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Original Article

General Characteristics of Palliative Care Patients Admitted to the Emergency Department

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ABSTRACT

Background This study aimed to analyze patients who apply to emergency services and need palliative care regarding appropriate patient care and effective use of health institutions.

Materials and Methods The study was conducted prospectively on patients who applied to the emergency services of Bursa Uludag University Health Application and Research Center, Health Sciences University Bursa Yüksek Ihtisas Training and Research Hospital and Bursa City Hospital between 15.08.2021 and 15.02.2022 and needed palliative care.

Results A total of 261 patients, 143 male (54.8%) and 118 female (45.2%), were included in the study. It was determined that 50 (19.1%) of these patients had previously received palliative care services. It was determined that the patients included in the study applied to the emergency services 7.52±6.77 times in the last year. The three most common diseases diagnosed in patients admitted to the emergency department were pneumonia (24.5%), urinary system infection (7.7%), and cerebrovascular disease (5.4%). Of the patients, 39.84% were referred/hospitalized, 25.28% were referred/hospitalized to intensive care units, 2.68% refused treatment, 2.68% died, and 29.5% have been discharged.

Conclusion As a result, it is understood that most of the patients in need of palliative care do not receive this service, and patients who can be treated in palliative care units are treated in clinics and intensive care units.

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Introduction

Palliative care (PC) is the care services that aim to make people with a progressive and life-threatening disease have a good end of life and to eliminate the problems they may encounter during this process.[1] Due to the gradual increase in the elderly population, cancer and other non-communicable diseases, the need for PC is increasing rapidly across the world.[2,3] Despite this need, PC has still not developed at the desired level in many parts of the world (except for North America, Europe and Australia).[3] In a study, it was reported that one-third of people with life-threatening diseases worldwide could not receive PC.[4]

It has been reported that the most common accompanying diseases in patients who need PC are motor neuron diseases and progressive neurological diseases (Alzheimer's, amyotrophic lateral sclerosis), advanced organ failures (heart, lung, kidney, liver), cancers that do not respond to treatment, acquired immunodeficiency syndrome (acquired immune deficiency syndrome, AIDS), and genetic/congenital and progressive diseases in children.[5] PC, which is usually provided in oncology units, has expanded to the extent that it can be served in other clinics and even in the emergency department (ED) with the increasing need.[6] However, EDs are not suitable for long-term treatment of terminal period patients due to their busy, crowded and tiring environments.[7] The aim of this study was to examine patients who apply to emergency services and need palliative care, and to analyze them in terms of both appropriate patient care and effective use of health institutions.

Material and Methods

Before starting the study, Bursa Uludag University Faculty of Medicine Clinical Research Ethics Committee was applied and an ethics committee report was obtained with the decision dated 28.07.2021 and numbered 2021-10/37. The research was performed prospectively on patients who admitted to Bursa Uludag University Health Application and Research Center, Health Sciences University Bursa High Specialization Training and Research Hospital and Bursa City Hospital EDs between 15.08.2021 and 15.02.2022 and needed PC.

Patients over the age of 18 who applied to the emergency medicine clinics of the health centers on the specified date and who met the criteria for hospitalization in the PC unit according to the Workshop Report for Palliative Care at Home and Hospital[8] prepared in 2013 were included in the scope of the study. The study included 261 patients (143 males, 118 females) who admitted to the emergency departments of the health centers on the specified date.

The patients included in the study or their relatives were informed and their consent was obtained. The data obtained were recorded in the patient file by the physician who evaluated the patient. The patient's file was including name, surname, date of application to the emergency room, hospital protocol number, age, gender, reason for applying to the emergency department, chronic diseases (diabetes mellitus, hypertension, malignancy, Alzheimer's, heart failure, etc.), whether or not he/she received PC before, who cares for the patient, the count of emergency department admissions in the last year, whether consultation was requested, patient outcome, duration of stay in the ED, and diagnosis. No interventional procedure, examination or medication was applied to the patient other than routine health care.

Information about whether the patients received PC service before and by whom the care was taken was obtained from the patient or his relatives. Patients who received home care even once, were hospitalized in the palliative care service or received hospice care were considered to have received PC. The E-Nabız system of the patients was used to calculate the ED applications of the patients in the last year. The E-Nabız is an personal health record system that Turkish Ministry of Health integrated all the information systems of all health institutions.

Statistical analysis

Statistical evaluation, descriptive statistics for continuous variables among the features discussed; mean, standard deviation, minimum and maximum values were expressed as numbers and percentages for categorical variables. One-way analysis of variance was performed to compare

group means in terms of continuous variables. Chi-square test was used to determine the relationship between categorical variables. The statistical significance level was taken as 5% in the calculations, and the SPSS (ver: 21) statistical package program was used for the calculations.

Results

The mean age of the 261 PC patients included in the study was calculated as 72.3±14.05 years. The mean duration of stay in the ED of patients was found to be 9.97±7.13 hours (*Table 1*). When the duration of stay in the ED of men and women was compared, the relationship was found to be statistically insignificant (p=0.710). When the mean age of men and women admitted to ED was compared, it was found that the mean age was higher in female patients than in male patients, but this difference was not statistically significant (p=0.339). The mean number of ED admissions made by the patients in the last year was calculated as 7.52±6.77 (*Table 1*). It was determined that men admitted to ED more than women, but the difference was found to be statistically insignificant (p=0.175).

As seen in Table 1, the average number of consultations requested from other departments for the patients was calculated as 1.75±1.17. It was determined that there was no statistically significant difference between men and women in terms of the number of departments for which consultation was requested (p=0.529). For patients admitted to the ED and in need of PC, the departments most requested consultation was detected as chest diseases (n: 97), internal medicine (n: 91), infectious diseases (n: 66), anesthesiology/reanimation (n: 53), and cardiology (n: 42), respectively.

The most common complaints of the patients admitted to ED were dyspnea (26.1%), poor general condition (17.6%), altered consciousness (8%), nausea/vomiting (4.9%) and fever (3.8%) respectively. The comorbidities of the patients are given in Table 2. According to Table 2, the five most common diseases in the patients were hypertension, malignancies, Alzheimer's/dementia, diabetes mellitus, and coronary artery

Table 1. Evaluation of the gender of the patients according to the duration of their stay in the emergency department, their age, the emergency department applications they have made in the last year and the number of consulted departments.

Variables		Count (n)	Mean±SD (Min-Max)	P-value
Age (years)	Male	143	71.54±12.692 (21-94)	0.339
	Female	118	73.21±15.549 (18-99)	
	Total	261	72.3±14.052 (18-99)	
Duration of stay in the emergency department (hours)	Male	143	10.12±6.914 (1-33)	0.71
	Female	118	9.79±7.426 (2-44)	
	Total	261	9.97±7.138 (1-44)	
Number of emergency department admissions in the last year	Male	143	8.04±7.25 (1-49)	0.175
	Female	118	6.9±6.13 (1-46)	
	Total	261	7.52±6.778 (1-49)	
Number of departments consulted	Male	143	1.71±1.167 (0-5)	0.529
	Female	118	1.81±1.179 (0-5)	
	Total	261	1.75±1.171 (0-5)	

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

Table 2. Comorbidities of patients and incidences of these diseases.

Comorbidity	n (%)
Hypertension	120 (46)
Malignancy	112 (42.9)
Alzheimer's disease/dementia	79 (30.3)
Diabetes mellitus	71 (27.2)
Coronary artery disease	58 (22.2)
Cerebrovascular disease	49 (18.8)
Asthma/COPD	37 (14.2)
Heart failure	20 (7.7)
Chronic renal insufficiency	19 (7.3)
Atrial fibrillation	13 (4.9)
Epilepsy	11 (4.2)
Parkinson's disease	11 (4.2)
Hyperlipidemia	7 (2.6)
Hypothyroidism	6 (2.2)
Rheumatoid arthritis	4 (1.5)
Hepatic cirrhosis	3 (1.1)

Table 3. Diseases of patients diagnosed in the emergency departments.

Diseases	n (%)
Pneumonia	64 (24.5)
Urinary system infection	20 (7.7)
Cerebrovascular disease	14 (5.4)
Heart failure	11 (4.2)
Pleural effusion	11 (4.2)
Pulmonary embolism	9 (3.4)
Acute kidney failure	8 (3.1)
Gastrointestinal tract bleeding	8 (3.1)
Hypernatremia	7 (2.7)
Intracranial mass-metastasis	7 (2.6)
Cardiac arrest	6 (2.3)
Cellulite	5 (1.9)
Hypercarbic respiratory failure	4 (1.5)
Other diagnoses	87 (33.9)

disease (CAD). The most common cancer types of the patients admitted to ED were lung (25.8%), gastrointestinal system (25%), urinary system (11.6%), hematological (8.6%) and neurosurgical (8%) respectively.

In the study, it was found that patient care was mostly (85.8%) provided by the patient's family. It was determined that the care of the patients was less frequently provided by the nursing home (6.5%), home caregiver (4.2%) and herself/himself (3.1%). It was determined that the patients who received PC service at the highest rate were those who stayed in the nursing home (*Figure 1*). It was examined whether the patients had received PC before, and 23 of 143 male patients (16.08%) and 27 of 118 female patients (22.88%) were found to have received PC. In total, 50 of 261 patients were found to have received PC (19.1%).

The ED processes of the patients are given in Figure 2. As seen in Figure 2, it was determined that 39.46% of the patients were hospitalized, 0.4% were referred to another hospital for clinical hospitalization because there was no room, 14.94% were hospitalized in the ICU, 10.34% were referred to another ICU, 2.68% refused treatment, 2.68% died, and 29.5% were discharged. The diagnoses of the patients admitted to EDs after their admission were analyzed. The most common diagnoses were pneumonia, urinary system infection, cerebrovascular disease, heart failure, and pleural effusion, respectively (*Table 3*).

The patients' length of stay in the ED, their age, the number of ED applications they made in the last year and the number of departments for which consultation was requested were compared according to whether they received PC service before admission and the results are given in Table 4. Accordingly, the time spent in ED was found to be longer in patients who received PC than in patients who did not receive PC, but the difference was not statistically significant (p=0.257). It was determined that the number of consulted departments was higher in patients receiving PC, but the difference was found to be statistically insignificant (p=0.330). The number of admissions to EDs in the last year (p=0.977) and age (p=0.686) of the patients were compared according to whether they received PC or not, and the differences were found to be statistically insignificant.

Table 4. Comparison of the patients' length of stay in the emergency department, their ages, the count of emergency service admissions they have made in the last year and the number of consulted departments according to whether they have received palliative care or not.

	Palliative care receiving or not	Count	Mean±SD (Min-Max)	P-value
Time spent in the emergency departments (hours)	Received	50	11.00±8.751 (1-44)	0.257
	Didn't receive	211	9.73±6.701 (1-30)	
	Total	261	9.97±7.138 (1-44)	
Age (years)	Received	50	73.02±16.517 (18-99)	0.686
	Didn't receive	211	72.12±13.441 (18-96)	
	Total	261	72.30±14.052 (18-99)	
Count of emergency departments visit in the last year	Received	50	7.50±5.530 (1-25)	0.977
	Didn't receive	211	7.53±7.053 (1-49)	
	Total	261	7.52±6.778 (1-49)	
Count of department consulted	Received	50	1.90±1.359 (0-5)	0.330
	Didn't receive	211	1.72±1.122 (0-5)	
	Total	261	1.75±1.171 (0-5)	

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

Discussion

As in other countries, it is observed that the elderly population is increasing due to the increase in the lifetime of people in Türkiye. Due to this increase, the need for PC centers is increasing due to the increase in life-threatening advanced chronic diseases in patients.[9,10] It is seen that the number of PC centers in Türkiye is lower than in some developed countries and the clinical experience of healthcare professionals in this field is limited.[11] The low number of PC centers increases the number of admissions to EDs and decreases the quality of health services due to the patient density in emergency services.[12]

In some studies, it was reported that the mean age of PC patients ranged from 62 to 73.[9,13-17] In our study, it was found that the mean age of the patients was 72.3. In some studies performed on PC, it was observed that the majority of the patients were women admitted to EDs.[13-16] In some other studies, it was found that male patients had a higher rate than females.[9,17,18] In our study, it was determined that 54.8% of the patients were male and 45.2% were female.

In a study conducted by Kirkland et al.[19], it was stated that 21.87% of the patients who applied to the emergency department received PC service before, and 78.12% did not. In this study conducted by us, it was determined that 19.15% of the patients had previously received PC service. In the study conducted by Green et al.[16], it was observed that 105 palliative care patients admitted to EDs a total of 112 times in a 10-week period. In a study by Lawson et al.[20], 1182 patients who received palliative care were reported to have admitted to EDs 2103 times over seven years. In this study conducted by us, it was determined that 261 patients applied to EDs a total of 1964 times in the last year, and the annual average number of admittions for each patient was calculated as 7.52±6.77.

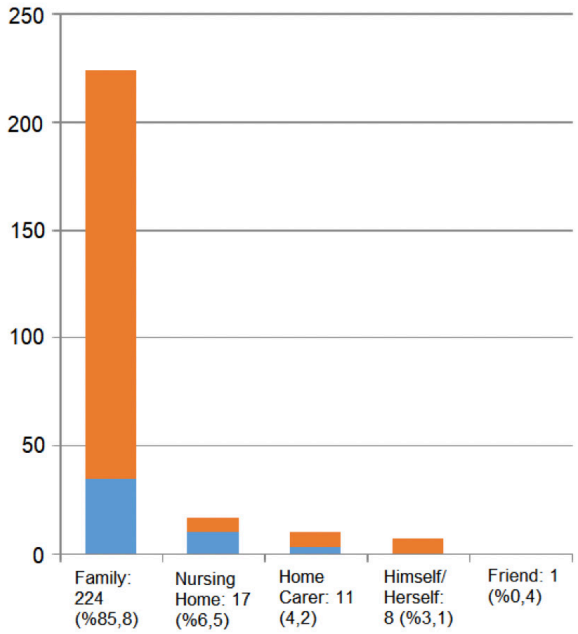

Figure 1. Patient care providers.

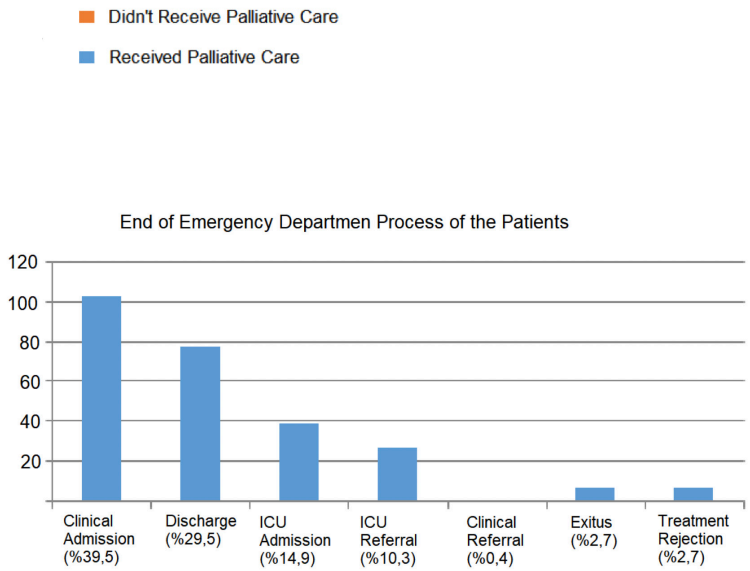

Figure 2. Emergency department processes of patients.

In a study conducted by Verhoef et al.[18], the most common presenting complaints of PC patients were dyspnea and pain. Similarly, in the study of Green et al.[16], dyspnea and pain were reported to be the most common complaints. In the study conducted by Algan et al.[17], the most common reasons for admission were shortness of breath, abdominal pain, general condition disorder, vomiting, gastrointestinal system bleeding, fatigue and falling were reported. In our study, the most common complaints were dyspnea, poor general condition, altered consciousness, nausea/vomiting and fever has been found.

In the study conducted by Kirkland et al.[19], malignancy was found in 41%, COPD 16.1%, heart failure 9.4%, chronic kidney failure 8.9% and cirrhosis 7.4% as an additional disease in palliative care patients. In the study conducted by Miniksar et al.[9], malignancy was found 43.3%, Alzheimer's 18.06%, cerebrovascular disease 12.77%, hypertension 12.77%, COPD 6.85%, coronary artery disease 5.6% and diabetes mellitus 4.67% in palliative care patients. In the study conducted by Algan et al.[17], in palliative care patients, 58.86% had cancer, 41.33% for hypertension, 29.72% for diabetes mellitus, 19.29% for coronary artery disease, 18.11% for congestive heart failure, 16.54% for cerebrovascular disease, 14.37% for dementia/neurodegenerative disease, 10.83% for COPD, 9.06% for atrial fibrillation, 7.68% for chronic renal failure, 4.92% for asthma and 3.35% for terminal liver disease were reported. In our study, the most common co-morbidities were hypertension (46%), malignancy (42.9%), Alzheimer's/dementia (30.3%), diabetes mellitus (27.2%) and coronary artery disease (22.2%), respectively. In the study conducted by Miniksar et al.[9], the most common cancer types in palliative care patients have been detected in lung, stomach, prostate, pancreas, colon and breast respectively. In the study conducted by Algan et al.[17], the most common cancer types in palliative care patients were gastrointestinal system, lung, urinary system, hematological tissues, endocrine system, neurosurgical, gynecological, head/neck, and bone/muscle/skeletal have been reported respectively. In our study, it was determined that the most common cancer types were lung, gastrointestinal system, urinary system, hematological and neurosurgical respectively.

In some studies performed on palliative care patients, it has been reported that the duration of stay in emergency services varies between 3.5-16 hours.[18,20-22] In our study, it was determined that the mean duration of stay in EDs was 9.97 hours.

In the study conducted by Algan et al.[17], the

most frequently diagnosed diseases in PC patients admitted to the emergency department were respectively COVID-19 (15.94%), urinary system infection (6.89%), pneumonia (6.5%), acute renal failure (6.3%), fracture/soft tissue trauma (6.1%), and gastrointestinal system bleeding (5.71%). In our study, the most frequent diagnoses in patients were pneumonia (24.5%), urinary system infection (7.7%), cerebrovascular disease (5.4%), heart failure (4.2%), pleural effusion (4.2%), pulmonary embolism (3.4%), acute renal failure (3.1%) and gastrointestinal bleeding (3.1%).

In the study performed by Kirkland et al.[19], it was reported that 65.2% of PC patients admitted to emergency services were hospitalized, 31.9% were discharged, and 2.5% were referred. In the study conducted by Algan et al.[17], it was reported that 49.61% of palliative care patients were discharged, 26.57% were hospitalized, 14.96% were admitted to the intensive care unit, 6.69% gave up treatment voluntarily, and 2.17% died. In this study conducted by us, it was determined that 39.84% of the palliative care patients were clinically admitted/referred, 25.28% were admitted/referred to the intensive care units, 2.68% refused treatment, 2.68% died, and 29.5% were discharged.

In a study conducted by Yang et al.[22], it was determined that 79.1% of PC patients live with their families, 8.4% live alone, 8.2% live in long-term care facilities and 2.6% live in nursing homes. In the study conducted by Green et al.[16], it was stated that 56.3% of the patients live with their families, 25% live alone, 9.8% live in nursing homes, and it is not known where 8.9% live. In our study, it was determined that 85.8% of the patients were cared for by their families, 6.5% by nursing homes, 4.2% by the caregiver at home and 3.1% by themselves.

