no statistically significant difference was found in the newly diagnosed DM group compared to the control group in the mean, superior, nasal and temporal quadrants (respectively, p=0.131, p=0.234, p=0.110, p=0.863). The statistically significant difference was observed in the inferior quadrant (p=0.0.46) and inferior quadrant were found to be significantly thinner. In addition, it was observed that there was a significant thinning in all quadrants of the pRNFL values of two patients diagnosed with diabetic neuropathy.
Conclusions When the data of our study is evaluated, it seems possible to say that thinning of the pRNFL can occur in newly diagnosed DM patients without DR findings, especially in the inferior quadrant. OCT for type 2 DM patients; we think that it can be a helpful method for the early detection of retinal neurodegeneration from the diagnosis.

OC029

Does COVID-19 Affect Prostate Specific Antigen Level?

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Background The coronavirus enters the body with the help of the angiotensin-converting enzyme 2 receptors and can target many organs where this receptor is located. One of these organs is the prostate, and if it is affected, the prostate-specific antigen level (PSA) may change. Our study aimed to reveal how the PSA level is affected in patients with active COVID-19 infection.
Material and Methods We recorded total PSA, free PSA, international prostate symptom score (IPSS) and the number of nocturia on the day of hospitalization in patients hospitalized in the COVID-19 service between April 2021 and June 2021. Total and free PSA levels and suprapubic prostate volume of the patients were examined in control of the urology outpatient clinic three months after discharge. Total and free PSA values of the patients with COVID-19 were compared to the baseline values.
Results The mean age of 33 patients included in the study was 61.7±10.7 years, IPSS 14.9±.8, nocturia number 2.6±1.6, prostate volume 47.7±27.3 g. Eighteen patients (55%) were receiving alpha-blocker drug therapy. While the total and free PSA values of the patients hospitalized due to COVID-19 were 2.05±2.3 ng/mL and 0.47±0.61 ng/mL, respectively, they were calculated as 1.99±2.1 ng/mL and 0.57±0.67 ng/mL at the after three-month control. While there was no statistical difference in the total PSA value measured after discharge (p=0.371), free PSA was found to be statistically significantly increased (p<0.001).
Conclusions While COVID-19 infection in the last three months does not affect the total PSA level in a

patient who applied to the urology outpatient clinic due to lower urinary tract symptoms, care should be taken to increase the free PSA level. This change may cause delayed diagnosis of a malignant formation by affecting the free/total PSA ratio, which can be used as a marker of prostate cancer.

OC030

Comparison of Aortic Elasticity Parameters with Transthoracic Echocardiography Measurements and Treadmill Exercise Test Data in Healthy Adults

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Background The elastic properties of the aorta are affected by many conditions, such as age, hypertension (HT), diabetes mellitus (DM), dyslipidemia, and smoking. Studies have shown that increased stiffness in the aortic vessel wall is associated with increased cardiovascular (CV) mortality and morbidity in various patient groups. In this study; It was aimed to compare aortic elasticity parameters with transthoracic echocardiography (TTE) measurements and treadmill exercise test (TET) data in individuals without known CV disease.

Material and Methods105 (mean age 40.19±9.06, 49.5% male) participants who applied to the cardiology outpatient clinic with various complaints or for check-up, had no known CV disease, were scheduled for TTE and TET were included. Patients with known DM, HT, moderate and higher degree of heart valve disease, congenital aortic valve or vascular anomaly, aortic dilatation, rhythms other than sinus and conduction defects on electrocardiography and patients with positive TET were excluded from the study. Aortic elasticity parameters (aortic strain, stiffness, and distensibility) were calculated with the relevant formulas from the M-mode images taken from the ascending aorta, in addition to the traditional measurements of cardiac structure and functions with TTE. These parameters were compared with the data obtained from TET (metabolic equivalents, maximum heart rate, exercise test duration, maximum systolic and diastolic blood pressure, percentage of predicted maximal heart rate, recovery time).

Results There was a significant negative correlation between age and aortic strain and distensibility (r= -0.561, p<0.001; r= -0.553, p<0.001, respectively), and a significant positive correlation with aortic stiffness (r=0.555, p<0.001).). A significant positive correlation was observed between aortic strain and metabolic equivalents (METs), which reflects effort capacity, maximum heart rate reached during exercise test (MHR) and exercise test duration (ETD) (r=0.238, p=0.016; r=0.373, p<0.001; r=0.227, p=0.22, respectively). A significant negative correlation was found between aortic stiffness and METs and MHR (r= -0.201, p=0.043; r= -0.396, p<0.001, respectively). In addition, a significant negative correlation was observed between aortic strain and distensibility and septum thickness, left atrial diameter and E/A values, and a significant positive correlation was observed between aortic stiffness and the same parameters. In the multivariate linear regression analysis, it was determined that all three parameters showed an independent correlation with age.

Conclusions In our study, a significant correlation was observed between aortic stiffness and strain values and age, exercise capacity and left ventricular diastolic parameters in healthy adults. The data we obtained showed that age is the most important factor affecting the aortic elasticity parameters, and that there is a relationship between these parameters and diastolic functions and cardiac structural changes. Low exercise capacity may also increase CV risk by affecting aortic elasticity.

Table 1. Demographic and laboratory features of the study group.

Variables	Values	Variables	Values
Age (years)	40.19±9.06	LDL cholesterol (mg/dL)	135.39±36.09
Male gender (%)	49.5 (n=52)	HDL cholesterol (mg/dL)	52.58± 13.97
BSA (m^2)	1.89±0.21	Total cholesterol (mg/dL)	198.72±38.95
Heart rate (bpm)	74.07±9.11	Hyperlipidemia (%)	40 (n=42)
SBP (mmHg)	109.14±10.03	Smoking (%)	15.2 (n=16)
DBP (mmHg)	68.42±7.14		

BSA: body surface area, bpm: beat per minute, SBP: systolic blood pressure, DBP: diastolic blood pressure, LDL: low density lipoprotein, HDL: high density lipoprotein.

Table 2. Echocardiographic measurements and treadmill exercise testing data of the study group.

Echocardiographic measurements			
Parameters	Values	Parameters	Values
LVEF (%)	60.6±1.77	IVRT (ms)	87.82±7.92
LVEDD (m)	45.73±4.52	DT (ms)	177.98±17.55
LVESD (mm)	29.74±3.22	E' (cm/s)	14.36±2.89
LA diameter (mm)	35.83±1.61	E/E' ratio	6.54±7.31
RA diameter (mm)	34.88±1.73	AoS (mm)	29.89±2.84
RV diameter (mm)	32.85±2.26	AoD (mm)	26.1±3.1
sPAP (mmHg)	22.09±3.13	Aortic strain (%)	14.62±3.56
E wave velocity (cm/s)	80.69±12.92	Aortic stiffness	3.38±0.91
A wave velocity (cm/s)	65.53±11.38	Aortic distensibility (cm^2.dyne-1.10^3)	7.32±2.09
E/A ratio	1.24±0.20		
Treadmill exercise testing data			
METs	9.73±1.34	Maximal DBP	86.85±9.93
Percentage of predicted MHR	96.4±13.26	Exercise test duration (s)	520.74±93.02
MHR with treadmill testing (bpm)	169.18±16.14	Recovery time (s)	187.14±57.63
Maximal SBP	144.66±13.66		

LVEF: left ventricular ejection fraction, LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter, LA: left atrium, RA: right atrium, RV: right ventricle, sPAP: systolic pulmonary artery pressure, IVRT: isovolumic relaxation time, DT: deceleration time, AoS: systolic aortic diameter, AoD: diastolic aortic diameter, METs: metabolic equivalents, MHR: maximal heart rate, SBP: systoic blod pressure, DBP: diastolic blood pressure.

Table 3. Statistically significant correlations between the parameters.

Parameter	r value	p value	Parameter	r value	p value
Age			Aortic strain		
Aortic strain	-0.561	<0.001	Age	-0.561	<0.001
Aortic stiffness	0.555	<0.001	BSA	-0.279	0.028
Aortic distensibility	-0.553	<0.001	E/A ratio	0.357	<0.001
LDL	0.247	0.021	A velocity	-0.277	0.006
Total cholesterol	0.252	0.019	e' velocity	0.279	0.008
E/A ratio	-0.462	<0.001	IVRT	-0.338	0.001
A velocity	0.355	<0.001	IVS	-0.394	<0.001
e' velocity	-0.380	<0.001	LA diameter	-0.274	0.005
IVRT	0.388	<0.001	METs	0.238	0.016
LA diameter	0.213	0.029	MHR with exercise	0.373	<0.001
SBP	0.217	0.026	Exercise test duration	0.227	0.022
IVS	0.296	0.002			
MHR with exercise	-0.323	0.001			
Aortic stiffness			Aortic distensibility		
Age	0.555	<0.001	Age	-0.553	<0.001
E/A ratio	-0.200	0.048	BSA	-0.250	0.012
e' velocity	-0.264	0.013	e' velocity	0.263	0.013
IVRT	0.281	0.05	A velocity	-0.265	0.008
IVS	0.239	0.016	E/A ratio	0.273	0.006
LA diameter	0.211	0.034	IVRT	-0.320	0.001
METs	-0.201	0.043	IVS	-0.319	0.001
MHR with exercise	-0.396	<0.001	LA diameter	-0.329	0.001
			MHR with exercise	0.298	0.002

BSA: body surface area, LDL: low density lipoprotein, IVRT: isovolumic relaxation, IVS: interventricular septum thickness, LA: left atrium, MHR: maximal heart rate, METs: metabolic equivalents.

OC031

The Importance of Family Support in the Treatment Process of Dialysis Patients

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Background Chronic diseases are irreversible, long-lasting, slowly progressing diseases that cause physical and functional disorders. One of the chronic diseases frequently seen in the world and in our country is chronic kidney failure. Many systems are affected due to the irreversible loss of kidney functions in chronic kidney failure.

Discussion In these patients, it is tried to ensure that they can live more comfortably and longer with dialysis treatment. Hemodialysis treatment brings many problems experienced by patients. These individuals enter the machine 2 or 3 days a week, a fluid they need to control constantly, the diets they need to follow, the drugs they need to use and the symptoms they have to deal with for life limit their daily activities. Most of the patients cannot continue their work because they are on dialysis on certain days a week. For these reasons, patients who undergo dialysis think that they are dependent on other family members and their psychological stress and anxiety levels increase due to role changes in the family. In all these processes, families have a role in ensuring the compliance of individuals with treatment. Families are one of the most important social support groups for these individuals.