Limitations

Although it is a multicenter and prospective study, the fact that the study was conducted only in Bursa and the low number of cases are the factors limiting our study.

Conclusions

As a result, it has been determined that most of the patients in need of PC do not receive this service and they frequently admitted EDs. In addition, it is understood that patients who need to be treated in PC units are treated in clinics and ICUs. These results suggest that the effective use of PC centers will contribute to more appropriate healthcare for patients, decrease in ED admissions and more economical use of healthcare institutions.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical Approval

Local Ethics Committee approved the study protocol.

Authors' Contribution

Study Conception: YAM; Study Design: CHI; Supervision: DYA; Literature Review: HOK; Critical Review: AE, CH; Data Collection and/or Processing: KB, AS, AS, SYY; Analysis and/or Data Interpretation: DVA, YAM; Manuscript preparing: YAM, CHI.

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Original Article

The Efficacy of The Direct-Acting Antiviral Combination in Hemodialysis Patients with Chronic Hepatitis C Virus Genotype 1 Infection

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ABSTRACT

Background Interferon and ribavirin treatments previously used in treating chronic hepatitis C virus (HCV) infection cannot be used effectively in hemodialysis patients due to dose adjustment and drug-related side effects. Direct-acting antivirals (DAAs) therapies have been reported to be effective in hemodialysis patients. This study aimed to evaluate the effectiveness of DAAs in hemodialysis patients with chronic hepatitis C.

Material and Methods Twenty hemodialysis patients with chronic hepatitis C followed in the gastroenterology outpatient clinic between 2016 and 2018 were evaluated retrospectively.

Results Twelve of the 20 patients were male, and eight were female. The mean age of the patients was 50.7±8.6 years. Six patients had no treatment experience. Fourteen patients had been previously treated with interferon and/or ribavirin but did not achieve sustained virological response (SVR). Genotype 1b was detected in 14 patients, genotype 1a in 4 patients, and genotype 1 in 2 patients. Patients were treated with ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) and dasabuvir (DSV) or ribavirin (RBV) for 12 or 24 weeks. Two patients were cirrhotic and had a Child-Pugh score of A. Treatment was discontinued in 2 patients due to thrombus formation in the arteriovenous fistula in the first month of DAAs treatment. SVR12 was evaluated in 14 of 18 patients and found to be 100%. One of the ten patients accepted as SVR24 had a relapse. This rate of SVR24 was similar to that in the general population.

Conclusions Our results supported that the OBV/PTV/r and DSV or RBV regimen was a safe and effective therapy for hemodialysis patients with chronic hepatitis C virus genotype 1.

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Introduction

Hepatitis C virus (HCV) is a hepatotropic virus with 9.6 kilobases, enveloped, and single-stranded RNA. The risk of becoming chronic is high, and the incidence is lower than other viruses (except hepatitis delta virus). Although the frequency of HCV varies according to regions in our country, it is 0.5-1%.[1] The transmission route is parenteral, and the main risk factors are hemodialysis, illegal drug use, blood and blood product transfusion, tattoos, organ transplants and acupuncture.[2] In the Transplantation Society registry data, the rate of HCV positivity (5.2%) in hemodialysis patients was reported to be higher than that of peritoneal dialysis patients (1.92%) and kidney transplant recipients (0.35%).[3] Hemodialysis carries a higher risk of hepatitis C transmission than peritoneal dialysis. In recent years, the number of peritoneal dialysis patients has decreased due to various factors, and HCV screening has become more prominent in this patient group. Chronic hepatitis C infection is a significant independent risk factor for mortality in hemodialysis patients. Chronic hepatitis C increases the risk of HCV-related liver disease, graft rejection, proteinuria, diabetes, and infection after kidney transplantation. Therefore, HCV eradication is of critical importance in this patient group. The first choice in treating HCV is interferon (INF) with or without ribavirin (RBV) therapy, but dose adjustment and nephrotoxicity risk limit its use in uremic patients. Direct-acting antivirals (DAAs) therapies have provided an advantage in treating chronic hepatitis C due to their ease of administration, shorter treatment duration, and higher sustained virological response (SVR) rates. This study aimed to evaluate the effectiveness of DAAs treatments in hemodialysis patients with chronic hepatitis C.

Material and Methods

Twenty hemodialysis patients with chronic hepatitis C followed in the gastroenterology outpatient clinic between 2016 and 2018 were included in this retrospective study. This study was conducted after the approval of the Local Ethics Committee (2019-2/21).

Six (30%) patients had not received any treatment before. Fourteen patients (70%) had been previously treated with INF and/or RBV but could not achieve SVR. A liver biopsy was not performed on the patients due to the risk of bleeding. All patients' medical information was obtained from hospital electronic system records. Hepatitis serologies, HCV-RNA, HCV genotype, complete blood count, biochemical test results and abdominal ultrasonography reports of the patients were recorded.

The patients were evaluated for cirrhosis by abdominal ultrasonography. Hepatitis C treatment was arranged according to the genotype type of the patients and the presence of liver cirrhosis. Nineteen patients were treated with ombitasvir/paritaprevir/ritonavir (OBV/PTV/r: 25/150/100 mg once a day) and dasabuvir (DSV) (250 mg twice a day) for 12 weeks. Two of the 20 patients whose laboratory genotype 1 could not perform subtype (1a/1b) analysis were accepted as genotype 1a and treated. RBV 200 mg daily was added to the treatment regimen of 6 patients (30%) with genotypes 1 and 1a. A 24-week treatment regimen was given to a cirrhotic patient with genotype 1a. Virological, biochemical and serological responses were evaluated 4, 12 and 24 weeks after the start of treatment.

Statistical analysis was performed using SPSS software version 23.0. Data were studied on descriptive statistical parameters (mean, standard deviation, median, percentage and min-max values).

Results

Twelve (60%) of the patients were male, eight (40%) were female, and their mean age was 50.7±8.6 years. Twenty patients had a median HCV-RNA level of 504,868.6 IU/mL (min 100 - max 3,218,282).

The mean laboratory values of the patients were as follows; hemoglobin 12.5±1.1 g/dL, platelet 169.591±72.576/mm^3, INR 1±0.1, serum creatinine 6.79±2.3 mg/dL, albumin 3.99±0.2 g/dL, and total bilirubin 0.6±0.2 mg/dL. Genotype 1b was detected in 14 patients (70%), genotype 1a in 4 patients (20%), and genotype 1 in 2 patients (10%). Two patients (10%) were cirrhotic and had a Child-Pugh score of A.

Nineteen patients received OBV/PTV/r + DSV treatment for 12 weeks. RBV was given additionally in 6 patients with genotypes 1 and 1a (30%). Only one patient received a 24-week treatment regimen for genotype 1a and cirrhosis. In 2 patients who received 12 weeks of treatment, a thrombus formed in the arteriovenous (AV) fistula in the first month of therapy and treatment had to be discontinued. No other side effects were observed in the other 18 patients. Post-treatment response was 100%. Since 2 out of 18 patients could not be reached, SVR values at the 12th and 24th weeks could not be evaluated in these patients. The 12th-week SVR of 14 of 16 patients was analysed, and the SVR rate was 100%. SVR24 was assessed in 8 of 14 patients with SVR12. Eight patients had 100% SVR at week 24. SVR24 of both patients whose SVR12 could not be evaluated was analysed. While HCV-RNA was negative in one patient, it was measured as 133 IU/mL in the other. The virological responses of the patients are given in Table 1.

Table 1. Virological response during and after the treatment.

HCV-RNA <25 IU/mL	n (%)
During the treatment	
4th week	7 (87)
12th week	18 (100)
After the treatment	
12th week	14 (100)
24th week	9 (95)
Virology refraction during the treatment	0
Relapse	1 (5)

Discussion

Although chronic hepatitis C increases mortality and morbidity in hemodialysis patients, it also prolongs the waiting time for kidney transplantation since SVR cannot be obtained. The risk of liver disease increases in patients not treated for HCV. These risks are liver cirrhosis, hepatocellular carcinoma and decompensated cirrhosis-related complications such as variceal bleeding, ascites, and encephalopathy.[4] Patients may die from these complications while waiting for a transplant. For chronic hepatitis C patients who underwent hemodialysis before DAAs, pegylated INF alpha 2a monotherapy was administered. The use of other pegylated INF alpha 2b and RBV used in chronic hepatitis C was not recommended since they are excreted from the kidneys, and they accumulate and lead to secondary toxic side effects in patients with chronic renal failure when the dose is increased for higher efficacy. In these patients, using RBV was found inconvenient, and combining it with INF at 200-800 mg doses was recommended through close surveillance. Due to the complex application of INF and the side effects of these drugs, sometimes the treatment cannot be continued. The long treatment periods may delay the waiting time for transplantation. In particular, patients considered for kidney transplantation should be given antiviral therapy to negate or reduce HCV-RNA because high levels of HCV-RNA can increase the risk of graft rejection. The relationship between cryoglobulinemia, membranoproliferative glomerulonephritis, membranous glomerulonephritis and focal segmental glomerulosclerosis with HCV infection is known. HCV treatment may also reduce the existing kidney failure in these patient groups.

The use of new DAAs is promising in this challenging group of patients. In our study, 20 hemodialysis patients with chronic hepatitis C were evaluated. Treatment was discontinued in 2 patients due to thrombus formation in the AV fistula in the first month of DAAs treatment. There is no data in the literature that DAAs increase the thrombus risk. Seventeen out of 18 patients received OBV/PTV/r and DSV ± RBV treatment for 12 weeks. Because the remaining one patient had cirrhosis and genotype 1, 24-week treatment was given. Post-treatment response was found to be 100%. SVR12 was evaluated in 14 out of 18 patients and found to be 100%. One of the ten patients whose SVR24 was considered had a relapse. This is similar to SVR24 in the average population. In a study executed by Pockros et al.[5] on 20 patients with chronic hepatitis C and stage 4 and 5 chronic kidney disease, OBV/PTV/r and DSV ± ribavirin treatment was reported to be efficient. Beinhardt et al.[6] investigated the efficacy of DAAs in 25 patients with chron-

ic hepatitis C, 10 of whom were on dialysis, eight of whom were kidney transplant recipients, and seven of whom were kidney and orthotropic liver transplant recipients concurrently. Although the number of patients in the groups was small in the study, it was emphasised that DAAs treatment was effective and usable in kidney transplant patients.[6]

In hemodialysis patients, the use of DAAs, in which's clearance occurs utilising renal, should be avoided to prevent the accumulation of drugs or metabolites. In several studies, the clearance of sofosbuvir metabolite, an NS5B polymerase inhibitor, is renal and is not recommended to be used in that end-stage kidney disease.[7,8] In various studies, sofosbuvir (SOF)-included regimens are efficient in patients on hemodialysis.[9-13] According to drug introduction monitored from studies in hemodialysis patients, the recent drug certification indicates that, however, reliable data are not enough in hemodialysis patients. Hemodialysis patients can be treated with SOF and velpatasvir (SOF/VEL) with standard drug doses.[10] Even though the clearance of simeprevir and daclatasvir is from the liver, some studies report toxicity in some patients with severe renal failure.[14,15]

In recent days, hepatitis C treatment has been updated with new studies. Previously, while treatment was given according to HCV genotype, in the current approach, the type and duration of use of the drug are determined according to the treatment experience independent of HCV genotype. The liver biopsy requirement is removed. HCV treatment recommendations in EASL, AASLD and our country have some differences. In all three guidelines, HCV treatment varies according to previous treatment experience, the presence of cirrhosis, and whether it is decompensated. In EASL guidelines, patients without cirrhosis are recommended SOF/VEL for 12 weeks or glecaprevir/pibrentasvir (GLE/PIB) for eight weeks, regardless of treatment experience. On the other hand, if there is treatment experience in Child-Pugh A patients, GLE/PIB treatment was prolonged to 12 weeks. In decompensated cirrhosis, SOF-based regimens are recommended.[16] EASL do not suggest testing of genotype for treatment. The genotype does not change the treatment. In AASLD, on the other hand, Child-Pugh A patients recommend eight weeks of GLE/PIB regimen for all genotypes or 12 weeks of SOF/VEL treatment for all except resistant genotype 3. If there is resistance in genotype three patients, a 12-week SOF/VEL/voxilaprevir (VOX) regimen is recommended. If there is treatment experience, they recommend 12 weeks of SOF/VEL/VOX or 16 weeks of GLE/PIB or SOF/VEL/VOX and RBV 24 weeks or GLE/PIB and SOF and RBV 16 or 24 weeks. In decompensated cirrhosis, they recommend genotypes 1, 4, 5, and 6 SOF/LED/RBV 12 weeks or SOF/VEL 12 weeks. If the patient is intolerant to RBV or has failed treatment SOF or NS5A, the treatment can be prolonged to 24 weeks. In our country, SOF/VEL/VOX 8 weeks or GLE/PIB 8 weeks are recommended for patients without cirrhosis. Unlike Child-Pugh A and all treatments experienced, it is recommended to increase sofosbuvir-based therapy to 12 weeks. In decompensated cirrhosis, all patients except genotype three are offered SOF/LED/RBV 12 or 24 weeks treatment. Genotype 3 patients with decompensated cirrhosis do not have a chance for therapy in AASLD and our country. SOF/VEL/VOX is also used in hemodialysis patients.

Cornberg et al.[17] assessed the effectivity of GLE/PIB in 59 chronic hepatitis C patients on hemodialysis. The SVR12 rate was 99%.[17] In the studies of Gane et al.[18], 104 patients with end-stage kidney disease were treated with GLE/PIB for 12 weeks. The SVR12 rate was 98%. The two of them had a virological failure.[18] Pol et al.'s[19] studies in which GLE/PIB was used for 12 weeks in 2,238 patients found a total SVR rate of 98%; it was found efficient in both chronic kidney disease stage 1-3 (98%; 2,087/2,135) and stage 4-5 (98%; 101/103). No dose adjustment was needed in mild, moderate and severe renal failure for GLE/PIB or OBV/r/DSV.[20,21] OBV/PTV/r and DSV are metabolised through the liver. OBV/PTV/r and DSV treatment is efficient in hemodialysis patients with chronic hepatitis C.

Conclusions

Treatment alternatives for chronic hepatitis C have increased since 2010. Our study has shown that OBV/PTV/r and DSV are effective regimens to rapidly and appropriately treat hemodialysis patients with chronic hepatitis C. New studies showing the long-term efficacy of DAAs thera-

pies, especially in hemodialysis patients on kidney transplant waiting lists, will provide more intensive use of these regimens.

Conflict of interest

The authors have no conflicts of interest to declare.

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Authors' Contribution

Study Conception: SG, TEO, AO, AE; Study Design: SG, TEO, AO, AE; Supervision: SG, TEO, AO, AE; Literature Review: TEO; Critical Review: TEO, SG; Data Collection and/or Processing: SG, TEO, AO, AE; Statistical Analysis and/or Data Interpretation: TEO; Manuscript preparing: TEO.

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Original Article

Pulmonary Complications in Kidney Transplant Recipients

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ABSTRACT

Background Kidney transplantation recipients are at an increased risk of lung complications due to infectious or non-infectious reasons. We aimed to determine the lung complications after transplantation and what we could do to prevent the complications during the follow-up, retrospectively.

Material and Methods The 296 patients who underwent kidney transplantation surgery in our centre between the years 1999 to 2006 were included in the study.

Results 75% of the patients were male (n: 222). 77% of the patients (n: 228) had a living-related donor. The mean hospitalisation duration in the post-transplantation period was 13.3±9.07 days. During the follow-up, 37.2% of the patients (n: 110) had rejection, and pulse steroid treatments were given to the 74.5% of these patients. In our study, the lung complication development ratio was 16.2%, and 84% of these complications were due to infections. A specific aetiology was not identified in 63.5% of patients. The patients with a living-related donor had more lung complications due to infection ($p<0.05$). We determine that the hospitalisation period following transplantation increases lung complication development ($p<0.05$). The patients with pulse steroid treatment had more lung complications ($p<0.05$).

Conclusions We showed that close follow-up of the patients prevents lung complications, and non-invasive diagnostic methods could be the first considered choice. In addition, our study showed the importance of a multidisciplinary approach to solid organ transplantation patients during the evaluation of complications.

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Introduction

Kidney transplantation affiliates significantly with a patient's life who has dialysis because of their non-functional kidneys with renal failure. In contrast, the immune system is chronically suppressed with immunosuppressive drugs given for life. Complications such as infections, tumours, lymphoproliferative diseases and chronic rejection occur with immune and non-immune mechanisms. Lungs are the organs under an increased risk of complications due to infectious or non-infectious reasons after renal transplantation.1 This study aimed to evaluate pulmonary complications in the post-transplant period in kidney transplant recipients and suggested preventive strategies against these complications in the future.

Material and Methods

This study, which was conducted after ethical approval of Baskent University medical school (E-51173401-900-123354), included 296 renal transplant recipients with pulmonary complications who were transplanted in our centre between January 1999 and July 2006. The patient's files were evaluated retrospectively. Demographic and clinical data were obtained from subjects with abnormal radiology suggestive of pulmonary complications and one or more respiratory signs such as cough, sputum production, hemoptysis, dyspnea, pleuritic chest pain, and decreased partial oxygen pressure, and other constitutional symptoms such as fever, fatigue etc. Patients were thoroughly evaluated for current respiratory disease history, immunosuppression regimens, and other risk factors. The results of general laboratory tests, radiological evaluation of the pulmonary lesion, and specific investigations to isolate causative agents, antibiotic therapy, and response to treatment were also recorded. Analysis was performed using SPSS 15.0 program. Mann-Whitney U Test, λ2 test and Student T Test were used for statistical analysis.

Results

Characteristics of the patients

All patients were transplanted due to chronic kidney disease (CKD). The aetiology of CKD was unknown in 124 (42%) patients. The most frequent etiologies of 172 patients were glomerulonephritis (n: 37, 12%), hypertension (n: 27, 9.1%) and vesicoureteral reflux (n: 20, 6.8%) (*Table 1*). Among 296 renal transplant recipients, 74 (25%) of 296 patients were female, and 222 (75%) were male. The mean transplantation age was 32.4±10.2 years. 228 (77%) of the patients had living-related donors, and 68 (23%) had deceased donors. Antiviral (aciclovir PO), antifungal (fluconazole PO) and antibacterial (TMP-SMX PO) prophylaxis treatments were given for six months to 293 (99%) of the patients. INH prophylaxis was given to 3 (1%) patients for nine months due to positive PPD tests before transplantation, and all patients were

Table 1. Primary disease etiologies of kidney transplant recipients.

Primary disease etiologies	n (%)
Unknown	124 (42)
Known	172 (58)
Glomerulonephritis	37 (12.5)
Hypertension	27 (9.1)
Vesicoureteral reflux	20 (6.8)
Nephrolithiasis	14 (4.8)
FMF	11 (3.8)
Alport syndrome	11 (3.8)
Vasculitis	9 (3.1)
ADPKD	6 (2.1)
SLE	6 (2.1)
Pyelonephritis	5 (1.7)
Nephrotic syndrome	5 (1.7)
Diabetes mellitus	4 (1.4)
Amyloidosis	4 (1.4)
Atrophic kidney	2 (0.7)
Ectopic kidney	2 (0.7)
Others*	9 (2.7)

FMF: familial Mediterranean fever; APKD: autosomal dominant polycystic kidney disease; SLE: systemic lupus erythematosus.

*Hypertension and diabetes (n: 1), Gilbert's disease (n: 1), methylmalonemic acidemia (n: 1), renal tuberculosis (n: 1), renal hypoplasia (n: 1), pregnancy (n: 1), hemorrhage (n: 1) and renal artery stenosis (n: 1), hyperreninemic hyperaldosteronism (n: 1).

vaccinated for influenza and pneumococcus. The mean hospitalisation time after transplantation was 13.3±9.07 days. Rejection which was diagnosed by the transplantation team by biopsy, was developed in 110 (37.2%) patients, and 82 (74.5%) of them were given pulse steroid treatment. The transplantation team determined the dose and duration of steroid treatment.

General demographics and features of the patients with pulmonary complications

Among 296 kidney transplant recipients, 48 (16.2%) patients had pulmonary complications. The male sex ratio was 71% (n: 34) in patients with pulmonary complications and 76% (n: 188) in patients without pulmonary complications (p>0.05). There was no statistically significant difference between the mean transplant ages of patients with and without pulmonary complications (33.5±9.5 vs 32.2±10.3, p>0.05, respectively). 15 of 48 patients had consecutive pulmonary complications (2 times in 10 cases, three times in 2 cases, four times in 1 case, five times in 1 case and six times in 1 case). And by the way, 75 pulmonary complications were detected in our transplant recipients. The mean hospitalisation time after transplantation were 17.9±11.5 days in the patients with pulmonary complication and 12.2±8.3 days in the patients with no pulmonary complications (p<0.05). Prolonged hospital stay was associated with the risk of developing pulmonary complications. Pulmonary complications developed at the earliest on the second day after transplantation and at the latest on the 2,289th day (mean 49.5±5.4 months). Thirty-seven (77%) of 48 patients with pulmonary complications and 191 (83.8%) of 248 patients without pulmonary complications were transplanted from a living donor, and there was no correlation between donor type and development of pulmonary complications (p>0.05). The history of rejection was significantly higher in patients with pulmonary complications than those without pulmonary complications (52% vs 34.3%, p<0.05, respectively).

Symptoms and radiologic findings of the pulmonary complication group

There was more than one symptom in the patients; cough in 51 (68%) patients, fever in 41 (54.7%) patients, sputum in 41 (54.7%) patients, extrapulmonary symptoms in 31 (41.3%) patients, dyspnea in 22 (29.3%) patients and hemoptysis in 2 (2.7%) patients.

Chest radiography was performed in all 75 pul-

Table 2. Radiological findings.

Chest X-ray	n (%)	Thoracic CT	n (%)
Normal	18 (24)	Normal	3 (5)
Pathologic	57 (76)	Pathologic	55 (95)
Heterogeneous density	37 (65)	Consolidation	30 (55)
Congestion	7 (12.3)	Patchy infiltration	8 (14.5)
Pleural effusion	5 (8.8)	Acinar infiltratation	8 (14.5)
Hiler pathology	4 (7)	Nodule	6 (11)
Atelectasis	3 (5.3)	Bronchiectasis	4 (7.2)
Patchy infiltration	3 (5.3)	Ground glass	3 (5.4)
Abscess	2 (3.5)	Pulmonary thromboembolism	3 (5.4)
Nodular lesion	1 (1.8)	Hiler or mediastinal lymphadenopathy	3 (5.4)
Pleural thickening	1 (1.8)	Cavity	2 (3.6)
		Abscess	2 (3.6)
		Alveolar filling	1 (1.8)
		Alveolar filling and ground glass	1 (1.8)
		Septic embolism	1 (1.8)
		Sequel changes	1 (1.8)

monary complications. Thoracic computed tomography (CT) was also performed in 58 cases of pulmonary complications for which chest X-ray images were not diagnostic. Thoracic CT findings were pathological in 12 (20.7%) cases of pulmonary complications with normal chest X-ray images. While chest X-ray was normal in 18 (24%) patients with pulmonary complications, it was pathological in 57 (76%) patients. Pathological findings of chest X-ray images were unilateral in 34 (59.6%), and bilateral in 23 (40.4%) pulmonary complications; 26 (49%) had pulmonary complications in one zone, and 27 (50%) had pulmonary complications in more than one zone. The most common findings were heterogeneous density, congestion, pleural effusion, hilar pathology, atelectasis, patchy infiltration, abscess, nodular lesion, and pleural thickening (*Table 2*).

The findings of thoracic CT were pathological in 55 (94.8%) of 58 pulmonary complications in which thoracic CT was performed. The pathological findings of thoracic CT were unilateral in 20 (36.4%) pulmonary complications, bilateral in 35 (63.6%) complications, at one lobe in 13 (23.6%) pulmonary complications and multilobar in 38 (69.1%) complications. The most frequent findings were consolidation, patchy infiltration, acinar infiltration, nodule, bronchiectasis, ground glass, pulmonary thromboembolism (PTE), hilar or mediastinal lymphadenopathy, cavitary lesion, abscess, alveolar filling pattern and ground glass and septic embolism (*Table 2*).

Infectious pulmonary complications

Sputum samples were taken from 28 of 41 pulmonary complications and evaluated with gram strain and cultures. 20 (71.4%) sputum samples were culture positive. 13 sputum samples were stained with Erlich Ziehl Nielsen (EZN), and the results were culture-negative. Fiberoptic bronchoscopy (FOB) was performed in 11 pulmonary complications who had no sputum and in 3 pulmonary complications whose sputum cultures were negative. For differential diagnosis, bronchial lavage was performed in 1 complication, bronchoalveolar lavage (BAL) in 7 complications, BAL and pro-BAL in 5 complications and BAL and biopsy in 1 complication. All samples were evaluated with gram strain and cultures. 12 FOB samples were stained with EZN, and the results were negative. 3 (21.4%) FOB samples were culture-positive. Thoracentesis (T/S) was performed in 4 complications with pleural effusion; exudative effusion was determined in 2 with negative cultures. FOB and deep tracheal aspiration (DTA) were performed in 4 complications who were intubated; 2 (50%) of DTA samples were cultures positive (*Table 3*).

It was applied to one of the three pulmonary complications (33.3%) in FOB and DTA. In the FOB sample culture, *M. tuberculosis* was positive, and *Enterobacter aerogenes* and *Candida spp.* were positive in DTA sample cultures. In one complication, cytomegalovirus (CMV) pneumonitis was shown in the FOB biopsy sample, and *C. albicans* were grown in culture. In sputum cultures, grown of *S. epidermidis* and grown of *Enterobacteria* in 1 patient with congestion were considered contamination. After all assessments, 12 (16%) of 75 pulmonary complications were diagnosed as non-infectious and 63 (84%) infectious complications. A specific agent was shown in only 23 (36.5%) of 63 infectious complications. The diagnosis was acute bronchitis in 9 (14.3%) complications, abscess in 2 (3.2%) complications, septic embolism in 1 (1.6%) complication and pneumonia in 51 (80.9%) complications.

The culture result was negative in one pulmonary complication, but with high serum LDH, hypoxemia and radiological findings, *Pneumocystis jirovecii* pneumonitis (PCP) was diagnosed. In six complications, the diagnosis was fungal pneumonia. In the first case of fungal pneumonia, S. epidermidis was grown in sputum culture, but this growth was considered contamination. Also, there was no growth in FOB samples, but *A. fumigatus* was shown in the skin lesion and was accepted as an etiological agent. In the second case, there were white plaques on the mucosa in FOB; yeast in the gram strain, but the culture results were negative. In the third case, there was yeast in the gram strain of the FOB sample, but the culture results were negative. The fourth case was diagnosed as invasive candidiasis; sputum cultures were positive for *P. aureginosa* and *C. albicans*, and hyphae were shown in the FOB biopsy sample. In the fifth case, CMV pneumonitis was demonstrated in the FOB biopsy sample, and the FOB culture was positive for *C. albicans*. The sixth case was intubated due to respiratory failure. BAL culture was positive for *M. tuberculosis*, and DTA culture was positive for

Table 3. Culture results in sputum, fiberoptic bronchoscopy and deep tracheal aspiration samples.

Sputum (n: 28)	n (%)
Culture (−)	8 (28.6)
Culture (+)	20 (71.4)
α-hemolytic streptococcus	5 (17.9)
Hemophilus influenza	3 (10.7)
Pseodomonas auregenosa	2 (7.1)
Enterobacteria	2 (7.1)
Pseodomonas auregenosa and *S. pneumonia*	1 (3.6)
Pseodomonas auregenosa and *C. albicans*	1 (3.6)
S. pneumonia	1 (3.6)
Enterococcus	1 (3.6)
α-hemolytic streptococcus and *Hemofilius influenza*	1 (3.6)
S. pneumonia and *Hemofilius influenza*	1 (3.6)
Enterobacteria and *α-hemolytic streptococcus*	1 (3.6)
S. epidermidis	1 (3.6)
Fiberoptic bronchoscopy (n: 13)	
Culture (−)	10 (76.9)
Culture (+)	3 (23.0)
Candida albicans	1 (7.7)
M. tuberculosis	1 (7.7)
Burkholderia cepacia	1 (7.7)
Deep tracheal aspiration (n: 4)	
Culture (−)	2 (50)
Culture (+)	2 (50)
Acinetobacter baumannii	1 (25)
Enterococcus ve *Candida spp.*	1 (25)

Enterococcus and *Candida spp.*; but before the culture results, the patient died. Cold agglutinins were positive in one of the complications diagnosed as pneumonia, and the case was diagnosed as atypical pneumonia according to the history, physical examination and radiological findings. In other pneumonia cases, an agent can not be defined or diagnosed with defined etiologies.

Non-infectious pulmonary complications were congestion in 7 (58.3%) complications, atelectasis in 3 (25%) complications and PTE in 2 (16.6%) complications.

Comparison of the patients with infectious and non-infectious pulmonary complications

Four (33.3%) of 12 non-infectious pulmonary complications were female, and 8 (66.7%) were male. 16 (25.4%) of 63 infectious pulmonary complications were female, and 47 (74.6%) were male. There was no statistically significant difference between the groups in gender ($p>0.05$). The mean transplantation ages of non-infectious and infectious pulmonary complication groups were 33.1±9.4 years and 33±9.8 years, respectively. There was no statistically significant difference between the groups in mean transplantation age ($p>0.05$). In the non-infectious complication group, 7 (11.5%) complications had living-related donors, and in the infectious complication group, 54 (8.5%) complications had living-related donors. Infectious pulmonary complications were

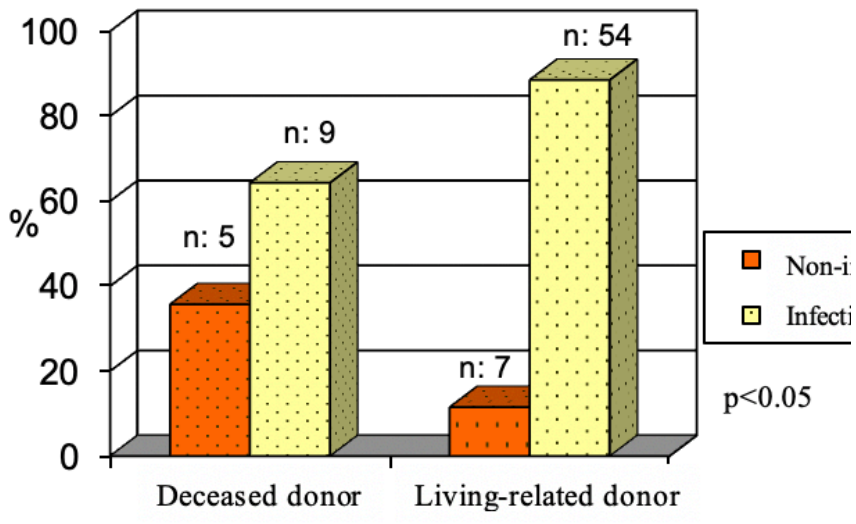

Figure 1. Frequency of infectious lung complications by donor types.

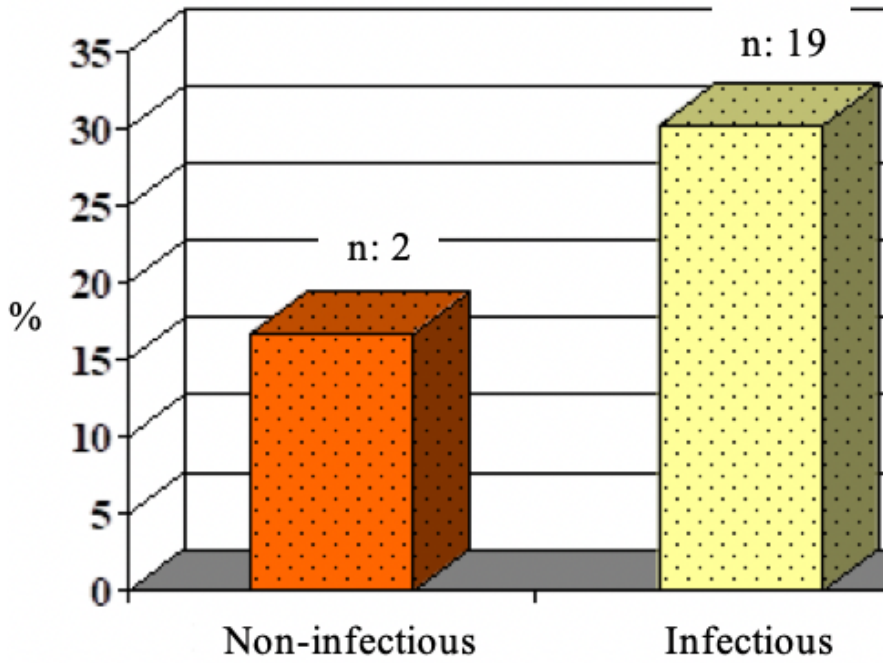

Figure 2. Pulmonary complication rates were higher in transplant recipients who were given pulse steroid treatment for rejection ($p<0.05$).

frequent in the patients with living-related donors (p<0.05) (*Figure 1*). Time of complication occurrence was 588.8±576.9 (range 0-2,289) days in the infectious complication group and 571.8±487.5 (range: 7-1,353) days in the non-infectious complication group (p>0.05) (the mean following time was 4.5 years). The mean hospitalisation time after transplantation was 17.1±11.9 days in the infectious complication group and 17.5±7.8 days in the non-infectious complication group (p>0.05). Rejection was developed in 6 (50%) complications in non-infectious complications and 34 complications in infectious complications (p>0.05).

Pulse steroid treatment

Pulse steroid treatment was given to the patients who were diagnosed with rejection. The transplantation team defined the dose and duration of the treatment according to the patient's situation. Pulse steroid treatment was applied to 14 (53.8%) recipients who developed rejection, while 12 (46.2%) did not receive treatment. Pulmonary complications were more frequent in the patients who were given pulse steroid treatment for rejection (p<0.05) (*Figure 2*). Pulse steroid treatments were given to 19 (30.2%) infectious pulmonary complications and 2 (16.7%) non-infectious pulmonary complications. There was no statistically significant difference between pulse steroid therapy and the occurrence of infectious or non-infectious pulmonary complications (p>0.05). The mean pulse steroid dose in infectious pulmonary complications was 3026.3±1989.3 mg.

Specific laboratory findings in pulmonary complications

Urine legionella antigen was studied in 10 patients with pulmonary complications; serum galactomannan in 14 patients; serum CMV pp65 antigen in 9 patients, and cold agglutinins in 8 urine legionella antigen was negative in 10 patients. Serum galactomannan was positive in one patient, serum CMV pp65 antigen was positive in two patients, and cold antigens were positive in two patients. □*-hemolytic streptococcus* was grown in the patient's sputum culture whose cold agglutinins were positive, and there was no growth in the sputum culture of the second patient with positive cold agglutinins. The patient with positive galactomannan was diagnosed with septic embolism. One of the patients with positive serum CMV pp65 antigen was diagnosed with CMV pneumonitis, and the preemptive treatment was given to the other patient in whom any microbiological agent could show. PPD test was performed in 6 patients with pulmonary complications and was positive (>5 mm) in 3 of them, but none were diagnosed with tuberculosis. One of the patients with negative PPD was diagnosed with tuberculosis due to the growth of *M. tuberculosis* in the FOB sample culture.

Treatment

The patients with pulmonary complications were treated through their diagnosis. Chest physiotherapy and mucolytic agent N-acetyl cysteine for atelectasis; diuretic agents, hemodialysis for congestion and transudative effusions; albumin replacement for hypoalbuminemia and anticoagulant treatment for PTE were given. Antibiotics were given to infectious pulmonary complications through the possible aetiology or defined microbiological agents. The rate of development of pulmonary complications after kidney transplantation in our centre was 25.3%. In the follow-up, 4 of these 48 patients died because of pulmonary complications. The cause of the death was sepsis due to pneumonia.

Discussion

Close follow-up is essential in these patients, as immunosuppressive treatment continues life-long and the immune system is suppressed chronically, so infections, lymphoproliferative diseases, and chronic rejection with or without immune mechanisms might occur, and dialysis could be required again. Transplant success rates are increasing with new immunosuppressive regimens.[1]

Solid organ transplant recipients are at an increased risk of infectious complications due to chronic immunosuppression. Pulmonary infections are one of the frequent causes of mortality in immunosuppressive patients.[2,3] Immunosuppressive drugs prevent rejection but increase the susceptibility to community-acquired and opportunistic infections. Also, the risk of non-infectious pulmonary complications is higher in these patients.[4-7] The risk of pneumonia is lower in kidney

transplant recipients than other solid organ transplant recipients due to the method of surgery and lower dose of immunosuppressive drugs.[8,9] Tveit et al.[10] described the risks of pneumonia in kidney transplant recipients who had no pneumonia history before as age (>65 years) and male gender. The pulmonary defence mechanism gets worse with age.[11] In our study, 48 (16.2%) of 296 patients had pulmonary complications, and none had lung disease before the transplantation. Our results showed no relationship between the mean transplantation age and posttransplant infectious or non-infectious pulmonary complications. In our group, the highest transplantation age (57 years) was lower than the literature, the patients had no history of lung diseases, and all our patients had received low-dose conventional immunosuppressive regimens and T-cell antibodies combination regimens as low-dose immunosuppressive drugs. By the way, our rate of pulmonary complications (25.3%) was lower. In the pulmonary complication group, 34 (71%) patients were male, and 14 (29%) patients were female, similar to the literature, whereas there was no correlation between age and developing pulmonary complications in our group.

Transplant recipients with deceased donor organs are supposed to receive higher doses of immunosuppressive drugs, and more severe and frequent infectious complications are thought to arise.[10,12,13] In one study, there was no statistically significant difference between having a deceased or living-related donor and developing an infection.[14] But another study showed that bacterial infections were frequent in transplant recipients with living-related donors.[15] Our results showed no relationship between donor type and developing pulmonary complications, but infectious pulmonary complications were frequent in patients with living-related donors. In our group, the number of patients with living-related donors was higher in the rejection group. This could be the reason for this result. Intensive immunosuppressive treatments are given for rejection, increasing the risk of pulmonary infections. The prolonged hospitalisation after transplantation, immobilisation and extended exposure to nosocomial flora increase the risk of developing pulmonary complications. Also, we showed that the increased mean hospitalisation time after transplantation increases the rate of pulmonary complications.

In our study, 12 (20.7%) of 75 pulmonary complication chest X-rays were normal, whereas thoracic CT findings were pathological. In the literature, if there is a clinical suspect, thoracic CT is recommended to define the pulmonary pathology in renal transplant recipients for early diagnosis and treatment.[16] Studies showed that consolidation was the frequent pathology in chest X-rays and thorax CTs.[17-19] Heterogeneous density in chest X-rays and consolidation in thoracic CTs were the frequent pathologies in our study. Also, we showed that every pathological finding was not specific to an infectious complication or a microbiological agent. Radiology also defines other than infectious complications.