Conclusions In this context, this review study aims to provide information about the importance of family support that dialysis patients receive during the treatment process.

OC032

Potentially Inappropriate Medication Use According to STOPP Criteria in Elderly Patients Admitted to the General Internal Medicine Outpatient Clinic

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Background The number of drugs used and the health risks related to drug use have increased in the elderly. In this study, it was aimed to determine the prevalence of potential inappropriate medication (PIM) use according to STOPP version 2 criteria in elderly patients admitted to Bursa Uludag University Hospital General Internal Medicine Outpatient Clinic.

Material and Methods It was planned as a prospective cross-sectional study. The patients' sociodemographic characteristics, diagnoses, concomitant chronic diseases, and drugs they used were recorded in detail, through face-to-face interviews with patients, in the pre-prepared questionnaire. Then, PIMs were determined according to STOPP version 2 Criteria. SPSS 21 package program was used for data analysis. In the comparison of categorical variables; Pearson x2 and Fisher's exact x2 tests, Kruskal-Wellis test was used to compare more than two independent groups, and Mann-Whitney U test was used to compare two independent groups.

Results Between March 1 and July 31, 2021, 411 (61.8% female, 38.2% male) patients aged 65 and over who agreed to participate in the study were interviewed, their files were examined and their disease and drug information were confirmed. The mean age of the patients was 71.5±5.9 years. (71 in women, 72.3 in men). The most common concomitant chronic diseases were hypertension (67.1%) and diabetes mellitus (39.8%). 93.7% of the patients were taking at least 1 drug per day. The rate of polypharmacy (using ≥5 drugs per day) was 55%, and the rate of excessive polypharmacy (using ≥10 drugs per day) was 11.2%. A total of 198 (48.2%) patients had PIM use according to the STOPP version 2 criteria (Table 1). Inappropriate use of proton pump inhibitors was the most common PIM (13.4%).

Conclusions In this study, it was observed that the rates of polypharmacy and PIMs were increased in the elderly, and the most common PIM was inappropriate use of PPI group drugs. Therefore, in order to reduce the potential risks related to drugs in the elderly, a comprehensive geriatric assessment should be performed for all patients, drugs should be prescribed in according to rational drug use recommendations, drugs used should be reviewed in terms of PIM use, and drugs should be questioned carefully in terms of adverse effects.

Table 1. Distribution of the number of drugs used and potential inappropriate medication use according to STOPP version 2 criteria by gender and geriatric age groups.

	Gender		Total	Age group	
	Female	Male		65-74 year-old	≥75 year-old
Number of patients	254 (61.8%)*	157 (38.2%)	411	306 (74.5%)*	105 (25.5%)
Number of drugs used					
No drug	13 (5.1%)	13 (8.3%)	26 (6.3%)	21 (6.9%)	5 (4.8%)
1-4 drugs	90 (35.4%)	69 (43.9%)	159 (38.7%)	118 (38.6%)	41 (39%)
5-9 drugs	120 (47.2%)	60 (38.2%)	180 (43.8%)	138 (45.1%)	42 (40%)
≥ 10 drugs	31 (12.2%)	15 (9.6%)	46 (11.2%)	29 (9.5%)	17 (16.2%)
Potential inappropriate medication use					
STOPP v2	130 (51.2%)	68 (43.3%)	198 (48.2%)	140 (45.8%)	58 (55.2%)

* p<0.05

OC033

Medication Errors and Potentially Inappropriate Medication Use in Elderly Patients Admitted to the General Internal Medicine Outpatient Clinic of a University Hospital

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Background The frequency of chronic diseases, number of drugs used, and number of medication errors have increased in the elderly. In this study, we aimed to determine the prevalence of potentially inappropriate medication use and medication errors in elderly patients admitted to a university hospital and to identify the influencing factors.
Material and Methods In this prospective cross-sectional study, the patients' characteristics, drug use patterns, and medication errors were recorded in detail. Following this, potential inappropriate medication use was assessed according to the 2015 Beers criteria.
Results A total of 721 elderly patients (60.9% female and 39.1% male) were included in this study. 94.9% of the patients had at least one concomitant chronic disease, and the most common chronic diseases were hypertension and diabetes mellitus. The mean number of drugs used by the patients per day was 4.6 ± 2.8 and the rate of polypharmacy was 49.4% and it was higher in women. The rate of medication errors was 54.2%, potentially inappropriate medication use was 30.1%, and adverse drug reactions was 22.5%; and these rates were higher in patients with polypharmacy. The most common medication error, potential inappropriate medication use, and adverse drug reaction were the omission of a daily dose (36.5%), inappropriate use of proton pump inhibitors (10%), and gastrointestinal system-related symptoms (7.7%), respectively (Table 1). Diabetes mellitus and depression were found to be independent factors associated with medication errors.
Conclusions In the present study, patient-related medication errors, potentially inappropriate medication use, and adverse drug reactions were more frequently observed in elderly patients with polypharmacy. In addition, medication errors were more commonly observed in elderly with diabetes mellitus and depression. Therefore, to reduce the potential risks in the elderly, a comprehensive geriatric assessment should be performed for all patients, drugs should be prescribed according to rational drug use recommendations and patients should be explained in detail about how to use their drugs. Following this, at each visit, patients should be carefully questioned how they use the drugs and about drug-induced adverse effects.

Table 1. Distribution of the number of drugs used, medication errors and potential inappropriate medication use by gender and geriatric age groups.

	Gender		Total	Age group	
	Female	Male		65-74 year-old	≥75 year-old
Number of drugs used					
1-4 drugs	178 (%40.5)	152 (%53.9)	330 (%45.8)	255 (%44.7)	75 (%50)
5-9 drugs	222 (%50.5)*	91 (%32.3)	313 (%43.4)	251 (%44)	62 (%41.3)
≥ 10 drugs	25 (%5.7)	18 (%6.4)	43 (%6)	32 (%5.6)	11 (%7.3)
Medication errors					
Dose omission error	165 (%37.6)	98 (%34.8)	263 (%36.5)	206 (%36.1)	57 (%38)
Wrong time error	137 (%31.2)	69 (%24.5)	206 (%28.6)	163 (%28.5)	43 (%28.7)
Wrong dose error	29 (%6.6)	22 (%7.8)	51 (%7.1)	35 (%6.2)	16 (%10.6)
Wrong drug error	4 (%0.9)	4 (%1.4)	8 (%1.1)	7 (%1.2)	1 (%0.6)
Total**	250 (%56.9)	141 (%50)	391 (%54.2)	314 (%55)	77 (%51.3)
Potentially inappropriate medications					
Table 2-related PIMs	121 (%27.6)	70 (%24.8)	191 (%26.5)	122 (%21.3)	69 (%46.0)*
Table 3-related PIMs	12 (%2.7)	7 (%2.5)	19 (%2.6)	12 (%2.5)	5 (%3.3)
Table 4-related PIMs	14 (%3.2)	8 (%2.8)	22 (%3.1)	3 (%0.5)	19 (%12.7)*
Table 5-related PIMs	18 (%4.1)	10 (%3.5)	28 (%3.9)	20 (%3.5)	7 (%5.3)
Table 6-related PIMs	3 (%0.7)	1 (%0.4)	4 (%0.6)	3 (%0.5)	1 (%0.7)
Total ***	136 (%31.0)	81 (%28.7)	217 (%28.3)	127 (%20.8)	90 (%56.7)

* p<0.001, ** Some patients have more than one medication error, *** Some patients have more than one potentially inappropriate medication use.

Poster Presentations

PP001

A Rare Case of Secondary Hypertension Accompanied by Low Renin and Low Aldosterone Level: Chronic Consumption of Supplement Consisting Licorice Root

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Background We have talked about a rare case of secondary hypertension caused by intake of licorice in an unusual way.
Case Report An 83-year-old female patient was consulted to our department for hypokalemia and resistant hypertension. In the initial evaluation, there was no history of drug use to explain the current picture. A detailed anamnesis was taken, and all medications used by the patient were questioned again and it was learned that the patient had been taking high amounts of supplements for a long time. Some of these supplements were contained licorice extract. Using of supplements which containing licorice were stopped. The supportive treatment relieved the patient's symptoms. Deadly complications were prevented thanks to early diagnosis.
Conclusions Our aim in sharing our case is to remind the importance of asking questions about herbal medicines and getting detailed medical history in all patients.

PP002

Parathyroid Carcinoma with Atypical Presentation

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Background Parathyroid carcinoma is a rare cause of primary hyperparathyroidism, usually caused by parathyroid adenoma and rarely by primary parathyroid hyperplasia. Its frequency varies between 0.3% and 2.1%. Patients are often (90%) symptomatic and have significant hypercalcemia, bone and kidney disease, neck mass, and significant parathyroid hormone levels. Studies have shown that patients have an average calcium level of 14.6-15.9 mg/dL. We aimed to present you with a normocalcemic and asymptomatic case.
Case Report A 22-year-old patient without any known comorbidity applied to the emergency service after falling. Magnetic resonance imaging was performed on the left knee due to lytic lesions in the radiograph of the left knee. Lesions with dimensions of approximately 30x10 mm in the anterior part of the proximal tibia and approximately 11x5 mm in the posterior part of the distal metaphysis of the femur, causing thinning of the cortex and protrusion from the contour, were detected. In the foreground, pathologies such as Langerhans cell histiocytosis, metastasis, or multiple myeloma were considered. Thereupon, the patient who had lytic lesions in many bones in PET-CT was referred to us. The patient who has no active complaints has calcium 10 mg/dL, phosphorus 2.1 mg/dL, parathormone 2,172 ng/L, 25-OH vitamin D level <3 ng/mL, ALP bone isoenzyme 636 (3-14) ng/mL, urea and creatinine were normal. In the neck ultrasound of the patient who was suspected of having parathyroid pathology, a 10x15 mm mass lesion was observed behind the lower pole of the left thyroid lobe and adjacent to the esophagus. Protein electrophoresis was normal. The 24-hour urine calcium level was 526 mg. Bone densitometry was performed, and the patient had lower bone mineral density than expected for her age. No nephrolithiasis was detected in the urinary ultrasonography. The patient underwent left hemithyroidectomy and left lower upper parathyroidectomy. Its pathology was reported as parathyroid carcinoma (KI67 25% GATA3+). The starving bone syndrome was considered in the patient with postoperative parathormone level of 43.8 ng/L, calcium 7.2 mg/dL, and phosphorus 1.4 mg/dL. Calcium was given, and vitamin D replacement was continued. Tests for MEN were sent. The cd73 (HRPT-2) mutation was submitted for genetic analysis. The patient was currently being followed up with parathormone and calcium levels.
Conclusions Parathyroid carcinoma can lead to many symptoms by causing hypercalcemia in more than 90% of patients. In our case, there was a concomitant low vitamin D. The patient was normocalcemic and asymptomatic. It should be kept in mind that calcium levels to screen for hyperparathyroidism may be normal due to concomitant vitamin D deficiency, and parathormone levels should be checked in patients with lytic lesions in the second bone osteoporosis, nephrolithiasis, and renal failure.