Despite all research, a specific microbiological agent could not be defined in immunosuppressive patients.[20] In the study of Rano et al.[21], a particular aetiology was determined in 46% of sputum cultures, 64% of DTA samples and 36.1% of FOB samples. They diagnosed 66% of the patients by FOB and could not define a specific aetiology in 12.5% of them. Chang et al.[17] could not determine a particular aetiology in 22.8% of the patients (10/27). BAL's diagnostic value was 80.5% in Xaubet et al.'s[22] study and 75.7% in Kalra et al.'s[23] study. Eyuboglu et al.[24] showed a specific aetiology in 66% of sputum samples and 11% of BAL samples. In their results, BAL was not superior to sputum cultures.[24] In one study that included 33,479 kidney transplant recipients, 4.7% of the patients were hospitalized due to pneumonia.[10] FOB was performed in 9.9% of the patients, and open lung biopsy in 4.8% of the patients. A specific aetiology could not be defined in 72.5% of the patients, and the authors indicated that invasive diagnostic methods were not superior to non-invasive methods. Our study's results were similar; we could not define a specific aetiology in 63.5% of our patients. In our research, the best method to determine specific aetiology was sputum cultures. A particular aetiology was shown in 20 (71.4%) sputum samples, 4 (28.4%) FOB samples and 2 (50%) DTA samples. In case of suspicion of infectious pulmonary complications, empiric antibiotic therapy was given to transplant recipients, and FOB was performed under this treatment. This

should be the reason for our negative culture. Invasive diagnostic methods like FOB in immunosuppressive patients can cause new colonizations and complications, whereas they do not contribute to the diagnosis. So non-invasive diagnostic methods should be the first choice for diagnosing the complications, and invasive methods should be considered in the presence of requirements.

Corticosteroids have catabolic effects, especially in lymphoid and connective tissue, muscles, adipose tissue and skin. They also cause weakness in respiratory muscles; predisposition to infections by affecting T-cells and macrophages in cellular immunity. Also, corticosteroids have anti-inflammatory effects.[25] In our study, there was a relationship between developing pulmonary complications and pulse steroid treatment. Still, there was no statistically significant difference between pulse steroid treatment and developing infectious or non-infectious complications. Recent studies showed that steroid treatment in maintenance therapy was not a risk factor for infectious complications.[15] But corticosteroids in transplant recipients are accepted as risk factors for bacterial infections and sepsis due to intravenous pulse steroid treatment should be emerged.[26] In one study, the cumulative dose of pulse steroid treatment for rejection in patients with pulmonary complications was higher (mean 7,160±1,590 mg), but there was no statistically significant difference.[27] In our study mean pulse steroid dose was 3026.3±1989.3 mg in patients with infectious pulmonary complications.

The potential and defined microbiological agents were compatible with the infection schedule in our patients. With the developing surgery techniques and efficient prophylaxis treatment, the infection agents in solid organ transplant recipients are changing.[28] After kidney transplantation, all recipients were given prophylaxis treatment (acyclovir, fluconazole and TMP-SMX PO). Thus no pulmonary infections due to HSV developed.[29] One of our patients was diagnosed with *P. jirovecii* pneumonitis with his clinic and radiological findings, whereas he was given TMP-SMX prophylaxis treatment. Infection rates of CMV in solid organ transplant recipients approach 70%.[30] In our centre survey for CMV infection is regularly done, and in the occurrence of infection, pre-emptive treatment is given. Gancylovir should be added to the prophylaxis protocol according to the donor's and recipient's CMV serology. There were no recipients with negative CMV serology in our patients, so gancyclovir prophylaxis was not given. Serum CMV PCR and pp65 antigen levels in solid organs could guide the clinician for preemptive or prophylaxis treatment in solid organ transplant recipients. By the way frequency of CMV infection should be decreased, as in our results. On the other hand, CMV causes opportunistic bacterial and fungal infections by suppressing cellular immunity.[31] The growth of *C. albicans* in the BAL sample of one of the recipients diagnosed with CMV pneumonitis was accepted as an opportunistic infection secondary to CMV infection.

In our study, six of the patients died in the follow-up. Four (1.3%) of the deaths were due to sepsis by pneumonia. Two of the deaths due to pneumonia were in the first month after transplantation, and the other two were after six months after transplantation. A specific aetiology was defined in the recipients who died; *A. baumani* in the DTA sample and *M. tuberculosis* in the BAL sample, and *Enterococcus* and *Candida spp.* in the DTA sample. In our centre, by the close follow-up of kidney transplant recipients, we aimed to diagnose mortal infections early and give efficient treatments.

Conclusions

Kidney transplant recipients are at high risk for infectious and non-infectious pulmonary complications due to surgery and immunosuppressive drugs. After the transplantation, efficient prophylaxis treatment should prevent potential infections. Non-invasive diagnostic methods should be the first considered choice in the presence of complications. In transplant recipients, symptoms and radiological findings are not specific. The aetiology of infections might be multifactorial in these patients. Immunosupressive drugs given after kidney transplantation increase infection risk, but close follow-up can prevent infections. Thus, low complication rates should be achieved in both the lungs and other systems. Also, non-infectious reasons should be considered in the presence of complications. The follow-up of transplant recipients must be multidisciplinary as other solid organ transplant recipients. The standard follow-up

transplantation team consisting of surgery and infectious disease specialists and pulmonologists should reach low rates of pulmonary complications.

Conflict of interest

The authors have no conflicts of interest to declare.

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Authors' Contribution

Study Conception: NTS, FOE; Study Design: NTS, FOE; Supervision: FOE, MH; Literature Review: NTS, NGA; Critical Review: FOE; Data Collection and/or Processing: NTS, NGA; Statistical Analysis and/or Data Interpretation: NTS, NGA; Manuscript preparing: NTS.

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Original Article

Positive Status of Hepatitis B Virus Seroprevalence in Local People and Immigrants

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ABSTRACT

Background In our study, we aimed to examine the seroprevalence of hepatitis B virus (HBV) infection and whether there is a sociodemographic difference between the two groups according to the hepatitis B surface antigen (HBsAg) results obtained in the blood samples given by the Turkish population and Syrian immigrants living in Bursa in their primary, secondary, and tertiary care applications.

Material and Methods All patients with HBsAg serology who applied to family health centers, migrant health centers, 2nd and 3rd level hospitals in Bursa province during the 5-year period from January 2017 to the end of December 2021 were included in our study.

Results During our study, HBsAg tests were taken from 955,528 people until the end of 2017-2021. The rate of Turkish citizens was 96.1% (n: 918,140), and the rate of Syrian origin was 3.9% (n: 37,388). Of all patients, 39.4% (n: 376,388) were male, and 60.6% (n: 579,140) were female. The HBsAg test was negative in 96.4% (n: 921,582) and positive in 3.6% (n: 33,946) of the patients. HBsAg positivity was found to be 3.6% in Turks and 2.4% in Syrians. HBsAg positivity was found to be 4.6% in men and 2.9% in women. The highest HBsAg positivity rate was 7.4% in the 50-59 age group.

Conclusions The dissemination of the hepatitis B vaccine, which is currently in use, seems to be the most crucial weapon in the hands of humanity to prevent this infection and the diseases it will cause.

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Introduction

Hepatitis B virus (HBV) infection is one of the most common infectious diseases in the world. Being responsible for acute hepatitis, chronic hepatitis, liver failure, hepatocellular cancer, and related deaths makes it a significant public health problem.1 It is estimated that over 2 billion people worldwide are affected by HBV. In 2019, nearly 300 million people, 5% of the world population, were infected with chronic HBV.2 1.5 million new cases are added to these cases every year. If we add that 820,000 people die every year due to HBV and its cirrhosis and hepatocellular carcinoma, we wouldn't be surprised that it occupies the world agenda more than we expected.2,3

The prevalence of HBV infection in developed countries varies between 2-8%.4 Shown risk factors for HBV infection include age, gender, geographical region, socioeconomic status, personal hygiene and hygiene status, lifestyle, and immune status.5 Due to the war that started in 2011, nearly 4 million civilians had to leave Syria. Turkey was the first to embrace the population forced to migrate from Syria. These civilians were resettled in various regions by the Turkish government. According to 2018 data, more than 150 thousand immigrants live in Bursa.6 The hepatitis B surface antigen (HBsAg) is the most commonly used serological agent in the detection of HBV infection, which is positive during all chronic hepatitis B infections, except for early acute hepatitis.7 Our study aimed to examine the seroprevalence of HBV infection and whether there is a sociodemographic difference between the two groups according to the HBsAg surface antigen results obtained in the blood samples given by the Turkish population and Syrian immigrants living in Bursa in their primary, secondary and tertiary care applications.

Material and Methods

The study was conducted after SBU Bursa Sehir Training&Research Hospital ethical Commitee approval (2019-KAEK-140). The blood test results of people who applied to all family health centers, immigrant health centers, and 2nd and 3rd level state hospitals during the five years from January 2017 to the end of December 2021 were studied in the public health laboratory. Of the 955,528 patients, 918,140 were Turkish, and 37,388 were Syrian. Then, the results of the Turkish and Syrian populations were compared. HBsAg results were also evaluated separately according to the gender and age groups of the patients (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89 and 90-99).

Chemiluminescent Microparticle Immunoassay detected the presence of HBsAg antigen. The samples obtained by separating 10 cc blood samples from serum in the fully automatic COBAS 4000 device were performed by centrifuging patient samples (Roche Diagnostics, Germany).

Statistical analysis

The data of the study were analysed using 'The Jamovi project (2021) (Jamovi, Version 2.0.0) [Computer Software]'. Categorical variables were expressed as numbers and percentages (%). Chi-square or Fisher's exact tests were used to analyse whether there was a relationship between categorical variables. $p<0.05$ was considered statistically significant. The power analysis of the study groups (Syria/Turkish) was calculated as 94% with G power 3.1.9.7 computer version.

Table 1. Sociodemographic features and HBsAg positive status.

Variables	n (%)
Gender	
Male	376,388 (39.4)
Female	579,140 (60.6)
HBsAg status	
Negative	921,582 (96.4)
Positive	33,946 (3.6)
Nationality	
Turkish	918,140 (96.1)
Syrian	37,388 (3.9)
Age status (years)	
0-9	23,323 (2.4)
10-19	56,768 (5.9)
20-29	242,241 (25.4)
30-39	190,213 (19.9)
40-49	131,712 (13.8)
50-59	109,654 (11.5)
60-69	99,445 (10.4)
70-79	66,834 (7.0)
80-89	29,557 (3.1)
90-99	5,781 (0.6)

Results

The sociodemographic characteristics of the study cohort were detailed in Table 1. Of the whole group, 60.6% were female, and 39.4% were male. The number of Syrian patients was less than that of Turkish patients (3.9% vs 96.1%). Most patients were in the 20-29, 30-39, 40-49, 50-59 and 60-69 age intervals, respectively.

In our study, the distribution by age and gender of 955,528 people who had the HBsAg test between 2017-2021 was given in Figure 1. The distribution of patients by nationality was shown in Figure 2 in detail. The distribution of HBsAg positivity in patients according to age was shown in Figure 3. Of the study population, 96.1% (n: 918,140) were Turkish citizens, and 3.9% (n: 37,388) were of Syrian origin. Of these patients, 39.4% (n: 376,388) were male, and 60.6% (n: 579,140) were female. 96.4% (n: 921,582) of the tests were negative, and 3.6% (n: 33,946) were positive. In the power analysis of the study groups (Syrian/Turkish), the effect size was calculated as d: 0.578 and N2/N1= 0.0407. The actual power was found to be 0.94.

The rate of HBsAg positivity in men was significantly higher than in women. HBsAg positivity was lower in the Syrian patient group than in the Turkish patient group (2.4% vs 3.6%). The highest HBsAg positivity rate was observed in the 50-59 age group (7.4%), followed by the 40-49 and 50-59 age groups (*Table 2*).

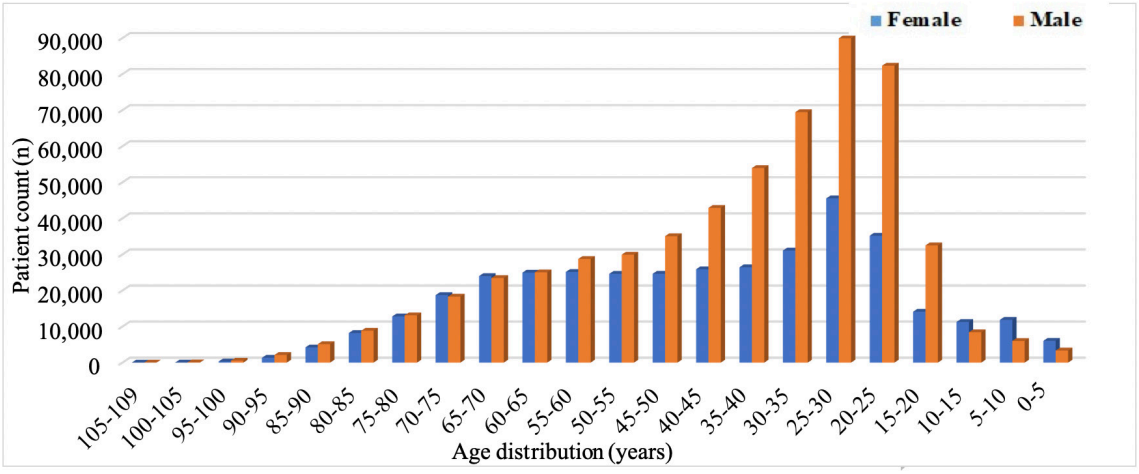

Figure 1. Distribution of patients by age and gender.

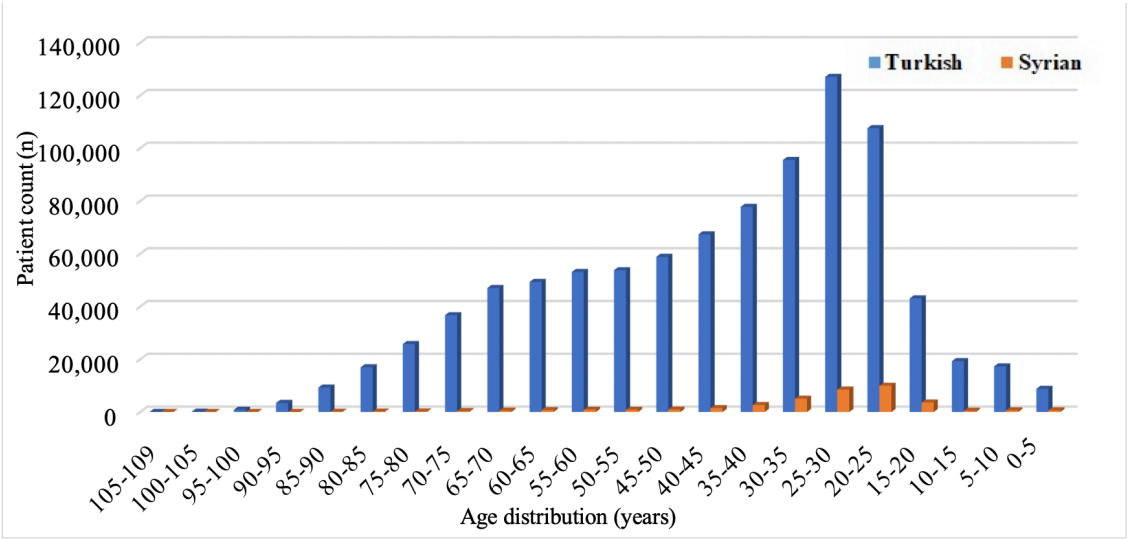

Figure 2. Age distribution of patients by nationality.

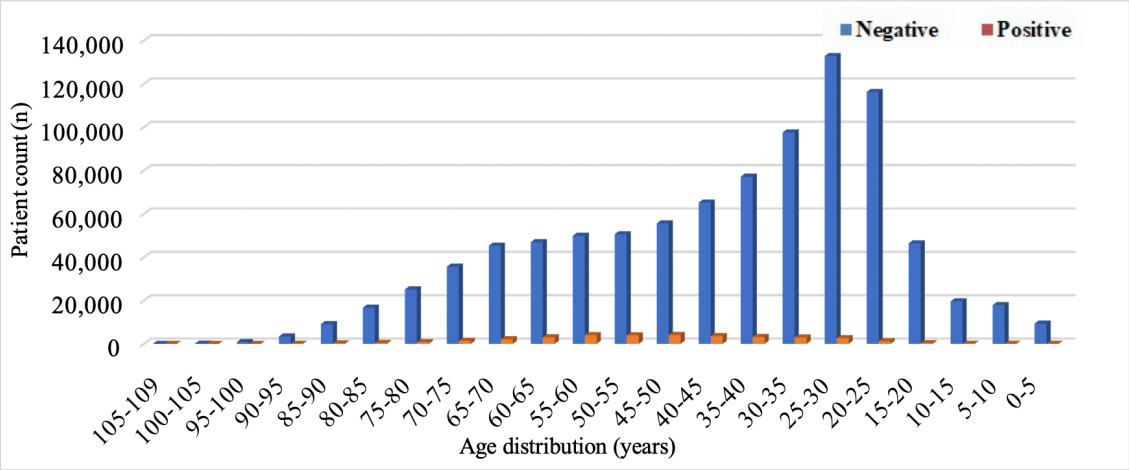

Figure 3. Distribution of HBsAg positivity in patients according to age.

Discussion

Regarding the prevalence of HBV, North America and eastern Europe are recognised as low-risk regions with a prevalence of <1%, the Middle East and India region with a prevalence of 2-5% are at intermediate risk, and southwest Asia, Africa and the eastern Pacific region with a prevalence of 5-10% are classified as high-risk regions.[7] Turkey is located in the low-level risk zone, unlike other middle eastern countries. When we look at the studies reported from our country, it is remarkable that the results reported in some regions where HBsAg seropositivity is in a wide margin between 1.3% and 13.8% are above 10%, which may lead to determination as a high-risk endemic region.[8] We attribute this result to the involvement of various sociodemographic factors since the studies conducted on different populations for HBV in different studies reported from our country included various geographical regions. In our research, HbsAg seropositivity was found to be 3.6% in Turkish cases, which confirms the data of the medium-risk HBV-risk region from Turkey and the world.

In a previous study in Bursa, HBsAg positivity was reported as 4.7% in Turkish patients, though it varies according to age groups.[9] In another study, the estimated overall population prevalence was 4.57%.[10] In a study conducted in Artvin province, HBsAg positivity was found to be 3.96%.[11] When we look at other studies reported from several regions of Turkey, it is seen that there is an increasing positivity rate going towards the Southeast Anatolia region. In the literature, there are studies in which HBsAg positivity was reported as 4.22%, 10%, 12.6%, 2.7%, 7%, and 5.5%.[12-17] our prevalence may be lagging behind the general prevalence rates reported from Turkey, which could be dependent on the high sociodemographic characteristics, relatively higher education level in the west, and it is based on a social life that is more compatible with hygienic conditions.

When the HBV prevalence by gender is examined in the literature, it has been observed that the prevalence of HBV is higher in males than females in all geographical regions. It has taken place in the global literature that predisposing factors such as more alcohol, smoking, not paying attention to hygiene conditions, and having more external procedures such as tattooing can be associated with a higher prevalence in the male gender.[18,19] In our study, the prevalence of hepatitis B was found to be 4.6% (n: 16,956) in Turkish men and 2.9% (n: 16,102) in Turkish women. In a study previously reported from our country, the rate of males was reported as 4.71% and 3.30% in females.[11] When we glance at the other literature information reported from our country, it is seen that the prevalence of hepatitis B in men is higher than in women.[12,13] In our study, the prevalence of HBV was 4.7% (n: 361) in Syrian men and 1.8% (n: 527) in Syrian women. Again, in line with the literature from the world, it is noteworthy that the prevalence is high in favour of men.[18,19]

In the center of the Middle East, hepatitis infections are still a significant public health problem. According to a study reported from Syria,

Table 2. HBsAg positivity status of the patients according to the distribution of sociodemographic data.

Variables	Total patient count (n)	HBsAg		Test statistics
		Negative n (%)	Positive n (%)	
Gender				χ^2=1.992
Male	376,388	359,071 (95.4)	17,317 (4.6)	p<0.001
Female	579,140	562,511 (97.12)	16,629 (2.87)	
Nationality				χ^2=157
Turkish	918,140	885,082 (96.4)	33,058 (3.6)	p<0.001
Syrian	37,388	36,500 (97.6)	888 (2.4)	
Age intervals				χ^2=13.634
0-9 years	23,323	23,274 (99.78)	49 (0.21)	p<0.001
10-19 years	56,768	56,516 (99.6)	252 (0.4)	
20-29 years	242,241	238,822 (98.6)	3,419 (1.4)	
30-39 years	190,213	184,233 (96.9)	5,980 (3.1)	
40-49 years	131,712	124,271 (94.4)	7,441 (5.6)	
50-59 years	109,654	101,521 (92.6)	8,133 (7.4)	
60-69 years	99,445	93,861 (94.4)	5,584 (5.6)	
70-79 years	66,834	64,490 (96.5)	2,344 (3.5)	
80-89 years	29,557	28,880 (97.7)	677 (2.3)	
90-99 years	5,781	5,714 (98.8)	67 (1.2)	

although there are regions such as the city of Aleppo where HBV prevalence is 10.6%, HBV in the general population has been reported as 5.62%.[20] The prevalence among Syrian immigrants in our country is 2.4%. The fact that they have a prevalence rate below the prevalence reported from their country can be explained by the fact that their living conditions are better than in the Middle East, that they do not apply for health care applications as quickly and frequently as in their own countries, and that they comply with the cleaning conditions during their stay in our country due to social pressure and traditions.

In our study, as we checked the age groups regarding HBsAg seropositivity, it was seen that the 50-59 age group had the highest rate. Other age groups were shown in Figure 3 in detail. In studies conducted in our country, it has been reported that the age groups 30-39, 41-50, 50-59 and 41-55 have the highest prevalence of HBV.[9,11,12,14] In the study conducted in our province, in which the infectious agents of the Syrian and Turkish populations were compared, the age group with the highest HBV prevalence in Syrians was the age group of 30-39, which is similar to our study.[9] When the world literature was reviewed, it was reported that the median age shifted from 44.1 to 50.2 and from 48.1 to 51.8, respectively, according to the analysis made from two separate health insurance data.[21] According to a large-scale cohort study conducted in Hong Kong, it was observed that the average age, which was 41 in the early 2000s, increased to 55 by 2020.[22] The routine vaccination of children in our country was started in August 1998, which may explain the high positivity in middle and advanced ages. It may also be associated with an increase in transmission during the sexually active period. The median age in the world literature is similar to the age group in our study. The advanced age group, the increasing life expectancy and the vaccination of young populations are compelling in that scene. It seems that HBV will keep its importance in our agenda for a long time, with the number of people infected with hepatitis B infection, to which more than 1.5 million new cases are added annually, and with the current 300 million cases.[23]

Limitations of the study

The main limiting factors in our study were that the transmission routes of HBsAg-positive

patients were not questioned, and the vaccination status was not investigated. In addition, since the university hospital in our province is not affiliated with the Provincial Health Directorate, the data of this center could not be included in the study.

Conclusions

The dissemination of the hepatitis B vaccine, which is currently in use, seems to be the most crucial weapon in the hands of humanity to prevent this infection and the diseases it will cause. Family physicians, the cornerstone of preventive medicine for the hepatitis B vaccine, which has been applied free of charge for more than 20 years in our country, have a lot of work to do in the name of vaccine awareness and persuasion. It seems possible to live our lives without getting this infection when we reinforce the small measures we will take, such as complying with hygiene rules, using disposable or personalised cleaning products, safe transfusion practices, increasing health literacy, paying attention to the personal use of all kinds of devices that come into contact with blood, by popularising vaccination.

Ethical Approval

This study was carried out with the permission of Bursa Health Directorate Scientific Research Commission (protocol number: 00177454797).

Conflict of interest

The authors have no conflicts of interest to declare.

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Authors' Contribution

Study Conception: SM, CD; Study Design: SM, CD; Supervision: SM, CD; Literature Review: SM, CD; Critical Review: SM, CD; Data Collection and/or Processing: SM; Statistical Analysis and/or Data Interpretation: SM; Manuscript preparing: SM.

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Original Article

Biological Agent Use in Behcet's Patients who are Resistant to Conventional Treatments: A Multidisciplinary Retrospective Study

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ABSTRACT

Background Comparing treatment modalities is difficult in Behcet's syndrome, even if tumour necrosis factor-alpha (TNF-α) inhibitors are a treatment option for all involvements resistant to conventional therapy. This study evaluated how different departments dealt with treatment, particularly with TNF-α inhibitors.

Material and Methods The study comprised 111 patients from our Behcet's syndrome cohort who were treated with TNF-α inhibitors between 2010 and 2019. Data on patients were retrieved retrospectively from the rheumatology, ophthalmology, and dermatology clinics' patient records.

Results Patients followed up in rheumatology (n: 40) were classified as Group 1, and patients followed up in ophthalmology (n: 49) and dermatology (n: 5) as Group 2. In Group 1, genital ulcers, erythema nodosum (p=0.009, p=0.003, respectively), lower extremity deep vein thrombosis, arterial aneurysm and neurological involvement were more common (p=0.005, p=0.008, p=0.001, respectively). In Group 2, the use of cyclosporine and interferon-□ before the anti-TNF agent was higher (p<0.001, p<0.001, respectively), and the use of cyclophosphamide were higher in Group 1 (p<0.001). Both groups preferred infliximab, and ocular involvement was the most common reason for starting.

Conclusions While TNF-α inhibitors were chosen equally across departments, conventional medicines, including cyclosporine, cyclophosphamide, and interferon-α, were not. This choice was determined by the departments' experience and the clinical traits that predominated.

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Introduction

Behcet's syndrome (BS) is an inflammatory multisystemic complex disease of unknown aetiology.[1-3] Turkey is the most frequent place in the world, with a prevalence of 420/100.000.[4] The course of the disease is in the form of attacks and remissions. While attacks are more frequent and severe in the early years, as time passes, the attacks become milder, and their frequency decreases.[2]

For treating BS, the main objective is to provide remission by ending acute attacks quickly and maintain remission by preventing attacks. While glucocorticoids are the primary drug in treating acute attacks, colchicine or immunosuppressive drugs such as azathioprine, cyclosporine, cyclophosphamide, and tumour necrosis factor-alpha (TNF-α) inhibitors or immunomodulatory drugs such as interferon-α, thalidomide, and apremilast are used for the maintenance of remission.[5]

Disease involvement types and severity of involvement are primarily considered in drug selection.[6] In the 2018 update of the European League Against Rheumatism (EULAR) recommendations, TNF-α inhibitors have found a role in treatment options of all involvements resistant to conventional treatment.[7]

The studies regarding the medication in BS are highly heterogeneous in terms of the patient population included in the studies, study duration, study design, primary/secondary endpoints, and outcome measures used. Therefore, it is challenging to compare different treatment methods with each other. Another significant limitation of the studies is that the number of patients included in many studies is low. Attacks and periods of well-being, characteristic of the natural course of BS, are among the other factors that cause problems in evaluating the efficacy of drugs.[8] Here, we aimed to evaluate clinical differences and treatment approaches in rheumatology, ophthalmology, and dermatology departments where various involvements are prioritised.

Material and Methods

Patient Selection

Retrospective cohort research was conducted between 2010 and 2019. The study included 111 patients with BS treated with anti-TNF agents and evaluated at least once by all three departments and examined for their own involvement. Additionally, selected patients were those in whom each department began with its anti-TNF agent and monitored by the primary self. The ethics committee reviewed and approved the present study protocol (approval no. 2019-8/14, dated 07.05.2019).

Forty-two patients from the rheumatology department, 64 from the ophthalmology department, and five from the dermatology department were included. Seventeen patients with insufficient data in the system were excluded from the study. Patients who followed up at the rheumatology clinic (n: 40) were classified as Group 1, and patients who followed up in ophthalmology (n: 49) and dermatology (n: 5) clinics were included as Group 2.

Patient Data

Using the patient files and archive records, age, gender, age at diagnosis, smoking, pathergy positivity, presence of human leukocyte antigen B51 (HLA-B51), family history, and medications used were recorded. The organ and system involvement such as mucocutaneous involvement (oral aphthae, genital ulcer, papulopustular lesion, erythema nodosum [EN]) and ocular involvement, musculoskeletal system involvement, neurological system involvement, gastrointestinal system (GIS) involvement, vascular (venous-arterial) involvement were questioned. The medications used before and after the anti-TNF agents were evaluated. It was examined whether anti-TNF agents and corticosteroids could be discontinued, and factors affecting this situation and differences between departments were assessed

Statistical Analysis

Mean, standard deviation, and median values weMean, standard deviation, and median values were used in the descriptive statistics of the data. The distribution of variables was measured using the Kolmogorov-Smirnov test. An independent sample

t-test was used to analyse quantitative independent parametric data and the Mann-Whitney U test for non-parametric data. The Chi-square test analysed the independent qualitative data. Analysis was performed using SPSS 26.0 program. A p-value of <0.05 was considered statistically significant.

Results

There was no difference between the two groups regarding age, age at the time of diagnosis, and duration of diagnosis. The number of female patients in Group 2 was significantly higher than in Group 1 (p=0.05). There was no difference between Groups 1 and 2 in terms of smoking, presence of BS in the family, and HLA-B51 and pathergy positivity (*Table 1*). The period between diagnosis and the onset of the anti-TNF agent was longer in Group 1 but did not show statistical significance (68.35±56.941 vs 59.06±52.116 months, p=0.363, respectively).

Clinically, mucocutaneous, ocular, vascular (venous-arterial), joint, neurological, and GIS involvements were examined separately in both groups. While the rate of mucocutaneous involvement was similar in both groups, genital ulcers and EN were more common in Group 1. The ocular involvement rate was significantly higher in Group 2 than in Group 1 (90.7% vs 50%, respectively; p<0.001), and this difference was also found when examined separately as posterior, anterior, and panuveitis. In vascular involvement, lower extremity deep vein thrombosis (DVT) and arterial aneurysm frequencies were significantly higher in Group 1 than in Group 2 (p=0.005, p=0.008, respectively). There were no patients with Budd-Chiari and intracardiac thrombosis in both group. While no difference was found between the groups in joint involvement, neurological involvement was more frequent in Group 1 (p=0.001). GIS involvement was not found in both groups (*Table 2*).

In addition to the TNF-α inhibitors used, the treatments they obtained before and after the TNF-α inhibitors were also assessed. The use of cyclosporine and interferon-α before TNF-α inhibitors was significantly higher in Group 2 (p<0.001, for both). Cyclophosphamide use was significantly higher in Group 1 (p<0.001). The use of colchicine after TNF-α inhibitors was higher in Group 1 (p=0.001), while cyclosporine use was significantly higher in Group 2 (p=0.004). Corticosteroid use before anti-TNF agents was 90% in Group 1 and 79.6% in Group 2 (p=0.175). Corticosteroid use after TNF-α inhibitors decreased to 60% in Group 1 and 46.2% in Group 2; however, no significant difference was found between the groups regarding corticosteroid discontinuation (p=0.189) (*Table 3*). In Group 1, the continuation rate of anti-TNF agents was 80%, while it was 81.4% in Group 2 (p=0.464).

The most commonly used TNF-α inhibitors in both groups were infliximab and adalimumab, respectively (*Figure 1*). In both groups, ocular involvement was the most common reason for initiating anti-TNF agents (*Figure 2*). When

Table 1. Patients' demographics and disease characteristics.

Variables	Group 1 (n: 40)	Group 2 (n: 54)[a]	P value
Age (years)	38.7±7.5 (40)	36.6±9.2 (35)	0.234[&]
Gender (female)	8 (25)	21 (38)	0.05[*€]
Smoking	12 (30)	16 (29.6)	0.969[€]
The presence of BS in the family	10 (25)	18 (33.3)	0.382[€]
HLAB51 positivity	26 (65)	42 (77.7)	0.171[€]
Pathergy positivity	15 (37.5)	16 (29.6)	0.422[€]
Diagnosis age (years)	28.5±7.7 (27.5)	27.7±9.3 (26.5)	0.674[&]
Disease duration (month)	121.8±60.0 (108)	108.0±60.6 (96)	0.200[¥]
Period between diagnosis and biological start (month)	68.3±56.9 (60)	59.0±52.1 (36)	0.363[¥]

Data were given as n (%) or mean±SD (median).
BS: Behcet's syndrome, HLA-B51: Human leukocyte antigen B51.
[a]Ophthalmology (n: 49) and Dermatology (n: 5), [&]Independent sample t test, [¥]Mann-Whitney U test, [€]Chi-square test.

Table 2. Comparison of the patients in terms of organ involvement.

Involvements	Group 1 (n: 40)	Group 2 (n: 54)[a]	P value[€]
Mucocutaneous (n/%)	40 (100)	51 (94.4)	0.259[α]
Oral aphthae	39 (97.5)	48 (88.8)	0.116
Genital ulcers	30 (75)	26 (48.1)	0.009**
Pseudofoliculitis/acneiform skin lesions	20 (50)	31 (57.4)	0.476
Erythema nodosum	16 (40)	7(12.9)	0.003**
Ocular (n/%)	20 (50)	49 (90.7)	<0.001***
Anterior uveitis	4 (10)	38 (70.3)	<0.001***
Posterior uveitis	7 (17.5)	45 (83.3)	<0.001***
Panuveitis	2 (5)	37 (68.5)	<0.001***
Other[∞]	9 (22.5)	9(16.6)	0.477
Vascular-venous (n/%)	15 (37.5)	4 (7.4)	<0.001***
Superficial thrombophlebitis	4 (10)	2 (3.7)	0.217
Lower extremity deep vein thrombosis	9 (22.5)	2 (3.7)	0.005**
Vena cava inferior	1 (2.5)	0	0.426[α]
Budd Chiari	0	0	-
Vena cava superior	1 (2.5)	0	0.426[α]
Intracardiac thrombosis	0	0	-
Dural sinus thrombosis	2 (5)	0	0.178[α]
Others	0	1 (1.85)	0.574[α]
Vascular-arterial (n/%)	5 (12.5)	1 (1.85)	0.037*
Thrombosis	1 (2.5)	1 (1.85)	1[α]
Aneurysm	5 (12.5)	0	0.008**
Musculoskeletal (n/%)	8 (20)	7 (12.9)	0.357
Neurological (n/%)	12 (30)	3 (5.5)	0.001**
Gastrointestinal (n/%)	0	0	

Data were given as n (%). [a]Ophthalmology (n: 49) and Dermatology (n: 5).
[€]Chi-square test, [α]Fischer-exact test, [∞] Active posterior segment findings outside the uveitis (retinitis, occlusive vasculitis, papillitis, vitritis), posterior segment sequelae outside uveitis (optic atrophy), ptosis, and conjunctivitis.
Group 1→ Retinitis: 4, occlusive vasculitis: 1, papillitis: 1, vitritis: 1, optic atrophy: 1, ptosis: 1.
Group 2→ Retinitis: 2, occlusive vasculitis: 5, periphlebitis: 1, conjunctivitis: 1.
Note: One patient had two simultaneous involvements.

patients with ocular involvement (n: 69, 73.4%) and those without (n: 25, 26.5%) were compared, genital ulcers, venous involvement (p=0.05, p=0.004 chi-square test, respectively), and arterial aneurysm (p= 0.017, Fischer exact test) were more frequent in those without ocular involvement. No statistical significance was found in the parameters compared in patients who continued and discontinued anti-TNF agents. Similarly, no statistical significance was found in the parameters compared between the patients who continued and discontinued corticosteroids.

Discussion

Uveitis, recurrent oral and genital ulcers are the most common clinical manifestation of BS.[2,3] In our study, oral aphthae were the most frequent mucocutaneous manifestations in both groups. However, group 1 had a higher prevalence of genital ulcer and EN. The typical ocular involvement of BS is bilateral non-granulomatous panuveitis and retinal vasculitis.[9,10] In our study, posterior uveitis was more common in both groups. Additionally, groups had similar rates of active posterior segment

Table 1. Comparison of the patients in terms of treatments.

Treatments	Group 1 (n: 40)	Group 2 (n: 54)[a]	P value[€]
Before TNF-α inhibitor			
Colchicine	27 (67.5)	26 (48.1)	0.061
Azathioprine	27 (67.5)	42 (77.7)	0.265
Mycophenolate mofetil	2(5)	7(12.9)	0.195
Methotrexate	2(5)	4(7.4)	0.637
Cyclosporine	8(20)	38 (70.3)	<0.001***
Cyclophosphamide	18 (45)	1(1.85)	<0.001***
Interferon-alpha	1(2.5)	30 (55.5)	<0.001***
Corticosteroids	36 (90)	43 (79.6)	0.175
After TNF-α inhibitor			
Colchicine	23 (57.5)	13 (24)	0.001**
Azathioprine	23 (57.5)	27 (50)	0.471
Mycophenolate mofetil	3(7.5)	4(7.4)	0.987
Cyclosporine	0	10 (18.5)	0.004**
Corticosteroids	24 (60)	25 (46.2)	0.189

Data were given as n (%). [a]Ophthalmology (n: 49) and Dermatology (n: 5).
[€]Chi-square test.

manifestations (retinitis, occlusive vasculitis, papillitis, and vitritis) and posterior segment sequelae (optic atrophy). Retinitis, inflammatory macular infiltrate, and vitritis are associated with poor vision.[11] It is vital to recognise active and sequelae findings in the ocular involvement of BS. Ocular involvement is more common in young male patients and has a more severe course. In female patients, involvement begins at older ages, and the prognosis is better.[12] In our study, the rate of women was significantly higher in Group 2. This observation motivated us to conclude that female patient should also be carefully evaluated for ocular involvement.

According to studies, ocular involvement is associated with pathergy positivity and vascular involvement.[12] While DVT is more likely in ocular involvement, pathergy positivity and ocular involvement are more common in patients with DVT.[13,14] In our study, venous involvement, arterial aneurysm, and genital ulcer were found more frequently in patients without ocular involvement. Similarly, ocular involvement was defined as a separate entity in the study by Tunç et al.[13] Different patient admission patterns and different approaches of clinics may be a reason for this inconsistency. Although uveitis alone is a distinctive finding for BS, patients should be carefully evaluated regarding other involvement. GIS involvement is more frequent in Far Eastern countries, especially in Japan.[15] The same feature is observed in the Korean patient group.[16] GIS involvement is rare in Turkish patients.[17] In our study, there were no patients with GIS involvement in both group. In our study, the rates of lower extremity DVT, arterial aneurysm, and neurological involvement were significantly higher in Group 1 compared to Group 2. Because Group 1 has more vascular and neurological involvement, cyclophosphamide is utilised more frequently, and cyclosporine is used less often.