PP003

Sheehan Syndrome and Central Hypothyroidism: A Case Report

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Background Sheehan's syndrome occurs as a result of ischemic pituitary necrosis due to severe postpartum hemorrhage. The syndrome is characterized by varying degrees of anterior pituitary dysfunction resulting from the deficiency of multiple pituitary hormones. The order of frequency of hormone loss has generally been found to be growth hormone and prolactin, gonadotropins, ACTH and thyrotropin. Women with Sheehan's syndrome exhibit a variety of signs and symptoms including failure to lactate or resume menses, loss of genital and axillary hair, and often occurring long after delivery clinical manifestations of central hypothyroidism and secondary adrenal insufficiency. Sheehan syndrome is one of the causes of secondary empty sella syndrome. Treatment of Sheehan's syndrome involves hormone replacement therapy. In our case, we evaluated a patient who had a history of severe vaginal bleeding at her third birth, followed by amenorrhea, developed slowly and was diagnosed years later, and was diagnosed with chronic sheehan syndrome, which primarily developed central hypothyroidism.

Case Report A 32-year-old patient who had a normal vaginal delivery, had a history of excessive bleeding at her third birth, was followed up with amenorrhea, and received intermittent oral contraceptive treatment. She was evaluated with complaints of type 2 diabetes mellitus and fatigue at the age of 46. There was no feature in her family history. In the physical examination, the patient was conscious, full of orientation and cooperation. Blood pressure was 125/80 mmHg, pulse 70/min, and temperature 36.6 °C. Other system findings were within normal limits. Hemogram and biochemistry are normal in the examinations, TSH: 0.6 mIU/L (0.27-4.20), free T4: 0.49 ng/L (0.93-1.71), and free T3: 1.75 ng/L (2.04-4.44) detected. File review revealed that free T3, free T4 levels were not measured for 2 years in previous examinations, and the TSH level measured was close to the lower limit. Evaluating the anterior pituitary hormone panel, cortisol 11.8 µg/dL (6.7-22.6), ACTH 28 ng/L (7.2-63.3), prolactin 7.74 ng/mL (5.18-26.53), LH 1.5 mIU/mL, FSH 2 mIU/mL, estradiol (E2) <5 pg/mL, growth hormone <0.05 µg/L (0.06- 5), IGF-1 54 µg/L (74-196), and thyroid function tests were found to be compatible with central hypothyroidism. No abnormal finding was detected in the thyroid ultrasonography of the patient. There was no sign of empty sella in the MRI of the sella. The pituitary parenchyma was minimally heterogeneous. In the images taken in the late phase, an unenhanced area of 2 mm in diameter was detected in the middle part of the pituitary gland. No pathology was detected in the hypothalamic, suprasellar or parasellar regions.

Conclusions Although rare, Sheehan's syndrome can occur months or even years after postpartum hemorrhage. Diagnosis may be missed due to slow development. Diagnosis of central hypothyroidism may be delayed by only looking at TSH level in patients. In our case, it was observed that Sheehan syndrome had a slow development, unusually presenting primarily with central hypothyroidism, the diagnosis was delayed because only TSH level was checked, and patients with central hypothyroidism and Sheehan syndrome should be followed up as pituitary hormone deficit may develop in the long term.

PP004

Diabetic Ketoacidosis Patient with A Painful Leg: Consider Pyomyositis!

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Background The risk of infection significantly increases in diabetes, especially among patients with uncontrolled disease. A rare but extremely serious type of infection called "pyomyositis" needs the close attention of physicians to recognize the case immediately as any delay in diagnosis might lead to severe complications, including septic shock, endocarditis, brain abscess, or even death. Pyomyositis is an uncommon purulent infection of skeletal muscle that usually presents with abscess formation. The main predisposing factors are immunodeficiency, temperate climates, trauma, drug injection, and malnutrition. Furthermore, patients mainly refer to a doctor with entirely obscure signs and symptoms which imitate other musculoskeletal issues, including osteomyelitis, septic arthritis, muscle

rupture, or deep venous thrombosis. Herein, we report a patient with diabetic ketoacidosis who presented with a painful leg and was diagnosed with pyomyositis. ***Case Report*** A 45 years-old female patient presented to the emergency room with meaningless speech. She was dehydrated, and her right thigh was warm and mildly erythematous. She had a diabetes mellitus diagnosis three years ago in past medical history. Her medical compliance to prescribed oral antidiabetics was minimal, though. She had no trauma or injection history. Her blood glucose level was 523 mg/dL with urine ketone positivity in the first workup. Blood gas analysis confirmed metabolic acidosis. Although the patient was afebrile, C-reactive protein was 344 mg/L, and white cell count was 24.55 K/μL. COVID-19 PCR test was negative, and other blood tests were normal. Cranial computed tomography ruled out acute infarction or hemorrhage in case of blurred consciousness. Following the monitorization, insulin infusion, potassium replacement, hydration, and ampicillin-sulbactam antibiotics therapy were immediately initiated, the patient was admitted to Endocrinology and Metabolism Clinic with diabetic ketoacidosis and cellulitis early diagnosis. Her HbA1c level was 117.5 mmol/mol Hb (12.9%). Doppler ultrasonography of the lower extremity did not infer any abnormal blood flow. Lumbosacral magnetic resonance imaging (MRI) showed a 30x5 cm sized abscess in vastus lateralis and quadratus femoris muscles. Additionally, right elbow ultrasonography demonstrated 1cm anechoic fluid as well. Drainage of abscess in the right thigh was urgently planned. In her blood culture tests, *Staphylococcus aureus* was isolated, and teicoplanin therapy was started as *Staphylococcus aureus* was ampicillin-resistant and teicoplanin susceptible in her abscess drainage culture. She was HIV-negative, and her immunoglobulin levels were normal. Her echocardiography did not show infective endocarditis findings. Her cranial MRI showed nasopharyngeal mass corresponding with cystic findings in the biopsy. After successfully treating pyomyositis with drainage and teicoplanin, the abscess completely disappeared in the right elbow and thigh without any sequelae. Her procalcitonin was negative, and C-reactive protein was below 10 mg/L at the time of discharge. Her stay at our clinic was 35 days.
Conclusions An uncommon complication of poorly controlled diabetes is pyomyositis with possible serious morbidity and mortality risk. Abscess drainage and appropriate antibiotic therapy are essential for managing diabetic pyomyositis following the confirmation of diagnosis with MRI. In the long term, control of diabetes is a must to minimize the infective and other systemic complications in these patients.

PP005

Nursing Management in a Patient Developing Pancytopenia After Chemotherapy: A Case Report

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Background Pancytopenia is a sudden decrease in the three main series of formed elements of the blood (erythrocyte, platelet and leukocytes). Pancytopenia can occur by various mechanisms. Combined chemotherapy used in cancer treatments can cause pancytopenia by affecting the bone marrow while affecting the cancer cell. As a result of pancytopenia, the patient may develop anemia, bleeding, and infection, and if not managed well, life-threatening conditions may occur. Here, an exemplary nursing management of a patient who developed pancytopenia after folfirinox chemotherapy is presented.
Case Report A 61-year-old female patient was diagnosed with hypertension and depression. She uses Fludex SR, esplus and redepra. He was examined for 6 months due to complaints of weight loss, abdominal and back pain. After the biopsy, he was diagnosed with metastatic pancreatic adeno cancer. The patient with liver, peritoneum and small intestine metastases was considered unresectable, and a port catheter was inserted, and the first course of folfirinox (irrinotecan, oxaliplatin, calcium leucovorin and 5-fluorouracil) was given. Durajesic 25 TTS was started for his pain. The patient went to the emergency room 10 days after chemotherapy treatment, body temperature 38.3 °C, blood pressure 120/70 mmHg, pulse 98/min, SpO_2 97% (without O_2), diarrhea 5 times a day and Grade 3 mucositis applied with. The ECG was unremarkable in the patient who had negative PCR test, cough, sputum and no symptoms. Laboratory tests (blood, urine, stool fresh) were checked and he was admitted to the oncology clinic. The patient's blood (peripheral and catheter), urine and sputum cultures were taken and treatment was started. Laboratory results in emergency: leukocyte 0.42 K/μL (4.5-11), neutrophil 0.010 K/μL (2-6.9), hemoglobin 7.8 g/dL (11.5-15), hematocrite 25.2% (33-44), platelet 6.5 K/μL (145-400), CRP 252.9 mg/L (<5), procalcitonin 1.64 μg/L (<0.05), potassium 3 mmol/L (3.5-5.1), sodium 132 mmol/L (136-145),

creatinine 2.52 mg/dL (0.56-0.85), BUN 42.1 mg/dL (9.8-20.1), urea 90 mg/dL (20.9-43). Urine sediment leukocyte 3, bacteria less, stool fresh no feature. The patient was promptly started on G-CSF, antibiotics and antifungal therapy. Necessary fluid, electrolyte and blood products were replaced. Tantum, mycostatin, gaviscon/lidocaine mouthwash, intravenous TPN were started. Durajesic dose was increased for his pain and interrupted with parol infusion. Vital signs, pain and fluid intake and output, daily laboratory follow-up were performed. Risk of falling, nutritional imbalance (less than requirement), electrolyte imbalance, risk of infection, deterioration of oral mucous membrane, lack of fluid volume, hyperthermia, change in bowel excretion habits (diarrhea), bleeding risk, self-care syndrome, discomfort in sleep pattern, ınformation deficiency, acute pain, anxiety and fatigue" nursing care diagnoses were made and the process was successfully managed by applying care for them.