Treatment for BS is based on the type and severity of involvement.[6] Colchicine appears more effective, especially in cases where the predominant lesion is EN or genital ulcer.[5] The higher use of colchicine after the anti-TNF agent in Group 1 was associated with the higher rate of these involvements. Interferon-α is among the treatment options in the EULAR 2018 update for mucocutaneous, ocular, vascular and joint involvement.[18] Although interferon-α is recommended for mucocutaneous, vascular, and joint involvement, the high preference for interferon-α in the ophthalmology department

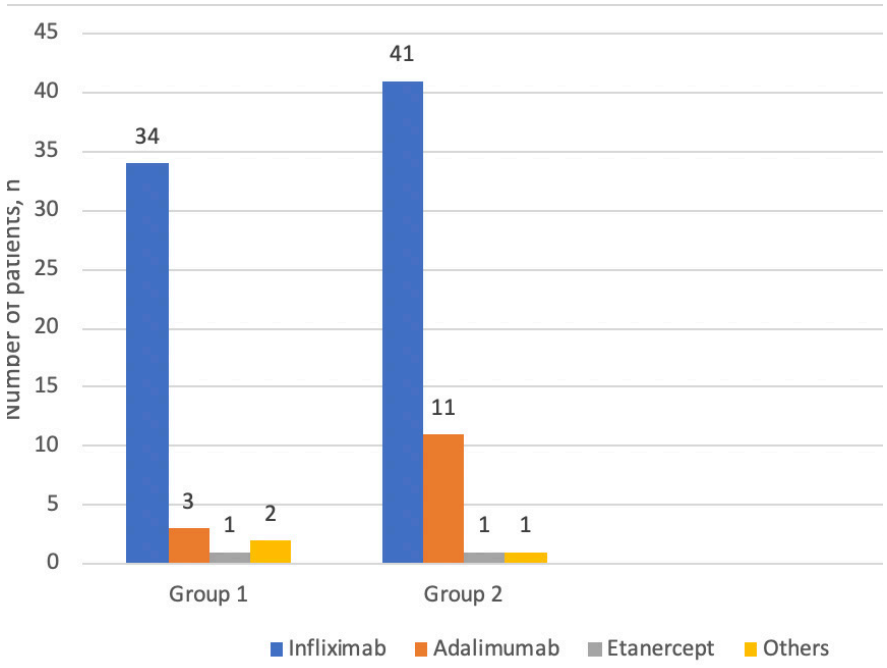

Figure 1. Comparison of TNF-α inhibitors between groups.

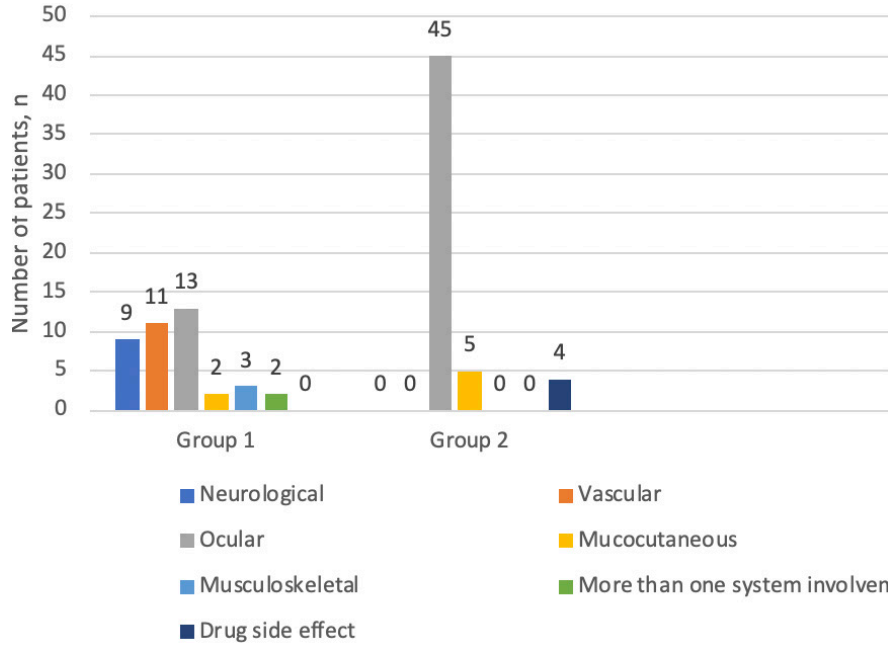

Figure 1. The reasons of initiation of the TNF-α inhibitors.
The order of involvement shown in colour at the bottom and graphic bars is the same from right to left. No patient in group 2 received TNFi for neurologic, vascular, musculoskeletal, or multiple organ involvement.

and the low preference for interferon-α in the rheumatology department in our study suggests that departments' experience may be important in drug selection.

There are no randomised controlled trials on 2nd line agents to be used in patients resistant to conventional therapy in ocular involvement. As there are clinicians who prefer interferon-α first, there are also clinicians who directly switch to anti-TNF agents.[12] In the EULAR 2018 update, although TNF-α inhibitors have found a place in any involvement resistant to conventional treatment, the most common reason for starting anti-TNF agents in our study was ocular involvement in both groups. Many studies have shown the effectiveness and reliability of infliximab[19-21] and adalimumab.[22] Similar to the literature, in our research, the most commonly used anti-TNF agents in both groups were infliximab and adalimumab, respectively.

Our study had some limitations. Our retrospective study and the small number of patients in the dermatology department made it difficult to evaluate the dermatology approach. On the other hand, our research is crucial because it sheds light on prospective studies in which patients were examined by three divisions, allowing for recognising symptom clusters and sharing treatment experiences.

Conclusions

Ocular involvement, a significant cause of morbidity in BS, is the most common reason for initiating TNF-α inhibitors. No difference was found in the agents selected between departments in our study. However, it was observed that there was a difference in the preference for conventional agents such as cyclosporine, cyclophosphamide, and interferon-α. In addition to the difference in the dominant clinical phenotype, it was thought that the departments' experience determined this preference, as it became prominent, especially in the selection of interferon-α. We can better treat BS with collaboration between departments and sharing experiences.

Conflict of interest

The authors have no conflicts of interest to declare.

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Authors' Contribution

Study Conception: BY, SY, HS, GUG, OY, YP; Study Design: BY, BNC, ZKC; Supervision: BY, ED, YP, HS, OY; Literature Review: KFB, KB; Critical Review: All Authors; Data Collection and/or Processing: GUG, SY; Statistical Analysis and/or Data Interpretation: BY, BNC, ZKC; Manuscript preparing: BY.

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Original Article

The Relationship Between the Frequency and Severity of Restless Legs Syndrome and Anemia in Patients With Ankylosing Spondylitis

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ABSTRACT

Background The study aims to determine the frequency of restless legs syndrome (RLS) in patients with ankylosing spondylitis (AS) and the relationship between the International Restless Legs Syndrome Study Group Rating Scale (IRLSSG-RS) score and anemia.

Material and Methods It was a case-control study that included 106 patients with AS and 106 age- and sex-matched healthy controls in the rheumatology clinic of a training and research hospital. The patients were divided into two groups according to their hemoglobin levels. A hemoglobin level lower than 12 g/dL in women and less than 13 g/dL in men was the criterion for anemia.

Results Although the frequency of RLS was higher in AS patients than in control groups, there was no significant difference in the IRLSSG-RS score between AS patients and control groups. 23 (57.5%) of the AS patients with anemia had RLS, and the IRLSSG-RS score was 21.3±5.7. Of the AS patients without anemia, 11 (16.7%) had RLS, and the IRLSSG-RS score was 15±6. Statistically significant differences between AS patients with and without anemia regarding RLS frequency and IRLSSG-RS score were found. The IRLSSG-RS scores of AS patients were negatively correlated with serum iron and hemoglobin level.

Conclusions Patients with AS had a higher RLS frequency than the control group; AS patients with anemia had a higher RLS and IRLSSG-RS score than AS patients without anemia. Also, a negative and significant correlation was found between the IRLSS-RS score and serum iron and hemoglobin levels in AS patients.

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that primarily leads to structural damage and functional limitation involving the axial skeleton and is more common in young adult men (male: female ratio 3-4:1).[1,2]

Anemia of chronic disease (ACD) due to underlying systemic inflammatory reactions, which is related to abnormal iron use, a decline in erythropoietin answer, and reduced red blood cell survival, is normochromic normocytic anemia.[3] The key role of increased liver production of hepcidin which is stimulated by excessive production of inflammatory cytokines, particularly IL-6, has been shown in the pathogenesis of ACD. Hepcidin regulates systemic and cellular iron metabolism, and its increased production reduces the reuse of iron in ACD, typically in macrophages.[4] Although ACD is the second most common type of anemia after iron deficiency anemia, it is most common among patients with chronic disease.[5] In addition to subclinical intestinal inflammation, non-steroidal anti-inflammatory drugs, which can lead to peptic and duodenal ulcers, can cause iron deficiency anemia in AS patients.[6]

Restless legs syndrome (RLS) is a neurological condition characterized by abnormal sensations that occur mainly at rest and at night. RLS primarily affects the legs and rarely the arms.[7] Many studies have found RLS between 2-15% of the healthy population.[8,9] An increased prevalence of RLS has been detected in some rheumatic diseases compared to the general population. Iron deficiency is associated with higher frequency and more severe RLS in various rheumatic diseases.[10,11] In several studies, the frequency of RLS was higher in AS patients than in healthy controls. In another study, iron deficiency anemia was more common in AS patients accompanied by RLS than in healthy controls.[12,13] The study aimed to determine the frequency of RLS in patients with AS and the relationship between the International RLS Study Group Rating Scale (IRLSSG-RS) score and anemia.

Material and Methods

One hundred and six patients who applied to the rheumatology outpatient clinic of Health Sciences University Erzurum Regional Training and Research Hospital and were previously diagnosed with AS according to the modified New York classification criteria14 were included in the study. In the control group, 106 healthy volunteers who applied to our hospital for routine controls were recruited. Patients with diabetes mellitus, other rheumatological diseases, kidney, liver, thyroid diseases, amyloidosis, chronic heart failure, respiratory disease, malignancies, chronic alcoholism, neurological diseases, autoimmune hemolytic anemia, vitamin B12 and folic acid deficiency were excluded from the study. Patients who were pregnant and taking medications that could potentially affect RLS were also excluded from the study. Complete neurological and rheumatological examinations were performed for all participants. The study did not include patients with abnormal neurological examinations, including sensory or motor impairments.

Since RLS can also be seen in patients with polyneuropathy, nerve conduction studies were performed on all patients to exclude the presence of polyneuropathy.

The patients were divided into two groups in terms of hemoglobin levels. The anemia criterion was determined as a hemoglobin level below 12 g/dL in women and 13 g/dL in men.[15]

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the disease activity of AS, was selected as the standard tool used in both daily practice and clinical trials. Patients with a total BASDAI score ≥4 indicate high disease activity.[16] The Turkish version of the Bath Ankylosing Spondylitis Functional Index (BASFI) was used to evaluate functional insufficiency.[17]

According to the criteria of the IRLSSG, the diagnosis of RLS was revised by the IRLSSG in 2014; unpleasant sensation of discomfort in the legs that is usually but not always followed by sudden leg movement, unpleasant sense of discomfort in the legs followed by abrupt movement occurs or worsens during rest or inactivity, this condition improves with movement, e.g. walking or stretching, at least as long as the movement continues, this happens only at night or worse at night than

during the day, which another disease cannot explain.[18] The patient who met all criteria was accepted as RLS. A face-to-face interview with an experienced neurologist determined the presence of RLS.

The severity of RLS was investigated using the IRLSSG-RS.[19] The IRLSSG-RS consists of ten questions linked to symptom severity, impact on daily functions, mood, sleep and symptom intensity and frequency, with a maximum total score of 40 (maximum RLS severity), graded on a 4-point Likert scale. The Clinical Research Ethics Committee of Erzurum Region Training and Research Hospital (decision no:2020/07-85, dated: 06.04.2020), Erzurum, Turkey, approved the study. The patients and the control group provided written, informed consent and the work was carried out by the Declaration of Helsinki.

Statistical Analysis

SPSS Inc.'s for Windows 14.0 (Chicago, IL, USA) Statistical Package for Social Sciences was utilized for statistical analysis. Norm-compliant data were presented as mean, standard deviation, while non-compliant data were presented as mean, standard deviation (median [range]). Categorical variables were presented as number (n) and percentage (%). In independent groups, variables matching the parametric assumptions were evaluated using the t-test and Mann-Whitney U-test, whilst categorical variables were examined using the chi-square test. A Pearson correlation analysis was performed to determine whether the variables were correlated. P-values of 0.05 or lower were considered significant.

Results

The general clinical characteristics of patients with AS and the control group and the medical treatment of patients are shown in Table 1. There was no significant difference between the patient and control groups regarding age, gender, level of iron, folic acid, vitamin B12 and hemoglobin. 34 (32.1%) of 106 AS patients had RLS. However, the frequency of RLS was higher in AS patients than in control groups, with no significant difference in IRLSSG-RS score between AS patients and control groups (*Table 1*). There were no statis-

Table 1. Baseline demographic and characteristics of ankylosing spondylitis patients and control group.

	Patients with AS	Healthy controls	P value
Age (years)†	35.04±7.92	36.49±12.05	0.432
Sex (male/female) n (%)	76 (71.6)/30 (28.4)	74 (69.8)/32 (31.2)	0.945
Hemoglobin (g/dL)†	14.08±1.94	14.09±1.68	0.816
Ferritin (ng/mL)†	80±67.36	46.68±48.17	0.000
Iron (µg/dL)†	65 (19-241)	71 (13-164)	0.761
Folic acid (ng/mL)†	6.77±2.74	6.85±2.82	0.982
Vitamin B12 (pg/mL)†	287.21±63.87	288.28±66.46	0.938
Presence of RLS n (%)	34 (32.1)	11 (10.4)	<0.001
IRLSSG-RS score†	19.3±6.5	17.1±3.1	0.195
Uveitis n (%)	20 (18.9)	-	-
Peripheral joint involvement n (%)	24 (22.6)	-	-
Inflammatory bowel disease n (%)	9 (8.4)	-	-
NSAID n (%)	46 (43.4)	-	-
Biological therapy n (%)	52 (49.1)	-	-
Salazopyrin n (%)	8 (7.5)	-	-

† Mean±standard deviation.
AS: ankylosing spondylitis, RLS: restless legs syndrome, IRLSSG-RS: International Restless Legs Syndrome Study Group Rating, NSAID: non-steroidal anti-inflammatory drug.

Table 2. Clinical characteristics and laboratory values of ankylosing spondylitis patients with and without anemia.

	AS patients with anemia (n: 40)	AS patients without anemia (n: 66)	P value
Age (years)†	36.60±8.48	34.09±7.47	0.045
Sex (male/female) n (%)	25 (62.5)/15 (37.5)	53 (80.3)/13 (19.7)	0.034
Hemoglobin (g/dL)†	12.9±0.73	15,30±1.35	0.000
Ferritin (ng/mL)†	96.8±98.5	70.3±35	0.662
Iron (µg/dL)†	43.3±20.1	96.1±42.7	0.000
Folic acid (ng/mL)†	7.77±3.44	6.17±2.02	0.001
Vitamin B12 (pg/mL)†	292.03±67.74	284.29±61.76	0.865
BASDAI†	5.28±1.77	4.08±2.04	0.008
BASFI†	3.86±2.16	3.18±2.06	0.148
CRP (mg/dL)†	11.08±8.86	7.22±5.25	0.043
ESR (mm/h) †	20.30±13.77	14.59±8.00	0.000
Presence of RLS† n (%)	23 (57.5)	11 (16.7)	<0.001
IRLSSG-RS score†	21.3±5.7	15±6	0.005

† mean±standard deviation.
AS: ankylosing spondylitis, RLS: restless legs syndrome, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, IRLSSG-RS: International Restless Legs Syndrome Study Group Rating Scale.

tically significant differences in serum ferritin, vitamin B12 levels and BASFI between AS patients with and without anemia (*Table 2*). 23 (57.5%) of the AS patients with anemia had RLS, and the IRLSSG-RS score was 21.3±5.7. Of the AS patients without anemia, 11 (16.7%) had RLS, and the IRLSSG-RS score was 15± 6. Statistically significant differences between AS patients with and without anemia were found in terms of RLS frequency and IRLSSG-RS score (*Table 2*). Iron levels were lower in patients with AS with anemia than those without anemia. However, folic acid levels, age of patients, BASDAI, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values were found to be statistically higher (*Table 2*).

In the anemia group of patients with AS, 18 had iron deficiency anemia, and 22 had chronic disease anemia. Ten patients (55.5%) in the iron deficiency anemia group had RLS, 13 patients (59.0%) in the chronic disease anemia group had RLS, and there was no statistically significant difference between these two groups (p=0.376). The IRLSSG-RS score was 15.4 ±10 in the iron deficiency anemia group and 15.7±8.9 in the chronic disease anemia group, with no statistically significant difference (p=0.185).

The IRLSSG-RS scores of AS patients were not correlated with age, CRP, ESR, folic acid level and BASDAI but were negatively correlated with serum iron (*Figure 1*) and hemoglobin level (*Figure 2*) (*Table 3*).

Table 3. Correlation between the IRLSSG-RS severity and age, CRP, ESH, hemoglobin, iron, folic acid, BASDAI in patient with ankylosing spondylitis.

	IRLSSG-RS	
	r	p value
Age	−0.193	0.203
C-reactive protein	0.258	0.141
Erythrocyte sedimentation rate	−0.273	0.118
Hemoglobin	−0.329	0.044
Iron	−0.395	0.007
Folic acid	−0.063	0.680
BASDAI	0.091	0.610

r: Pearson and Spearman's correlation coefficient.
IRLSSG-RS: International Restless Legs Syndrome Study Group Rating Scale, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

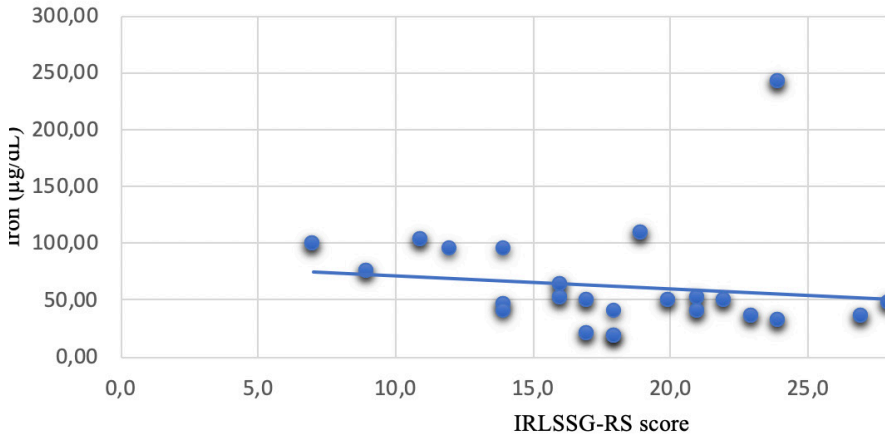

Figure 1. Serum iron level was significantly and negatively correlated with IRLSSG-RS (International Restless Legs Syndrome Study Group Rating Scale) scores.

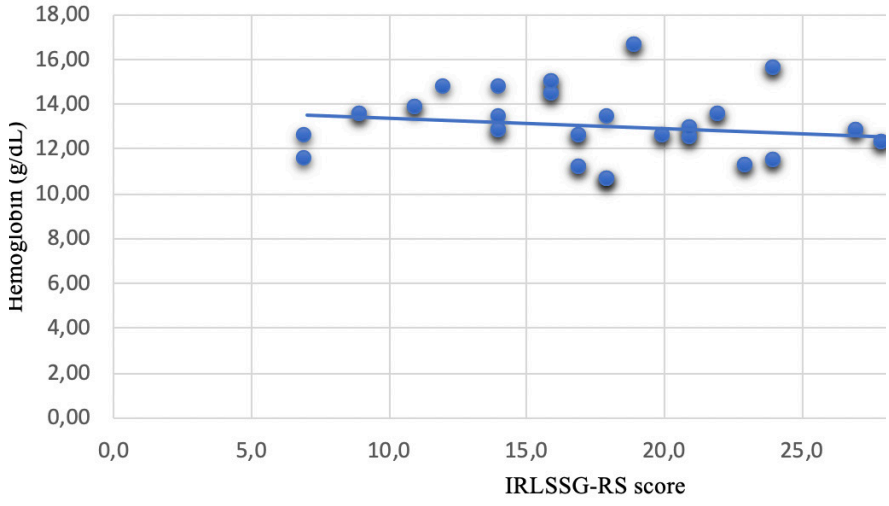

Figure 2. Hemoglobin level was significantly and negatively correlated with IRLSSG-RS (International Restless Legs Syndrome Study Group Rating Scale) scores.

Discussion

Three main findings emerged from this study. Firstly, patients with AS have a higher RLS frequency than the control group. Secondly, AS patients with anemia had RLS more often, and IRLSSG-RS scores were higher than AS patients without anemia. Third, a negative and significant correlation was found between the IRLSS-RS score and serum iron and hemoglobin levels in patients with AS.

Dopaminergic dysfunction is thought to be the underlying cause of the pathophysiology of RLS.[20] Studies have shown that RLS occurs more frequently in patients with rheumatological disorders such as rheumatoid arthritis, scleroderma, Sjogren's syndrome, and fibromyalgia.[21-24] Tekatas and Pamuk[13] and Demirci et al.[12] reported that the frequency of RLS in patients with AS was 30.8% and 36.4%, respectively. We found the frequency of RLS in patients with AS to be 32.1%. The frequency of RLS in healthy people in our control group was 10.4%, and the rates were similar to the frequency in the range of 2-15% determined in the general population.[9,13,25,26]

Several reasons have been suggested for the relationship between AS and RLS. First, long-term use of nonsteroid antiinflammatory drugs for chronic pain conditions is common in patients with AS. It may lead to gastrointestinal blood loss, resulting in higher subclinical iron deficiency.[27] There is also an association between chronic pain and RLS, and it may also be associated with a neurochemical predisposition resulting from chronic pain conditions and an abnormality of the immune system.[28]

Küçük et al.[29] also showed that in patients with systemic lupus erythematosus (SLE), the prevalence of RLS is higher than in the normal population, and anemia appears to be an essential determinant of the presence and severity of RLS in SLE patients. Our study revealed the presence of RLS more frequently in patients with AS compared to the healthy population. There was a negative correlation between hemoglobin and serum iron levels and IRLSS-RS score in AS patients.

This study had several limitations. It had a relatively limited number of patients. The cross-sectional planning of the study is one of the other limitations.

Conclusions

In this study, patients with AS had a higher RLS frequency compared to the control group, AS patients with anemia have a higher RLS and higher IRLSSG-RS score than AS patients without anemia, and also a negative and significant correlation was found between IRLSS-RS score and serum iron and hemoglobin levels in AS patients.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Ethical Approval

For this study, approval was obtained local ethics committee with decision number 2020/07-85.

Authors' Contribution

All authors shared responsibility for the study's conception, literature review, critical review, data processing, statistical analysis, and manuscript preparation.

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Case Report

The Use of Ultrasonography to Guide Diagnosis and Treatment in Resuscitation in a Case of Arrest Due to Pulmonary Embolism

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ABSTRACT

Pulmonary embolism is one of the reversible causes of death. Simultaneous diagnostic procedures are beneficial for successfully resuscitating patients brought to the emergency department as an arrest after pulmonary embolism. Ultrasonography is one of the few diagnostic procedures to be performed on an unstable patient during resuscitation and is a direct guide for treatment. We followed the passage of the thrombus from the inferior vena cava to the right atrium in the ultrasonography performed simultaneously with the resuscitation of the 76-year-old male patient who was brought to the hospital with arrest, and we started thrombolytic therapy simultaneously with resuscitation. Thrombus enlargement was observed in the right atrium. The patient who did not respond to resuscitation died. Although the causes of reversible arrest are known, there may be uncertainties in diagnostic procedures and treatment during resuscitation. Classical resuscitation practice may be insufficient to solve reversible problems such as pulmonary embolism. Although there are reservations about the inclusion of point-of-care ultrasound in resuscitation, it can play a life-saving role.

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Introduction

Rapid diagnosis and treatment decisions are vital during cardiopulmonary resuscitation (CPR). Ultrasonography (USG) is highly valued in life-threatening conditions because of its non-invasive and easily accessible properties. Recent studies have shown that USG can contribute to the management of resuscitation.[1] In addition to traditional methods such as pulse control, auscultation or capnography, USG provides accurate real-time information about cardiac/circulatory, airway and ventilation status in patients undergoing CPR.[1] Massive pulmonary embolism is one of the possible reversible noncardiac causes of cardiac arrest and has a poor prognosis. Targeted cardiac-circulatory ultrasonography (POCUS) can guide rapid diagnosis, treatment and advanced diagnostic tests, especially in patients who are too unstable to undergo computed tomography imaging.[2] Here, we presented a case brought to the emergency department as a cardiac arrest. The passage of a dynamic thrombus from the inferior vena cava to the right atrium was detected in bedside USG.

Case Report

A 76-year-old male patient was brought to the unconscious emergency room by his family. Cardiopulmonary resuscitation was started in the patient whose pulse was not detected on examination and who did not have spontaneous respiration. POCUS was applied at the 5th minute when we received a temporary pulse during the intervention. Since there was no need for cardiopulmonary resuscitation during this application, there was no disruption. Subsequently, the patient recovered, and the intervention was resumed. POCUS was not performed during CPR. During resuscitation, blood gas pH was 7.18, pCO2 64 mmHg, pO2 55 mmHg, bicarbonate 19.5 mmol/L, lactate 6.33 mmol/L, potassium 4.72 mg/dL, and glucose 121 mg/dL. Reversible arrest etiologies were investigated in the patient. Echocardiography showed enlargement of the right atrium and right ventricle simultaneously with targeted resuscitation. The micro convex (cardiac) probe was used in the POCUS application. In addition, a thrombus was seen in the right ventricle and right atrium and extending to the inferior vena cava. Tissue plasminogen activator therapy was started during resuscitation. The patient was thought to have developed cardiac arrest due to a massive pulmonary embolism. Despite thrombolytic treatment, thrombus continued to be observed on echocardiography. The patient whose spontaneous circulation could not be achieved despite adequate cardiopulmonary resuscitation for 45 minutes was considered dead.

Discussion

In high-risk pulmonary embolism cases, 90% of cardiac arrests occur within 1-2 hours after the onset of symptoms.[3] Therefore, most of these patients will require cardiopulmonary resuscitation long before any attempt to diagnose the cause of cardiac arrest. In most cases, the diagnosis is made at autopsy after failed resuscitation. The mechanism of cardiac arrest due to pulmonary embolism is based on pulmonary main flow obstruction and increased right ventricular afterload due to the release of vasoconstrictive mediators from the thrombus. The right atrial pressure rises when right ventricular failure develops, and cardiogenic shock develops. Overloading of the right ventricle causes the ventricular septum to shift to the left, resulting in decreased left ventricular diastolic filling and end-diastolic volume. Thus, circulatory failure and cardiac arrest occur with a profound decrease in left ventricular preload.[4] In this case, a massive pulmonary embolism was quickly diagnosed by bedside ultrasonography. However, although thrombolytic therapy was started immediately, the patient died. Treatments such as thrombolysis or surgical embolectomy are assumed to reduce mortality in cardiac arrest due to thrombosis. Both methods can be used alone or in combination therapy for ongoing cardiopulmonary resuscitation. In cases where rapid treatment decision is required, possible causes of cardiac arrest such as pulmonary embolism, myocardial infarction and cardiac tamponade and reversible causes such as hypovolemia can be detected noninvasively and quickly with targeted ultrasonography. Thus, it can provide timely administration of effective treatments such as thrombolytic therapy or mechanical embolectomy, coronary intervention, pericardiocentesis and

fluid resuscitation.[1] The major controversy regarding the use of USG during resuscitation is the concern that it delays chest compressions and prolongs the interval between compressions.[5] To maintain the quality of chest compressions found beneficial to develop the ultrasound protocol To maintain the quality of chest compressions, it has been found beneficial to develop the ultrasound protocol and to assign an experienced ultrasound person to the resuscitation team only for marking.[6] An emergency medicine specialist, who has been practising ultrasonography for five years, made the POCUS application. The Turkish Emergency Medicine Association implemented a certified-trainer emergency medicine specialist.

Concluisons

As a result, this case revealed the importance of ultrasound application that guides diagnosis and treatment simultaneously with resuscitation. Simultaneous USG with the examination should be considered in medical applications.

Conflict of Interests

The author declare that there is no conflict of interest about this manuscript.

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Authors' Contribution

Literature Review, Critical Review, and Manuscript preparing held by author.

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Case Report

An Unusual Association of Folic Acid Deficiency with Gastric Neuroendocrine Tumor Type I

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ABSTRACT

The association of gastric neuroendocrine tumour type I with macrocytic anaemia due to vitamin B12 deficiency is commonly encountered. For the subsequent treatment guidance, the etiological cause of macrocytic anaemia must always be precisely established. We presented the case of a 63-year-old patient admitted for marked physical asthenia, palpitations, abdominal pain, flatulence, paresthesia in the upper and lower limbs and concentration difficulties. Clinical examination revealed pale, dry skin, Hunter's glossitis, and tachycardic heart sounds. Bloodwork showed pancytopenia with macrocytic normochromic anaemia, vitamin B12 within normal limits, but with low folic acid levels. The reticulocyte crisis was documented on day 3 after initiating folic acid treatment. Exploration by upper digestive endoscopy and colonoscopy described multiple polypoid tumours in the greater curvature of the stomach. The histopathological and immunohistochemical examination lead to the diagnosis of gastric neuroendocrine tumours (NET) type G1. To our knowledge, there are no reports in the literature about an association of this type of tumour with folate deficiency-induced anaemia.

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Introduction

Gastric neuroendocrine tumours (G-NET) type 1 are often accidentally diagnosed after a biopsy of gastric polyps. They are found during endoscopy performed to explore macrocytic anaemia due to vitamin B12 deficiency or pernicious anaemia, which is currently associated with G-NET type 1. This type which characterizes our patient is found in 70-80% of cases in women aged 50-60.[1] It arises on the background of chronic atrophic gastritis (CAD), the parietal cells being unable to secrete gastric acid. CAD represents the common cause for both folate deficiency and G-NET type 1. It is an inflammatory condition in which the gastric glandular structures are replaced by glandular structures inappropriate for the location or by connective tissue. The most frequent etiologies of CAD described in the literature are chronic infection with Helicobacter pylori and autoimmune gastritis.[2]

We presented a unique combination of G-NET type 1 with macrocytic anaemia due to folic acid deficiency, with vitamin B12 values within normal limits, in the case of a 63-year-old patient who was admitted for palpitations, marked physical asthenia, abdominal pain, paresthesia in the upper and lower limbs and concentration difficulties. Histopathological examination of samples taken from upper digestive endoscopy revealed G-NET type 1. Contrary to our expectations, it was determined that the symptoms of macrocytic anaemia were not due to vitamin B12 deficiency but to folic acid deficiency.

Case Report

A 63-year-old woman was admitted to the emergency department for palpitations, marked physical asthenia, retrosternal chest pain relieved by rest, lasting about 3-4 minutes, dyspnea, productive mucopurulent cough, abdominal pain in the hypogastrium, loss of appetite, headache and vertigo, concentration difficulties, paresthesia in the fingers of the upper and lower limbs, constipation, flatulence, symptoms that have worsened in the week before hospital admission. The patient's medical history revealed smoking (0.3 pack year) and chronic alcoholism (75 g pure alcohol/day). She had no regular treatment at home. The patient declared she knew about her anaemia and sinus tachycardia for about 40 years but showed no medical records. The RT-PCR test excluded SARS-COV2 infection upon admission.

Clinical examination revealed an underweight patient (a body mass index of 16.94 kg/m^2) with pale and dry skin, Hunter glossitis, total edentation, tachycardic heart sounds 106 beats/min, a blood pressure of 99/57 mmHg, rhonchi at the right basal hemithorax, SpO_2 98% in room air, tenderness on palpation in the hypogastrium. Bloodwork showed leukopenia (GA: 2020/mm^3), macrocytic normochromic anemia (hemoglobin 5.3 g/dL), FEV 143.5/fL, folic acid 1.7 ng/mL (reference range 3.1-20.5 ng/mL), vitamin B12 221 pg/mL (reference range 187-883 pg/mL), thrombocytopenia (53,000/mm^3), nonspecific inflammatory syndrome (CRP 3.5 mg/dL, ferritin 92 ng/mL), hypoproteinemia (total proteins 5 g/dL) with hypoalbuminemia (albumin 3.06 g/dL) in context of poor diet due to total edentation, protein electrophoresis within normal limits, elevated NT-proBNP (1,246 pg/mL), cholestasis syndrome (GGT 345 U/L, total bilirubin 1.68 mg/dL, direct bilirubin 1.20 mg/dL), hyperuricemia (uric acid 6.3 mg/dL), pathological urinalysis test, but with negative urine culture, and negative

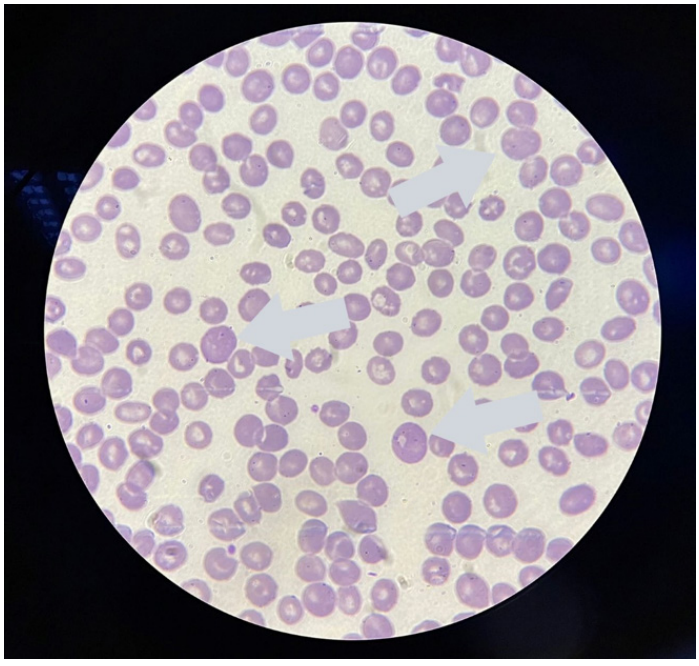

Figure 1. Peripheral blood smear: microscopic aspect in HE stain x100 immersion objective (with a drop of cedar oil) – anisocytosis: normo- and macrocytes (arrows).

blood culture. A peripheral blood smear showed anisocytosis with macrocytosis (place for *Figure 1*). The thyroid function and markers for viral hepatitis, CEA and CA 19-9 were within normal limits. Microbiological examination and sputum culture revealed infection with beta-lactamase-producing *Neisseria meningitides* and *Streptococcus pneumonia*. Antibiotic treatment was initiated with amoxicillin and clavulanic acid 1.2 g every 8 hours, combined with gentamicin 160 mg every 24 hours for seven days, with favourable evolution of respiratory symptoms.

ECG upon admission showed sinus tachycardia, with repolarization changes (negative T waves in V2-V5, DII, and flattened T waves in V6, DIII, aVF, aVL). Cardiac enzymes were normal, thus ruling out an acute event. The echocardiographic examination described normal-sized heart cavities without kinetic alterations, thrombus, or pericardial fluid.

Thus, we interpreted the anaemia as due to folic acid deficiency. Because of its severity, we did not repeatedly delay the treatment to measure vitamin B12 levels. The diagnosis was further supported by the reticulocyte crisis documented 3 days after the initiation of folic acid treatment with a dose of 15 mg per day (reticulocytes increased from baseline 40,000/mm^3 to 250,000/mm^3).

The abdominal ultrasound examination revealed an enlarged, hyperreflective liver (right hepatic lobe 162 mm and left hepatic lobe 57 mm) with a fine granular surface, without macro nodules; vascular dilatations on the topography of the round ligament up to 6 mm; rectum with thickened walls, rectilinear, layered, apparently regular, about 13 mm thick; portal vein with normal diameter; spleen with bipolar diameter 113 mm, homogenous structure; perihepatic fluid - 15 mm thick, perisplenic - 14 mm, fluid in hypogastrium containing fibrin septa, vesicouterine fluid - 30

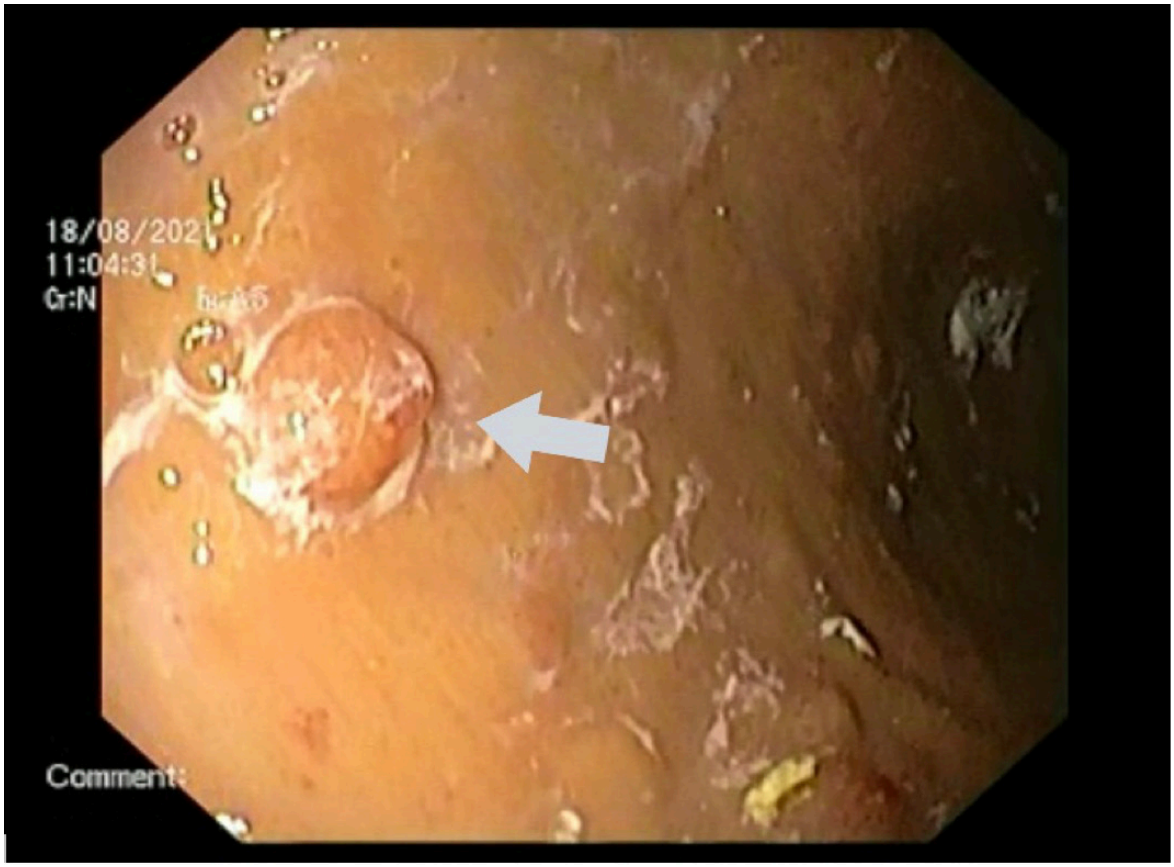

Figure 2. Upper digestive endoscopy: atrophic gastritis, sessile polyp (arrow).