Conclusions In the direct microscopic examination of only the sputum culture of the patient, gram (+) cocci, gram (+) bacilli were observed, there was no growth in other cultures. On the 6th day of treatment, her neutropenia resolved. Mucositis continues to decrease (Grade 2). The patient continues to be followed in the clinic. When his general condition improved, it was planned to change the chemotherapy regimen. Pancytopenia that develops after chemotherapy can be prevented, especially in patients receiving high-risk chemotherapy regimens, with close monitoring, and education of the patient and their relatives on chemotherapy and symptom control, or it can be detected in the early period and prevented from serious conditions. In such cases, oncology nurses play a key role.

PP006

Nursing Management in a Patient Developing Grade 4 Infusion Reaction Due to Chemotherapy: A Case Report

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Background Infusion reactions (IR) may develop frequently in systemic chemotherapy applications. The incidence of IR may increase when chemotherapeutics and different agents are used together. IR appears as an allergic reaction (usually IgE-mediated response) or non-immune-mediated reactions to foreign proteins. IR can be seen especially due to taxanes, platinum derivatives, pegylated liposomal doxorubicin, monoclonal antibodies and immunotherapy. Although IR usually occurs during drug infusion or within a few hours, it can also be seen in the late period. The severity of Irs is often mild and is accompanied by symptoms such as chills, fever, nausea, skin rash, itching. But some can also be severe and deadly. Here, as an example, a case of nursing management in a patient who developed a Grade 4 infusion reaction due to carboplatin is presented.

Case Report A 65-year-old male patient has diagnoses of diabetes, hypertension, heart disease (stent) and chronic obstructive pulmonary disease (COPD). Beloc uses diaformin, karrum, monolong. He has no known history of allergies. He is constantly using nasal oxygen. He was examined for 6 months due to cough complaints. In December 2018, he was diagnosed with lung squamous cell carcinoma (AC SCC) as a result of biopsy from the left lower lobe of the lung. The patient presented to the council received 6 courses of neoadjuvant paclitaxel + carboplatin. After the operation, she received radiotherapy to the mediastinum for 18 days and weekly paclitaxel + carboplatin simultaneously. 1,8,15 paclitaxel+carboplatin was continued after radiotherapy. The patient came to the unit on 24 November 2021, on the 15th day of the 4th cycle, in a wheelchair with O2 accompaniment, conscious and cooperative. Initial vital signs were normal (Blood pressure 130/80 mmHg, pulse 88/min, temperature 36.5 °C, SpO_2 97% [with O2 3 L/min]). Paclitaxel infusion was administered in 1 hour after premedication (pheniramine in 100 cc isotonic + 16 mg dexamethasone + granisetron) was administered

according to the physician's request. Intermediate washing was done with isotonic and carboplatin was started. At the 15th minute of the carboplatin infusion, due to the development of redness on the face and hands and respiratory distress, chemotherapy treatment was stopped and vascular access was established with isotonic and intravenous 80 mg methylprednisolone and pheniramine were administered. He was brought to the recovery position, monitored, and the physician was informed. Blood pressure 100/60 mmHg, pulse 134/min, temperature 36.4 °C, SpO_2 75% (with O_2). Oxygen was switched to the mask and increased to 10 L/min. The patient relaxed a little, but after his resaturation decreased, SpO_2 60% (with O_2), and he became unconscious. Epinephrine 0.5 mg was administered intramuscularly to the right thigh lateral and the ambu mask was switched. The patient who developed cardiac arrest at 11.05 was given a blue code. With CPR, the apex beat was taken at the 2nd minute. His dentures were removed and he was intubated with sedation upon resistance. Aspiration was provided, blood gas was sent and a second vascular access was established. He was delivered to the emergency room intubated in the presence of a physician, with blood pressure 110/70 mmHg, pulse 108/min, temperature 36.4 °C, SpO_2 98%. The patient was taken to the intensive care unit from the emergency room and was extubated 24 hours later and taken to the oncology service. He was discharged home two days later.

Conclusions of platinum derivatives and concomitant drug use are factors that increase the risk of IR. The patient's co-morbidities such as COPD and heart disease caused more severe hypoxia and cardiac arrest when IR developed. Necessary equipment ort he management of these reactions should always be kept ready and easily accessible. Life-threatening infusion reactions that develop within seconds can be effectively managed as a team with timely and correct intervention. The knowledge and experience of nurses on the subject is important in positively influencing patient outcomes.

PP007

Thyrotoxic Hypokalemic Periodic Paralysis: A Case Report

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Background Thyrotoxic hypokalemic periodic paralysis (THPP) is a rare complication of hyperthyroidism, characterized by low serum potassium levels and acute muscle weakness, without any sensory deficit or confusion. Increased beta-adrenergic stimulation and overactive Na-K-ATPase channels cause potassium leak into muscle cells, and muscle cells can not be stimulated due to hyperpolarization.

Case Report A 22-year-old male patient who was diagnosed with Graves' disease three years ago admitted to the emergency department with the complaints of weakness in his upper and lower limbs. He did not use his antithyroid medication for eight months. Physical examination revealed his upper and lower limb power as grade 1/5 with intact sensation. Electrocardiogram showed sinus tachycardia. Serum biochemical parameters were potassium 2.2 mmol/L (3.5–5.5), thyroid-stimulating hormone <0.01 mU/L (0.35-4.94), thyroxine 2.92 ng/dL (0.7-1.47), free triiodothyronine 14.31 ng/L (1.71-3.71). All the other parameters were within normal limits including venous blood gas analysis. Based on the neurological examinations and the biochemical results, THPP was diagnosed. 30 mEq intravenous potassium chloride in %0.9 sodium chloride solution was started immediately and the patient was treated with 40 mg oral propranolol every six hours and 30 mg methimazole daily. After intravenous potassium replacement, complete clinical recovery and normalization of potassium levels were seen.

Conclusions Thyrotoxicosis is the most common cause of acquired periodic paralysis. In the absence of a family history of paralysis, renal tubular acidosis should also be kept in mind. Symptoms of hyperthyroidism may not always be evident in patients, or muscle paralysis could be the first manifestation of thyrotoxicosis. In summary, THPP is an infrequent complication of hyperthyroidism that can be fatal. The most important step in preventing THPP is to achieve euthyroidism.

PP008

Acute Lymphoblastic Leukemia Presenting with Loss of Bilateral Visual Acute: A Case Report

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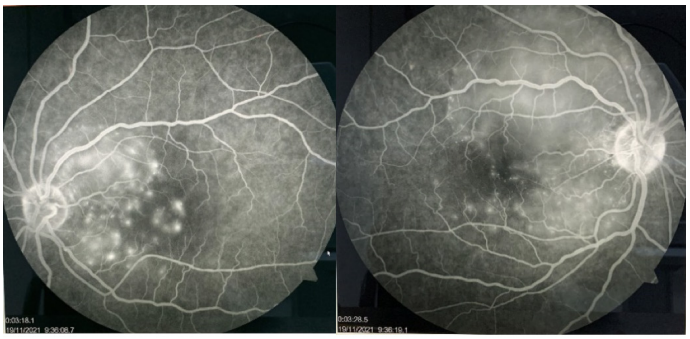
Background Acute lymphoblastic leukemia (ALL) is an aggressive disease caused by the expansion of lymphoid blasts in the blood, bone marrow and other organs. It makes its first peak at the age of 4-5 and the second at the age of 50. In less than 5% of cases, genetic syndromes play a role in the etiology. Other risk factors include advanced age (>70 years) and radiation exposure. Patients may present with non-specific symptoms and signs (fever, night sweats, weight loss). Other symptoms such as infection, easy bruising/bleeding, dyspnea and fatigue are among the applications. On physical examination, pallor, petechiae, purpura, ecchymoses and hepatosplenomegaly (20%) may be present. Other extramedullary involvement areas can be testis, skin or mediastinum (especially in T-cell ALL). CNS involvement (cranial neuropathies and meningeal infiltration) at the time of diagnosis is found in 8% of cases. More than 30% of patients have ocular complaints. However, significant eye involvement is rare. Orbital involvement is specific to children. It is generally found unilaterally, under 10 years of age, and is very rare in adult patients. Presentation with bilateral loss of visual acuity is extremely rare. Herein, we presented a case who had bilateral visual acuity loss and was diagnosed as common B ALL with exudative serous retinal detachment.

Case Report A 49-year-old female patient with a history of chemotherapy and radiotherapy with a diagnosis of breast cancer and in remission for 5 years applied to the ophthalmology outpatient clinic with blurred vision in both eyes for the last two days. Fundus fluorescein angiography performed in the ophthalmology outpatient clinic revealed diffuse fluorescein leaks (pinpoint leaks) and exudative serous retinal detachment (SRD) due to choriocapillaris involvement.

Thereupon, he was referred to the hematology outpatient clinic with the preliminary diagnosis of ALL and Vogt Kayanagi Harada disease. On physical examination, blood pressure, pulse and temperature were within the normal range. The patient had weakness, loss of appetite, night sweats and involuntary weight loss (5 kg) for the last 15 days. There was a decrease in visual acuity in both eyes. Peripheral lymphadenopathy and hepatosplenomegaly were not detected. Other system examinations were normal. There was no finding in favor of ALL in the complete blood count examination, which was requested for a different reason 10 days before the admission. In the examinations performed at the time of application: leukocyte 58,200/mm^3, neutrophil 36,400/mm^3, lymphocyte 14,000/mm^3, monocyte 2,830/mm^3, eosinophil 20/mm^3, hemoglobin 12.9 g/dL, platelet 198,000/mm^3, D-dimer 3.61 mg/dL, fibrinogen 342 mg/dL, sedimentation rate 21 mm/h, urea 19 mg/dL, creatinine 0.7 mg/dL, uric acid 7.4 mg/dL, AST 48 U/L, ALT 41 U/L, ferritin 1,070 µg/L. Granulocytic precursor cells and blastic cells were seen in the peripheral blood smear. The patient was diagnosed with common B ALL by evaluating the bone marrow with aspirate, imprint and flow cytometry. In the cerebrospinal fluid flow cytometry examination, 10.7% blastic cells were seen. CD10, CD19, CD22, CD33 and HLA-DR were positive. He was admitted to the hematology clinic to evaluate the extent of the disease and to plan chemotherapy. In the follow-up of the patient who started HyperCVAD chemotherapy protocol, Philadelphia chromosome was found to be t(9;22) positive. Due to cytopenia, dose modification was made and tyrosine kinase inhibitor imatinib (400 mg) was added to his treatment.

Conclusions As in our case, ALL may present with rare clinical findings. The patient presenting with bilateral visual acuity loss should also be examined with the preliminary diagnosis of ALL. SRD is a rare manifestation of ALL. A comprehensive literature review was conducted in a case report published in the American Society of Ophthalmology in September 2021, and presenting ALL with 11 other SRDs reported worldwide was shown. Early recognition of this hematological malignancy is crucial for prompt initiation of life-saving therapy.



Picture 1.

PP009

Bilateral Gout Arthritis Developing After Covid-19 Infection: A Case Report

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Background SARS-CoV-2 virus started in Wuhan, China in 2019 and caused the COVID-19 pandemic by affecting the whole world in a short time. Arthralgia is one of the symptoms that can be seen after COVID-19 infection and can be seen in 14.9% of the cases. However, data on rheumatic and inflammatory symptoms such as arthritis are scarce. Viral infections are known causes of acute arthralgia and arthritis. In the literature, there are many examples of reactive arthritis cases developing after COVID-19 infection. Gouty arthritis is the most common form of inflammatory arthritis. Acute gouty arthritis most often affects the first metatarsophalangeal joint in the foot.
Case Report A 76-year-old male patient with chronic kidney disease, hypertension, and a history of coronary artery bypass using both leg saphenous 12 years ago was admitted to the emergency service with chest pain and increasing fatigue. Since the COVID-19 PCR result was positive, he was hospitalized for further examination and treatment. On the 14th day of hospitalization, the patient complained about pain around both big toes that started suddenly at night and worsened in the morning. In the patient's history, he stated that he had completely similar complaints several times with an interval of one year in the last 3 years and he recovered spontaneously in 10-15 days. There was limited redness, swelling, and tenderness in the bilateral foot metatarsophalangeal joints on physical examination. It was evaluated as bilateral gouty arthritis according to the 2015 gout classification criteria, and the patient was treated with colchicine 3x0.5 mg and methylprednisolone 8 mg/day. His complaints regressed after treatment. At the end of 6 days, the physical examination findings improved, and the complaint decreased. It was completely healed after 14 days.
Conclusions Although developing gouty arthritis etiology is not clear for our patient in this case, it is thought to be a secondary condition due to the development of the disease after COVID-19 infection. It was considered that our patient has bilateral gouty arthritis triggered primarily by COVID-19. Due to the limited number of studies, more case reports should be added to the literature on this subject.

PP010

Cetuximab-Induced Acneiform Eruption: A Case Report

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Background Colorectal cancer is the third most common cancer globally. About a quarter of them are metastatic at diagnosis, and metastasis develops in 40-50% of early-stage cancers. Cetuximab is an epidermal growth factor receptor (EGFR) inhibitor drug used to treat metastatic colorectal cancer and head and neck cancer. Since EGFR inhibitors target specific molecular pathways, systemic severe side effects seen in cytotoxic chemotherapy are not observed. Cutaneous side effects have been reported frequently during cetuximab treatment. Acneiform eruptions, one of the severe side effects of cetuximab treatment, are usually reversible but rarely lead to dose reduction or discontinuation. We presented a case with cetuximab-induced acneiform eruption.
Case Report A 54-year-old male patient with no known comorbid disease was taken to emergency operation due to colonic obstruction in March 2020 and was diagnosed with colon adenocarcinoma due to a left hemicolectomy operation. As a result of the systemic evaluation at the diagnosis, multiple liver metastases were seen. Since K-ras/nras/braf mutations were not detected, the patient was started on mFOLFOX (folinic acid + fluorouracil + oxaliplatin) + cetuximab in April 2020. The patient, who had no history of rash (acneiform) and had not used systemic steroids recently, developed pruritic papules and pustular lesions on the nose and sides of the nose and in the nasolabial grooves after the ninth cycle of chemotherapy. No pathology was detected in the evaluation of the skin and mucosa of the whole body, except for the lesions. Comedones did not accompany the lesions. Laboratory examinations were unremarkable. Based on the current clinical findings, the patient was diagnosed with cetuximab-induced acneiform eruption, and clindamycin + 10% sodium sulfacetamide cream treatment was started once a day, and protection from sunlight was recommended. In control on the seventh day of the treatment, it was observed that the skin lesions regressed almost wholly. The patient's treatment was continued at the current dose. In outpatient follow-ups, no recurrence was

observed.

Conclusions Cetuximab inhibits the EGFR pathway in the skin, causing various dermatological side effects by impairing keratinocyte proliferation, differentiation, and hair follicle development. Among these dermatological side effects associated with EGFR inhibitors, the acneiform eruption is the most common and the earliest. Papulopustular rash, nail and hair disorder, xerosis, telangiectasia, hyperpigmentation, seborrheic dermatitis are other cutaneous side effects. Acneiform lesions are usually seen on the face, scalp, trunk, and upper back. Topical metronidazole, clindamycin, and salicylic acid can be used in mild cases and systemic tetracyclines in moderate and severe cases. It is recommended that patients be protected from sunlight during and up to 2 months after cetuximab treatment, and sunscreen creams are recommended. As a result, cetuximab-related skin rashes may develop in patients, and the lesions must be recognized and treated to continue their treatment.

PP011

A Rare Cause of Anemia Etiology: Gastrointestinal Stromal Tumours

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Background Gastrointestinal Stromal Tumours (GIST) are rare neoplasms orginating from the interstitial cajal cell in the gastrointestinal tract. They constitute 1-2% of gastrointestinal system tumours. The predominant localization of GISTs seems to be the stomach and small intestine, but GISTs may develop any level of the gastrointestinal tract and sometimes in the omentum, mesentery, and peritoneum. 18% of cases are asymptomatic and diagnosed during CT scans, endoscopic procedures or surgical procedures. GISTs can be identified on ultrasound examination of the abdomen, computerized tomography (CT) scanning, magnetic resonance imaging (MRI), and positron emission tomography. The definitive diagnosis of GIST is made by histopathological examination and immunochemistry. We presented the case of GIST which we investigated the etiology of iron deficiency anemia and found the tumour.

Case Report A 51-year-old male patient was evaluated by abdominal ultrasonography at an external center 8 months ago with the complaint of pain in the right upper abdomen. The patient with cholelithiasis had a laparoscopic cholecystectomy operation. The patient re-evaluated in an external center with complaints of weakness, fatigue, contiuned swelling in the right upper abdomen and weight loss 12 kg in the last 6 months. Iron deficiency anemia was observed in the examinations. Upper gastrointestinal system endescopy and colonoscopy were performed. No abnormal observed in endoscopic procedures. Duodenal wall thickening was detected in non-contrast abdominal CT. After transfusion of 2 units erythrocyte suspension, iron treatment was given. In the physical examination of the patient whose complaints continued to increase, his vital signs were normal, his conjunctiva was pale and there was fullness in the epigastric region. The hemoglobin value; 7.5 mg/dL, which was consistent with iron deficiency anemia. MR enterography was planned to investigate small bowel diseases because the patient's endoscopic evaluations were normal. A mass lesion of approximately 13.5x15.5x16 cm in size at the level of the 3-4 th part of the doudenum was detected. The mass had a connection with the intestinal lumen and air and fluid levels were monitored in its central unit. Contrast-enchanced abdominal CT was performed. Diffuse wall thickening was observed in a 14 cm segment in the distal part of the duodenum. An exophytic mass, approximately 14x8 cm in size, with cavitation in the center was observed. Combined MRI and CT evaluations reported that the mass lesion describe was consistent with GIST a malignant mass. The patient was referred to the general surgery department. The patient was operated and biopsy was performed from the mass. Patalogy examination results; high grade malignant mesenchymal tumour, morphological and immunohistochemical findins were interpreted as compatible with GIST. The patient was reffered to oncology and imatinib was started as preoperative chemoteraphy.

Conclusions The etiology of iron dificiency anemia is a finding must be found. Underlying gastrointestinal system losses should be investigated. Normal endoscoping procedures do not mean that there is no gastrointestinal disease. Other small bowel diseases such as GIST, which are rare, should also be investigated.

PP012

Preventable, Mitigable, and Treatable: Oral Mucositis

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Background Mucositis is a common complication of radiotherapy (RT), chemotherapy (CT), combination of RT and CT, and hematopoietic stem cell transplantation (HSCT). It is characterized by erythema and ulceration. Oral mucositis (OM) may result in pain, dysphagia, need for enteral or parenteral nutrition, increased consumption of opioid drugs, and interruption of cancer treatment. In immunocompromised patients, OM may increase the cost of treatment by prolonging the length of hospital stay and increasing mortality in relation to bacteremia.

Material and Methods Evidence-based practice guidelines have been created by conducting many studies to prevent, alleviate and treat the symptoms of cancer-related mucositis. The Multinational Society for Supportive Care in Cancer and the International Society of Oral Oncology (MASSC/ISOO) published its first guideline in 2004, then updated it in 2009 and 2013. Finally, it collected and updated the collected evidence in one article, 1,197 published in 2020.

Results According to this;

• Basic oral care; It is recommended in all cancer treatment Material and Methods. Basic oral care includes teeth cleaning, mouthwash, rinsing and moisturizing. Dental evaluation and treatment is recommended before cancer treatment to reduce the risk of local and systemic infections. It is recommended to give basic oral hygiene education to ensure oral hygiene. Expert opinion assumes that there are gentle rinses for both saline and sodium bicarbonate that increase oral hygiene and can help to maintain oral hygiene and improve patient comfort. Data on this subject are limited and there is insufficient evidence (level of evidence 3).

• Cryotherapy; Oral ice use for 30 minutes is recommended for patients taking 5-FU and high-dose melphelan (level of evidence 2).

• Chlorhexidine; It is recommended not to use chlorhexidine for the prevention of OM in patients undergoing RT in head and neck cancers (level of evidence 3).

• Benzydamine hydrochloride; Use of benzydamine hydrochloride is recommended for the prevention of OM in patients with moderate RT (<50 GA) in head and neck cancer (level of evidence 1). The use of benzydamine hydrochloride is recommended in combinations of RT and CT in head and neck cancer (level of evidence 2).

• Low level laser therapy; Low-level laser therapy is recommended for the prevention of OM in adult patients undergoing HSCT. Low-level laser therapy is recommended in patients with head and neck cancer who receive RT and CT together (level of evidence 1). Low-level laser therapy is recommended for patients with head and neck cancer who only receive RT (level of evidence 2).

• Recombinant human keratinocyte growth factor-1 (KGF-1); Intravenous use of KGF-1 is recommended for the prevention of OM in hematological cancers undergoing autologous HSCT (level of evidence 1).

• Granulocyte-macrophage colony stimulating factor (GM-CSF); It is recommended not to use topical GM-CSF for the prevention of OM in patients undergoing HSCT (level of evidence 2).

• Analgesic drugs; Topical morphine 0.2% mouthwash is recommended for the treatment of OM-related pain in patients with head and neck cancer receiving RT-CT (level of evidence 3). Sucralfate (combined topical and systemic) is not recommended for the prevention and treatment of OM-related pain in solid cancer patients receiving CT and head and neck cancer patients receiving RT (level of evidence 2).

• Natural products; Parenteral glutamine: Careful use is recommended because parenteral glutamine administration for OM in patients undergoing HSCT shows higher mortality (level of evidence 1). Oral glutamine: Oral glutamine is recommended for the prevention of OM in patients with head and neck cancer receiving RT-CT (level of evidence 2). Honey: Honey is recommended for the prevention of OM in patients with head and neck cancer treated with RT or RT-CT (level of evidence 2).

Oncology nurses should evaluate their patients in terms of mucositis using the Oral Evaluation Guide and determine the frequency of oral care and the oral care protocol to be used in accordance with the clinical evidence according to the score they get.

Conclusions The main purpose in the fight against mucositis; identifying risk factors, taking protective measures and preventing disruptions that may occur in the treatment process. For this purpose, oral mucositis will become a preventable, mitigable and treatable problem with the use of evidence-based practices and guidelines by oncology nurses, who are responsible for oral care and education of patients.

PP013

A Finding That Is Not Clear What Will Emerge When You See It: Hypoalbuminemia

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Background Hypoalbuminemia can occur for many different reasons such as chronic kidney damage, nephrotic syndrome, chronic liver diseases, malnutrition. We presenteded a case of protein-losing enteropathy due to gastrointestinal malignancy presenting with symptoms such as hypoalbuminemia and edema in the hands and legs.
Case Report A 67-year-old male patient with no known history of chronic disease had come to the emergency department with an increase in swelling in both legs that had increased, soft, pitting edema for the last week.His albumin level is 19.7 g/L, total protein value was 4.25 g/L. The patient was admitted to our internal medicine clinic for hypoalbuminemia examination. The patient's echocardiography was normal. When the causes of hypoalbuminemia were examined, abdominal ultrasound and abdominal tomography and liver function tests requested for a possible liver disease were normal. Albumin loss was thought to be due to renal causes, but urea and creatinine levels and 24 hour urine protein level were normal. In our research on malnutrition, which may be the cause of hypoalbuminemia, there were no malnutrition findings.In the gastrointestinal system screening, the patient underwent colonoscopy. Colonoscopy revealed an ulcerovegetant mass in the transverse colon that almost completely occluded the lumen.
Conclusions In this case, who underwent colonoscopy two months ago, systematically examining the causes of hypoalbuminemia and excluding other causes, and advocating the idea that the case was of gastrointestinal origin, led to the renewal of the colon screening of the patient and the early detection of malignancy and seconder protein losing enteropathy.

PP014

Combination with Azathioprine and Allopurinol Causes of Anemia in Kidney Transplant Patients

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Background Patients with solid organ transplantation have an increased risk of developing hyperuricemia. When hyperuricemia develops after kidney transplantation, the combined use of these two drugs should be avoided because azathioprine and allopurinol interact and cause cytopenia. Here, we presented a case of cytopenia developing after starting allopurinol due to hyperuricemia in a kidney transplant patient using azathioprine.
Case Report A 57-year-old male patient underwent living donor kidney transplantation in 1997 due to the development of chronic renal failure secondary to Alport syndrome. While he was using cyclosporine 125 mg and azathioprine 100 mg, he applied to the rheumatology department due to the development of gout. When he applied to the hospital with the complaint of weakness 1 month after starting the use of allopurinol for gout prophylaxis, low hemoglobin was detected in the examinations. He was admitted to the nephrology-tx clinic for the etiology of anemia. Iron was 263 mcg/dL, iron binding capacity 285 mcg/dL, ferritin 519 mcg/L, vitamin B12 281 ng/L. Peripheral smear was evaluated; 50 cells were counted: 20 segments, 5 rods, 15 lymphocytes, 5 atypical lymphocytes, 3 monocytes, 2 eosinophils were seen. No blast was seen. The platelet count was consistent with the complete blood count. The erythroid series was normochromic normocytic. No schistocyte or fragmented erythrocytes were observed. B symptoms were not detected in the examination for the exclusion of malignancy. Neck and abdomen ultrasonography were taken and there was no malignancy findings. Anemia was thought to have developed primarily due to the combination of azathioprine and allopurinol. Azathioprine was discontinued and followed up. Hemogram was followed at one-week intervals. It was observed that the hemoglobin value increased to 13.3 g/dL.
Conclusions Gout has been reported in 28% of solid organ transplant recipients. Gout can become a challenging clinical problem in solid organ recipients due to

potential drug interactions. Nausea, vomiting, and reversible bone marrow suppression leading to anemia, leukopenia, and thrombocytopenia are the hallmarks of azathioprine toxicity. Concomitant use of the two drugs is not actually possible due to drug interactions, but it is recommended to reduce azathioprine doses by 66-75% when co-administered with allopurinol. Although reducing the dose of azathioprine when administered together with allopurinol leads to a relative decrease in the risk of myelosuppression, it does not completely eliminate the risk. After stopping azathioprine, his anemia improved. Therefore, these two drugs should preferably not be used together. However, if necessary, it should be followed up with frequent complete blood count.

PP015

Proteinuria Secondary to Renal Vein Thrombosıs associated with Oral Contraception

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Background The common symptoms of renal vein thrombosis are flank pain, hematuria, and acute kidney injury. Nephrotic syndrome, renal cell carcinoma, trauma, renal transplantation, hypovolemia, and hereditary procoagulant defects are reasons for RVT in the foreground, and it is a complication observed in the course of COVID-19 in recent times. Oral contraceptives can be accounted for rare causes. Commonly, RVT can occur due to hyper coagulants formed during nephrotic syndrome. It is mainly seen as bilateral RVT. In our case, we wanted to show that renal vein thrombosis secondary to oral contraceptives may cause subnephrotic proteinuria.
Case Report A 29-year-old female patient, who has followed up with trigeminal neuralgia, applied with complaints of left flank pain and nausea-vomiting for two days. The left costovertebral angle tenderness revealed positive, and pretibial edema revealed +/+ during physical examination. It was learned that she used non-steroidal anti-inflammatory and oral contraceptives during the drug inquiry. In complete urine analysis, protein 2+, erythrocyte 38/HPF, and leucocyte 15/HPF. In the results of biochemistry, creatinine was 0.92 mg/dL, urea 10 mg/dL, albumin 31 g/L, D-dimer 13 mg/L, LDH 351 U/L, triglyceride 334 mg/dL. A thrombus that induces total occlusion inside the left renal vein extends from the left renal vein to the inferior vena cava observed from the contrast-enhanced computerized tomography taken from the acute abdomen. The thrombolytic treatment, thrombectomy, and balloon angioplasty procedures were applied by interventional radiology by considering acute renal vein thrombosis. The flow was coded in both renal veins in control doppler ultrasonography. The ANA, ANA profile, anticardiolipin IgM, IgG, beta-2 glycoprotein IgM, IgG of the thrombosis were reported as negative. The Thrombophilia Panel results in PAI as 4g/5g, MTHFR as heterozygote, f13 as normal, prothrombin gene mutation as negative, factor V Leiden mutation as negative, and it was thought that thrombosis developed secondary to the oral contraceptive used in the foreground from these results. The patient whose proteinuria was 2,562 mg/day in urine before the procedure followed up with anticoagulant therapy after the procedure. The patient was not receiving any other treatment for nephrotic syndrome. Her albuminuria had decreased to 150 mg/day in urine. In her control 5 months after the discharge, her kidney functions were normal ranges.
Conclusions When patients using oral contraceptives apply with flank pain and hematuria, acute renal vein thrombosis should be considered among differential diagnoses. The treatment can change depending on the patient's prognosis and clinic. Patients who do not develop acute kidney injury should generally be followed up with anticoagulant therapy. Thrombolytic treatment and thrombectomy should be considered primarily in patients that are in acute kidney injury table, have transplanted kidneys, and with bilateral RVT or unilateral patients with a high thrombus load.

PP016

Thrombocytopenic Thrombotic Pupura Presenting with Neurological Symptoms: A Case Report

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Background Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy (TMA) caused by severely reduced activity of the von Willebrand factor-cleaving protease ADAMTS13. Complete pentad includes thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fever, neurological findings and renal failure. However, the complete pentad may not be detected in most patients. In this article, we aimed to present a case of TTP presenting with neurological symptoms.
Case Report A 53-year-old male patient was admitted to the emergency service with the complaints of slurring of the tongue, headache and weakness. The patient's temperature was 36.2 °C at the time of admission. Cranial computed tomography (CT) or magnetic resonance imaging (MRI) was found to be normal in the patient whose neurological and systemic examination did not reveal any obvious pathology. Complete blood count (CBC) revealed anemia and thrombocytopenia (leukocyte 6,070/mm^3, neutrophil 4,220/mm^3, hemoglobin 8.9 mg/dL, platelet 20,300/mm^3) and features of hemolysis (lactate dehydrogenase [LDH] 821U/l, total bilirubin 2.9 mg/dL) was detected. In biochemical parameters, creatinine 1.17 mg/dL, urea 35 mg/dL were found to be normal. In the peripheral blood smear; schistocytes were seen in 3-4 high power field and 1 orthochromatophilic cell was seen also. The platelet count and frequency were consistent with the hemogram. Evaluated with these findings, the patient was admitted to the hematology clinic with a preliminary diagnosis of TTP. The blood sample was stored at -80 °C for the ADAMTS13 test at the patient's admission. Therapeutic plasma exchange (TPE) and 1mg/kg methylprednisolone were initiated. With 15 sessions of TPE, the platelet count increased to 154,400/mm^3, and LDH levels decreased to 207 U/L. The complaints of slurring of the tongue and headache disappeared. After the patient received 19 sessions of TPE, the platelet count were 183,500/mm^3 and the LDH levels were within the normal range, so it was decided to open the intervals between the TPE sessions. The diagnosis of TTP was confirmed after ADAMTS13 activity was reported as 6.84% (low), ADAMTS13 antigen 0.096 (low), and ADAMTS13 inhibitor 16.07 (high). TPE was performed two days a week for three weeks. Afterwards, he was discharged with stable vitals and hemodynamics. After discharge, TPE was performed once a week for a total of five weeks. Methylprednisolone treatment was tapered and discontinued. The patient is being followed up.
Conclusions Deficiency of the ADAMTS13 is seen in 90-95% of TTP cases. Microangiopathic hemolytic anemia (MAHA) and thrombocytopenia are hallmarks of TTP. Neurological symptoms are seen in 39-80% of cases, fever in 27-42%, renal failure in 10-75% of cases, while the complete pentad is seen in only 7%. According to A review of 78 patients with acquired TTP from the Oklahoma, published by Evaren E. Page et al. in 2017, 41 (53%) had neurological symptoms, 8 (10%) had fever, 11 (14%) creatinine level ≥2.5 mg. /dL, 4 (5%) had acute kidney injury. In the first presentation of our patient, neurological findings, microangiopathy and thrombocytopenia were present, but there was no fever and elevated creatinine. In conclusion considering that complete pentad is seen in only 7% of patients, possibility of TTP should be suspected in any patient presenting with MAHA findings and thrombocytopenia with or without symptoms of organ involvement and without an alternative explanation.

PP017

Juvenile Idiopathic Arthritis Complicated with Atlantoaxial Subluxation: A Case Report

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Background Juvenile idiopathic arthritis (JIA) is a disease that onsets before the age of 16, manifestations persist for at least six weeks, cannot be explained by any other reason, and can progress with uveitis as well as arthritis involving one or more joints. Bone erosions and joint destruction, osteopenia and osteopoposis, temporomandibular joint anomalies, mobility problems

due to contractures, and ocular complications such as anterior uveitis can be seen in the course of JIA. We aimed to present our case who was diagnosed in pediatric rheumatology and followed up in adult rheumatology, which was complicated by atlantoaxial subluxation.

Case Report A 25-year-old male patient, who had been followed up with the diagnosis of JIA for 14 years, described a complaint of dizziness during the control of the adult rheumatology outpatient clinic. The foreign national patient, who was diagnosed with JIA and given steroid, methotrexate and nonsteroidal anti-inflammatory drug treatment after being examined in his home country with a complaint of swelling in the knee and foot joints when he was 11 years old, was transferred to us by pediatric rheumatology at the age of 19. In the examinations performed in pediatric rheumatology, HLA B27 (+) and FMF gene test M694V and E148Q were found as (+). The patient, whose treatment was planned as an anti-TNF agent, had a history of irregular drug use due to social reasons. The patient had significant mobility restriction. Findings of arthrosis were observed in both knees and hip joints. The patient, who was evaluated in the rheumatology council after the transfer to us, was referred to orthopedics because of arthrosis in both hip joints. Anti-TNF was planned to be started and he was followed up. In the systemic and neurological examination of the patient who had been using etanercept for 5 years, no features were found except that he had 2/5 paraparasia (joint movements were completely limited due to bilateral frozen hip). Cranial MRI was performed on the patient and the MRI shows a ''4.9 mm displacement of C2 vertebra odontoid process towards the cranial, in sections passing through the level of the skull base (basilar invagination). Both cavernous segments are mildly dolichoectatic.'' The patient was consulted to the neurosurgery department with the preliminary diagnosis of atlantoaxial subluxation. Surgical intervention was not considered for the patient who had no neurological symptoms, and control was recommended 6 months later. The patient is being followed up in our outpatient clinic with anti-TNF therapy, and periodic neurosurgery control was recommended for atlantoaxial subluxation.

Conclusions Cervical joint destruction in patients with rheumatoid arthritis and JIA may lead to vertebral malalignment (e.g., subluxation), causing pain, neurologic deficit, and deformity. It should not be forgotten that atlantoaxial subluxation findings can be detected by imaging patients without symptoms. The young age of the patients is essential in terms of being careful before the surgical procedures that may take place. Although routine imaging is not required in asymptomatic patients, cervical spine imaging is recommended before elective surgery that will require neck manipulation.

PP018

A Case Report of Subacute Thyroiditis After MRNA COVID-19 Vaccine

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Background COVID-19 causes a variety of clinical scenarios, from a flu-like syndrome to more serious conditions such as acute respiratory distress syndrome and death. As a result of recent research, it is known that many complications related to the endocrine system develop in patients with COVID-19. COVID-19 infection causes thyroid dysfunction through destruction of the thyroid gland and immune-mediated mechanisms. Discovery of an effective vaccine against COVID-19 is an important step in the fight against the epidemic. Although the relationship between upper respiratory tract viruses and subacute thyroiditis is well known, rare cases have been reported with inactivated vaccines or live attenuated vaccines such as influenza. There are very limited data on subacute thyroiditis following COVID-19 vaccine. To date, only a few cases of subacute thyroiditis have been reported in the literature after mRNA COVID-19 vaccination. Here, we present a case diagnosed with subacute thyroiditis following COVID-19 mRNA vaccine (Pfizer/BioNTech®) administration.

Case Report A 44-year-old Caucasian female patient was admitted to our Endocrinology Clinic with complaints of anterior neck pain, headache, palpitation, sweating and tremor for about 2 months. She did not use any medication regularly, but her pain was relieved when she used non-steroidal anti-inflammatory drugs during periods of increased pain. She had received two doses of COVID-19 mRNA vaccine (Pfizer/BioNTech®) on July 22, 2021 and August 20, 2021. She stated that her symptoms started after the first dose of vaccine and gradually increased after the second dose of vaccine. She did not have a recent upper respiratory infection or COVID-19 infection. On her physical examination, her heart rate was 88/min; body temperature was 38.5°C; blood pressure was 110/70 mmHg; respiratory rate was 14/min. Thyroid gland was sensitive, painful, and enlarged. Laboratory examination revealed elevated fT4 and fT3 levels, as well as suppressed TSH. Anti-TPO: 362 IU/mL (Reference range: 0-75 IU/mL) was detected. Erythrocyte sedimentation rate (ESR), elevated C- reactive protein (CRP) levels were high. Diffuse heterogeneity and hypoechoic

areas were observed in thyroid USG. Thyroid blood flow was decreased in doppler oltrasonography. The Tc99 pertechnetate radionuclide thyroid scan showed poor thyroid uptake The patient was considered for subacute thyroiditis associated with the COVID-19 mRNA vaccine (Pfizer/BioNTech®). Ibuprofen 600 mg/8 h treatment was started. Within the next weeks, the symptoms resolved completely. At the first month control, TSH, fT3 and fT4 were in the normal range and acute-phase reactants were normal. Thus, ibuprofen treatment was terminated. The patient was called for outpatient follow-up 1 month later in terms of the risk of developing hypothyroidism after subacute thyroiditis.

Conclusions Vaccination rates against COVID-19 infection are increasing rapidly all over the world. Considering the vaccine recommendations against COVID-19 infection, we think that we will see more cases as a result of increased immunological reactions. Therefore, clinicians should be aware of the possible side effects of the vaccine.

PP019

Development of AA Amyloidosis in a Patient with Psoriasis: A Case Report

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Background Psoriasis is a chronic, recurrent, inflammatory and common skin disease of unknown etiology. Amyloidosis is defined as a heterogeneous group of diseases in which normally soluble plasma proteins accumulate in the extracellular space in an insoluble abnormal fibrillar form. Diagnosis is made by demonstrating the accumulation of these proteins in the tissue sample. AA type amyloidosis is a late and serious complication of chronic inflammatory diseases and some chronic infections. Although psoriasis is a common inflammatory skin disease, the development of amyloidosis is rare. Here, we presented a case of AA type amyloidosis accompanying the diagnosis of psoriasis.

Case Report A 64-year-old female patient has been diagnosed with plaque psoriasis on the scalp and joint extensor surfaces for two years. She applied to an external center with complaints of weakness and dry mouth. She was referred to our emergency service because of high creatinine in laboratory tests. In the laboratory tests of the patient evaluated in the emergency department hemoglobin 8.9 g/dL, creatinine 6.4 mg/dL, urea 195 mg/dL, potassium 7.2 mmol/L and metabolic acidosis was detected, the patient was taken to hemodialysis (HD) for 2 hours. Afterwards, she was admitted to the nephrology clinic for further examination and research with the diagnosis of acute renal failure. Complete urinalysis revealed protein (+) and hematuria. When serum albumin was 2.6 g/L and proteinuria was found 3,300 mg in 24-hour urine analysis, renal biopsy was performed for etiology: the pathology result was compatible with AA type amyloidosis. Our patient was born in Azerbaijan and it was learned from her history that she did not have abdominal pain and fever attacks in her childhood, and there was no family history of FMF. Therefore, FMF was not considered. Antinuclear antibody (ANA), anti-dsDNA, anti-Sm, anti-Ro, anti-La, rheumatoid factor (RF), anti-CCP, and HLA B27 were requested for the aetiology of AA amyloidosis and the results were negative and serum immunoglobulin levels, serum complement levels were within the normal range. Both sacroiliac joints were found to be of normal width in the sacroiliac joint radiography. Eye examination was performed and uveitis was not detected. The patient received 4 sessions of HD in total, and then she did not need HD anymore. Colchicine 0.5 mg 2x1 was started and she was discharged.

Conclusions A case of psoriasis-associated amyloidosis was first reported in 1965. Few cases with coexistence of psoriasis and amyloidosis have been reported to date. Therefore, we tried to exclude other diagnoses accompanying amyloidosis in our patient, who did not have any other known comorbidities apart from the diagnosis of psoriasis. Amyloid deposition accompanying psoriasis is a rare complication and is detected later than other diseases accompanied by amyloidosis. However, in our case, it was observed that this situation was not always late, and amyloid deposition could be observed earlier.

PP020

Post-COVID ANCA-Associated Vasculitis: A Case Report

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Background COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-coV-2). Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are life-threatening autoimmune diseases frequently accompanied by necrotizing rapidly progressive crescentic glomerulonephritis, which include findings of glomerulonephritis in mononuclear cell infiltration of small and medium-sized vessels and kidney biopsy. In cases with a history of COVID-19 disease, various complications and symptoms spread over a long period have been identified. We presented a case of ANCA-associated vasculitis after COVID-19.
Case Report A 51-year-old male patient has a diagnosis of chronic obstructive pulmonary disease and diabetes mellitus, and is being followed up in the chest diseases clinic with the diagnosis of post-COVID-19 pneumonia with the complaint of shortness of breath about one month after the COVID-19 treatment is completed. In the physical examination of the patient, there was ral in the bilateral bases upon listening to the lung, there was no feature in the cardiovascular system and abdominal examination, pretibial edema was negative. When he was consulted to the nephrology department due to high creatinine and urea levels during his hospitalization, he was taken to hemodialysis (HD) intermittently, considering acute kidney injury (AKI). In the follow-ups, hematuria was observed in the complete urinalysis and 2 g proteinuria was accompanied in the 24-hour urine analysis. PR3, ANA, ANA profile and anti-GBM were negative. C-ANCA, P-ANCA and MPO were positive at 1/10 E.P. C3 and C4 complements were normal, immunoglobin G, A, and M were within normal ranges. The hepatitis markers were negative. Thoracic computed tomography (CT) taken after anti biotherapy was completed: Bilateral pulmonary infiltration and nodular cavitary lesions were evaluated as ANCA-associated vasculitis and 500 mg cyclophosphamide treatment was given and methylprednisolone was continued as a sustained dose of 0.5 mg/kg. The patient was taken into the 2 HD program per week and discharged.
Conclusions The relationship between COVID-19 disease and acute kidney injury is well known, but the number of cases in which COVID-19 and ANCA-associated vasculitis coexistence are rare in the literature. It is possible to make a differential diagnosis with detailed anamnesis, physical examination, imaging findings, laboratory parameters, and especially in selected cases, kidney biopsy. In this case, we wanted to emphasize that AAV should be kept in mind in the etiology of AKI developed after COVID-19 and appropriate treatment should be started without wasting time.

PP021

Drug Eruptions with Cases: Fixed Drug Eruption and DRESS Syndrome

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Background Adverse drug reactions are undesirable side effects of routinely used or newly started drugs, and the skin is the organ where these side effects are most commonly seen. Cutaneous drug reactions (CDR) are common and usually occur with mild and self-limiting lesions, and some of its severe forms can be life-threatening. The drug groups to often cause drug reaction for the skin are non-steroidal anti inflammatory drugs (NSAIDs), antibiotics and anticonvulsants. In our study two immunological drug reaction cases are presented. One with a mild and localized fixed drug eruption, and the other one with a more severe and generalized DRESS syndrome.
Case Report The first case was a 56-year-old female patient with a diagnosis of ankylosing spondylitis. She stated that she was using diclofenac sodium. The patient applied to the dermatology outpatient clinic with a sharply defined, hyperpigmented macular-looking lesion on the dorsal aspect of the left hand. She stated that for the last year, similar lesions appeared in the same area from time to time, and it was a more vivid purple color when it first appeared and the color became brownish over time, also it was accompanied by complaints such as itching and burning. For the patient, fixed drug eruption was considered due to diclofenac sodium drug use history and lesion characteristics. The second case, a 35-year-old female

patient, started treatment of carbamazepine 400 mg/day with the diagnosis of epilepsy 1 month ago. The patient applied to the hospital with the complaint of widespread erythematous maculopapullar rash on the body and itching, which started 3 days ago and is becoming increasingly severe. Bilateral cervical lymphadenopathy was detected in lymph node examination. According to the laboratory evaluation; in liver function tests more than 10 times increase was observed. The patient was evaluated as DRESS syndrome with clinical and laboratory findings.

Conclusions As a result, physicians of all branches should be familiar with cutaneous drug reactions that they may encounter frequently in their daily practice for early diagnosis and treatment. When cutaneous drug reactions are suspected, it is necessary to approach the patient holistically and systematically.

PP022

Methotrexate Toxicity in a Hemodialysis Patient: A Case Report

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Background Methotrexate (MTX) is widely used in the treatment of various malignancies and chronic inflammatory diseases. It is an antimetabolite agent that impairs DNA synthesis by competitively inhibiting the dihydrofolate reductase enzyme. Side effects such as nausea, stomatitis, myelosuppression, hepatic, renal and pulmonary toxicity may occur due to high doses of MTX, decreased elimination and polypharmacy. Since the primary excretion site (90%) is the kidneys, toxicity may develop by accumulation in cases with impaired renal function. Here, we presented a case who is in the hemodialysis (HD) program and developed pancytopenia and mucositis as a result of using low-dose MTX for the treatment of psoriasis.

Case Report A 30-year-old female patient presented to the emergency department with complaints of abdominal pain and bloody diarrhea. She has chronic renal failure, psoriasis and hypertension diagnoses secondary to membranoproliferative glomerulonephritis, and she is also included in routine HD. The drugs she was using were ramipril, amlodipine, carvedilol, doxazosin and moxonidine. In the patient who was started MTX 7.5 mg/week subcutaneously by dermatology for the treatment of psoriasis two weeks ago, diarrhea started four days after the first dose. After the second MTX administration, diarrhea increased and severe diffuse abdominal pain developed two days later. On physical examination: Plaques in the oral mucosa, there were crusty ulcerations on the lips, widespread erythematous plaques in the body, widespread tenderness in the abdomen, voluntary defense and rebound, other system examinations were normal. Abdominal CT Angiography performed to exclude surgical emergencies showed diffuse edematous wall thickening, increased mucosal staining, and prominent valarectasis in colonic loops, ascending colon, and cecum. In the laboratory examination, leukocyte was 1,910/mm³, neutrophil 1,360/mm³, hemoglobin 8.7 g/dL, platelet 76,000/mm³, CRP 207 mg/L, vitamin B12 level 125 ng/L. Blood MTX level was 0.03 mcmol/L. Blood CMV-DNA PCR was negative. No parasite was detected in the stool. Bone marrow biopsy was performed when one atypical cell was seen in the peripheral smear. In the bone marrow imprint material, an increase and pause in early myeloid elements were observed. Although the serum MTX level was low due to the serum half-life of MTX of 6-8 hours, MTX toxicity was considered due to the recent MTX treatment, pancytopenia and mucositis, and hospitalization was made. Total parenteral nutrition was started due to folinic acid 3x50 mg, granulocyte colony stimulating factor 5 mcg/kg/day, vitamin B12 replacement and oral inability due to mucositis. Upon the deepening of pancytopenia, erythrocyte and thrombocyte suspensions were replaced. He recovered from neutropenia on the 8th day of his hospitalization. The patient's routine HD program was continued. Ciprofloxacin and metronidazole treatment was completed in 10 days. After 15 days of hospitalization, the patient's clinical improvement was discharged.

Conclusions Tight binding to plasma proteins and accumulation of metabolites in the cell is one of the reasons why MTX is not sufficiently removed by dialysis. While MTX treatment is not recommended in HD patients under normal conditions, it can be applied by reducing the dose, especially in malignant diseases that do not have an alternative treatment. In this case, MTX was started for the treatment of psoriasis because there was no response to secukinumab; It has been emphasized that toxicity may develop even with the use of low-dose MTX in HD patients.

PP023

Primary Mediastinal Large B-Cell Lymphoma: A Case Report

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Background Primary mediastinal large B-cell lymphoma (PMLBCL) is a rare tumour in the world. Non-Hodgkin lymphomas (NHL) 2%-3% diffuse large B-cell lymphomas (DLBCL) 6%-10% constitutes. We reported a 19-year-old male patient diagnosed with primary mediastinal large B-cell lymphoma.
Case Report 19-year-old male patient with no known disease, night sweats that started for about 1 month, weight loss (25 kilograms in 1 month), cough, and a palpable mass in the neck on thorax tomography performed with packed lymph filling the anterior mediastinum and reaching both cervical subzones. When nodules (bulky mass) were detected, a tru-cut biopsy was performed by the thoracic surgeon, and the patient was referred to us when PMLBCL was received as a result of the material sent to pathology. PET-CT was taken for staging and bone marrow biopsy was performed on the patient. The patient, who was accepted as stage 2B, was started on rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) treatment. Inadequate response after four cycles of R-CHOP was considered as refractory disease and the patient was given 2 cycles of R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) as salvage therapy. During these treatments, a tracheal stent was inserted by the thoracic surgeon due to tracheal compression. When the cervical lymph nodes progressed 72 hours after the end of the treatment, the patient was consulted to the radiation oncology department and four sessions of radiotherapy were given. The patient was started on a targeted PD-1 blocker, nivolumumab, together with brentuximab, an anti-CD30 monoclonal antibody, for at least four cycles, once every three weeks. Three courses of treatment were given. It was learned that the patient died due to sudden respiratory arrest while he was at home in the seventh month of his illness.
Conclusions The disease is a rare, aggressive lymphoma with good prognostic features, which is usually seen at a young age and present with the presence of mass disease. R-CHOP treatment is the most commonly used chemotherapy protocol and it has been reported that radiotherapy has a positive effect on the prognosis in selected cases. In resistant patients, autologous stem cell transplantation can be progressed after the chemotherapy.

PP024

Pityriasis Rosea After Pfizer-BioNTech Covid-19 Vaccine: A Case Report

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Background Vaccines against SARS-CoV-2 are being developed and implemented at a rapid pace. With COVID-19 vaccine applications; some skin side effects can be seen. Examples of these are local skin reactions at the injection site, urticaria, maculopapular rash, and pityriasis rosea-like reactions. Pityriasis rosea-like eruptions (PR-LE) may be seen after vaccination or as a drug reaction. Although pityriasis rosea can rarely be seen due to chickenpox, tuberculosis, influenza, HPV, poliomyelitis, diphtheria, pneumococcus, tetanus, hepatitis B vaccines, there are also cases of pityriasis rosea after COVID-19 vaccine. In this study, a case of pityriasis rosea developing after Pfizer-BioNTech COVID-19 vaccine was presented.
Case Report The case was a 31-year-old woman with no known comorbidity and regular medications. The patient, 5 days after the administration of the 3rd dose of Pfizer-BioNTech mRNA COVID-19 vaccine, described the lesions on her back as 2x3 cm in diameter, oval, sharply limited, pale erythematous, in the form of a herald patch with pitriasic scales observed in the periphery. The patient was evaluated to have pityriasis rosea due to the medallion plaque presence, rash and the distribution character of the rash, and the absence of symptoms other than itching, therefore the patient was given topical steroid therapy.
Conclusions Today, like with many vaccines, there are also cases of pityriasis rosea developing after COVID-19 vaccines. Further studies on tissue and serological examination are needed to establish a causal link between PR/PR-LE and COVID-19 vaccines.