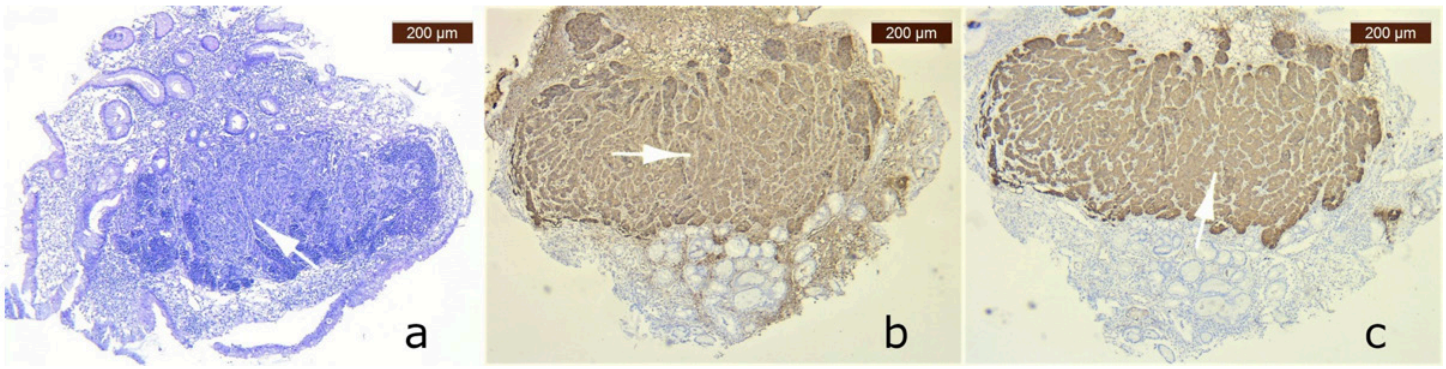

Figure 3. Polyp biopsy: histological aspect in: HE stain x50 - Tumor isle (arrow) with round and prismatic cells, hyperchromic nuclei and pale eosinophilic cytoplasma (a); immunohistochemical tests for Chromogranin A x50 (b) and Synaptophysin x50 (c).

mm, fluid in the pouch of Douglas - 20 mm, right pleural fluid - 39 mm. The upper digestive endoscopy revealed a small sliding hiatal hernia, Schatzki ring, atrophic gastritis, friable gastric mucosa, bleeding easily when touched; 4 sessile polyps (Paris Is) on the great curvature of the stomach, which were biopsied (place for *Figure 2*). Exploration of the large bowel by colonoscopy did not show any abnormalities.

The biopsy showed the absence of mitoses and the Ki-67 index <1%. Alcian blue stain showed goblet cells and sustained complete type intestinal metaplasia. Immunohistochemical tests for chromogranin A and synaptophysin showed diffuse positivity in the majority of the tumour cells and the neuroendocrine cells from the adjacent mucosa, highlighting neuroendocrine cells' hyperplasia foci. It concluded that the morphological and immunohistochemical aspects correspond to a multifocal gastric neuroendocrine tumour type 1 (G1) with neuroendocrine cell hyperplasia (place for *Figure 3* and *Figure 4*).

The paraclinical examination showed normal ESR, gamma globulins and transaminase levels, no signs of hepatocellular insufficiency (normal coagulation profile), except a low albumin level and total proteins, interpreted as secondary to the patient's dental problems, and elevated levels of total and direct bilirubin. There were no signs of portal hypertension (absent oesophagal varices in upper digestive endoscopy, normal diameter of inferior vena cava, portal vein and spleen at abdominal ultrasound), which, combined with the paraclinical profile, reduced the probability of a diagnosis of hepatic cirrhosis. However, we do not exclude chronic alcoholic liver disease. Upon discharge, the patient was scheduled for an endocrinology consultation and was recommended specific blood tests to rule out celiac disease to expand the investigation and start the specialized treatment, but the patient didn't comply.

Discussion

G-NETs originate in stomach enterochromaffin-like (ECL) cells, which regulate gastric acid production. They represent less than 1% of stomach neoplasms but still constitute ¼ of all gastro-pancreatic neuroendocrine tumours and 10-30% of all NETs, with an incidence of 0.002-0.1 per 100,000 population per year.[1] Most G-NETs are accidentally diagnosed by anatomopathological examination of polyps identified during upper digestive endoscopy. These represent 0.6-2% of the identified and biopsied gastric polyps.[1]

According to the gastro-pancreatic NET classification systems proposed by ENETS, NANETS and WHO 2019, they are histologically divided into low (G1), intermediate (G2) and high (G3) grades. This classification is based on the rate of cell proliferation (mitosis rate, Ki-67 index) as followed: G1 – <2 mitoses/2 mm^2, Ki-67 index <3%; G2 – 2-20 mitoses/2 mm^2, Ki-67 index 3-20%; G3 – >20 mitoses/2 mm^2, Ki-67 index >20%.[3] G-NETs are also subclassified into type

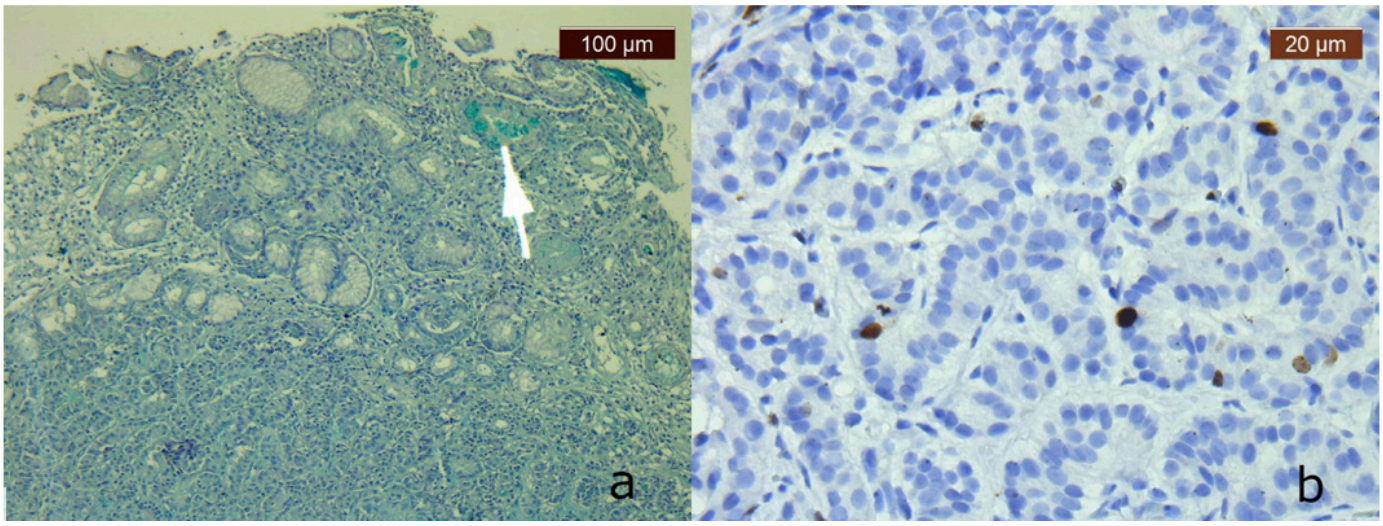

Figure 4. Polyp biopsy: histological aspect in: Alcian blue stain x 100 –goblet cells stained in light blue (arrow (a); Ki-67 immunostaining x400 –positive in less than 1% of the tumor cells in the most active area (b).

1 (occurs on the background of atrophic gastritis type A, is the most common), type 2 (occurs on the background of Zollinger-Ellison syndrome or in MEN I) and type 3 (sporadic).[1]

Type 1, described in the case of our patient, is represented by non-secreting tumours, most commonly asymptomatic, but which can ulcerate and thus lead to bleeding and secondary anaemia.[5] This type arises on the background of chronic atrophic gastritis, leading to hyperplasia of gastric antral G cells and consecutive hypergastrinemia. Gastrin binds to the colecystokinin2 (CCK-2) receptor on the ECL cells, determining hyperplasia and subsequently the development of G-NET type 1.[2,4] Also, the destruction of parietal cells in the long-term evolution of atrophic gastritis can lead to decreased intrinsic factor secretion and, consequently, decreased absorption of vitamin B12. Thus, vitamin B12 deficiency and macrocytic hyperchromic anaemia are frequently associated with autoimmune gastritis and hypergastrinemia, but only 5% of people with chronic atrophic gastritis develop G-NET.[1,6]

In our case, it was impossible to determine serum intrinsic factor and gastrin levels to characterize the detected macrocytic anaemia completely. The symptoms presented upon admission and the anaemic syndrome detected place the patient in the clinical-paraclinical description typical to G-NET type 1. One of the particularities of this case was the low values of folic acid and normal values of vitamin B12 level. Folate absorption is mainly influenced when transported across the intestinal wall. This process is pH dependent and is optimal at low pH. In the case of achlorhydria, found in CAD, the gastric pH is elevated above the level necessary for folate to be absorbed, thus leading to folate deficiency and macrocytic anaemia.[7]

The diagnosis of folate deficiency anaemia was based in our case on the clinical symptoms and signs, the low acid folic levels and the reticulocytes crisis documented after three days from folic acid administration. Optimally, the differential diagnosis between folate and vitamin B12 deficiency is based on serum homocysteine, methylmalonic acid, intrinsic factor and anti-parietal cell antibodies levels, but we could not perform these tests in our hospital due to technical difficulties during the patient's hospitalization.

As stated earlier, CAD represents the common cause of folate deficiency and G-NET type 1. On the other hand, we cannot exclude the coincidental association between macrocytic anaemia due to folate deficiency and G-NET type 1 described in our case. Our patient presented a history

of chronic alcoholism and was underweight, suggesting poor folate intake. Both conditions can cause folate deficiency. G-NET type 1 is found most commonly in the gastric fundus, having a polypoid appearance in 78% of cases and a small size (5-8 mm).[8] The peculiarity of the presented case is the location of the neuroendocrine tumour on the great curvature of the stomach.

As stated in the 2021 NCCN guidelines, the optimal strategy for G-NET type 1 is endoscopic resection in prominent tumours. However, it does not provide a limit value for the tumour size that defines the notion of "prominent" and according to which the decision of resection should be taken.[9] According to the NCCN guidelines from 2015, our patient falls into the category of "multiple tumours under 2 cm", with the recommendation to monitor the evolution or to resect the tumour and the adjacent mucosa. The guideline recommends clinical-paraclinical and endoscopic re-evaluations every 6-12 months in the first three years, then annually (if no changes are observed), and imaging when the clinical examination indicates it. In the event of new lesions or an increase in the size of existing tumours, an antrectomy is recommended to remove the source of gastrin secretion.[10] The ENETS 2016 guidelines recommend using conservative treatment strategies in the case of small G-NETs type 1, as the risk of metastasis of this type is small and directly related to the tumour size (the cut-off value being 10 mm). Thus, the recommendation of endoscopic mucosal resection or dissection of the submucosa is made in the case of 10 mm or greater tumours.[11]

Regarding folic acid deficiency anaemia, the recommended dose for treatment is 5 mg per day of folic acid for four months. The patient also needs further investigation to rule out possible celiac disease.[12] The best serological screening tools for this diagnosis are the determination of IgA anti-tissue transglutaminase and IgA anti-endomysial.[13] As we could not perform during hospitalization due to technical problems, we recommended the patient undergo them upon discharge. However, the patient didn't experience typical symptoms of Celiac disease. The patient did not comply with the recommendations and failed to return for a scheduled checkup one month after discharge.

Type 1 G-NET has a very good prognosis and a 5-year survival rate of 95%.[14] Due to the low potential of metastasis, this type is considered benign, with only three deaths due to evolution to secondary lesions in 724 cases evaluated.[15] However, we must not ignore the potential of this type of tumour to progress to a malignant lesion. For instance, in 2012, Spampatti and co-workers described a case of G-NET type 1 with an unusually aggressive evolution, resulting in death, in the case of a 60-year-old patient with type 2 diabetes and pernicious anaemia.[15] The reason for G-NET type 1 recurrence, with a median recurrence of 24 months and a 3% rate of transformation into poorly differentiated G3 neuroendocrine carcinoma, is the persistence of gastric hypersecretion at the antral level.[1]

Concluisons

When evaluating a case of chronic megaloblastic anaemia, we should not forget this rare association with G-NETs. They can perpetuate the anaemia through ulceration and bleeding. There is also the risk, even in sporadic cases, for them to evolve into a malignant lesion, thus changing the patient's prognosis. The most commonly known is the association of gastric neuroendocrine tumour type I with macrocytic anaemia due to vitamin B12 deficiency. To our knowledge, there are no reports in the literature about an association of this type of tumour with folate deficiency-induced anaemia. Therefore we consider the publication of this case to help our colleagues.

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Conflict of Interests

The authors declare that they have no conflict of interest.

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Informed Consent

Written consent was obtained from the patient.

Authors' Contribution

Literature Review, Critical Review, Manuscript preparing held by all authors.

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Case Report

Nursing Management of the Patient Developing Quadriplegia Due to Neurological Involvement After COVID-19: A Case Report

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ABSTRACT

COVID-19 first emerged in China, spread quickly, and was declared a pandemic by the World Health Organization. Neurological complications have led to important symptoms in patients diagnosed with COVID-19. These symptoms have substantially affected patients' quality of life, caused them to depend on others, and prolonged their recovery processes with anxiety and hopelessness. In this case report, the care process applied to an individual who developed quadriplegia due to neurological involvement after COVID-19, according to the "Nursing Model Based on Activities of Living", is shared. With effective evidence-based nursing care, the patient's quality of life was improved, existing problems were alleviated, and the patient was protected against complications.

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Introduction

COVID-19 emerged in Wuhan, China, in December 2019 when a person exhibited symptoms in the seafood market, resulting in a severe pandemic spreading rapidly.[1] After the first positive case was revealed in our country in March 2020, the World Health Organization declared COVID-19 a pandemic. The spread of COVID-19 through droplets has been the most critical factor in increasing the rate of spread. The infection can be spread by pre-symptomatic or asymptomatic carriers who do not show symptoms. The average time elapsed after illness until the beginning of the symptoms is five days.[2] While the most common symptoms are cough, weakness, joint pain, high fever, shortness of breath, respiratory failure, and acute respiratory failure may develop in advanced cases of COVID-19.[3] It is reported that COVID-19 adversely affects the respiratory and nervous systems, can lead to central nervous system involvement through the ACE2 receptor, and coronavirus nucleic acid is seen in the cerebrospinal fluid.[4] The neurological symptoms include headache, change in consciousness, vertigo, inability to smell and paresthesia, and even symptoms similar to Guillain-Barré syndrome.[5] Muscle-joint pain and weakness are described due to the affected skeletal muscle, and the increased serum creatine kinase (CK) level is noteworthy.[6] Moreover, COVID-19 is thought to trigger many neuromuscular diseases through the genetic or immune system or cause the progression of the existing neuromuscular disease.[7] In neurological symptoms occurring in COVID-19 infection, a multidisciplinary approach should be adopted.

This case report was prepared to classify the basic nursing care needs of the patient, who was conscious, in need of care and admitted to the palliative care clinic with quadriplegia developing after COVID-19 infection, according to the "Nursing Model Based on Activities of Living" (NMBAL), to specify nursing diagnoses and evidence-based nursing interventions, and to present them in the nursing care plan.

Case Report

A 42-year-old male patient received treatment for complications related to COVID-19 infection for 1.5 years. The patient, who was infected with COVID-19 in 2020, received symptomatic COVID-19 therapy in the hospital for four days. During the treatment, his general condition was good; he had no complaints other than weakness, tingling in his feet and mild loss of sensation and was discharged at the end of 4 days. Loss of sense increased in the feet of the patient, who continued to work for 15 days, and urinary incontinence started in the following days. No pathology was observed in the electroneuromyography screening performed on the patient, who presented to the neurology outpatient clinic with these complaints. However, he was admitted to the neurology ward for follow-up. The patient, who started to experience weakness and loss of sensation in the upper extremities within two days, became immobile after developing quadriplegia on the third day and underwent plasmapheresis. During this period, the patient had no problems with the respiratory system, and no pathological condition was observed in the laboratory tests. A cervical lesion was detected in the patient who underwent cervical magnetic resonance imaging (MRI), but no pathological formation was encountered due to the biopsy. The individual was followed up in the neurology ward as a person with quadriplegia and an immobilised patient for about one month and referred to another hospital outside the province for advanced physical therapy and rehabilitation. In the third week of the treatment in the referral hospital, a pulmonary embolism occurred due to respiratory distress, chest pain and loss of consciousness. Cardiopulmonary resuscitation (CPR) was applied to the patient who had a cardiac arrest during the embolectomy procedure. He continued to receive treatment in the intensive care unit for approximately one week. After the treatment, the patient was referred to the intensive care unit of the province where he lived upon his request. After receiving treatment for about two weeks, the patient was admitted to the palliative care clinic. The patient was hospitalised in the clinic and given basic physical therapy exercises, medical treatment and nursing care for six months. Upon his request, he was referred to a hospital in

another province after he gained partial strength in his extremities and his clinical condition improved to a certain extent.

Care Plan According to the Nursing Model Based on Activities of Living

The patient's problems were determined according to the Nursing Model Based on Activities of Living.[8,9] They are also presented in detail in Table 1.

Table 1. Identification of descriptive characteristics according to the NMBAL

Activities of Living	Descriptive Characteristics/Signs and Symptoms	Nursing Diagnosis
Maintaining a safe environment	Loss of function in the extremities caused by neurological involvement, dependence on in-bed movement, weakness Frequent urinary catheter change, neurogenic bladder, invasive procedures	Risk of injury Risk of infection
Communication	Inability to accept the disease, having to receive treatment for a long time, being away from the family and work, fear of death	Anxiety
Respiration	Permanent dysfunction in the right lung following the embolectomy procedure	Ineffective respiratory pattern
Nutrition	No problem	
Excretion	Neurological involvement, inactivity and stress	Constipation
Individual cleaning and dressing	Dependence on the family in personal care, lying down continuously without moving, and weight gain	Risk of deterioration in skin integrity
Control of body temperature	Hyperthermia due to urinary tract infections (38.3 °C), reproduction in urine culture	Risk of infection
Movement	Immobility caused by quadriplegia, weakness in extremities, and loss of function Involuntary contractions in different muscle groups caused by neurological involvement and intense physical exercises	Impairment of physical movement acute pain
Work and entertainment	Inability to work, the transition from active social life to the dependent isolated life	Ineffective role performance
Expressing sexuality	No problem	
Sleep and rest	No problem	
Death	Uncertainties about the disease process, extremely slow progress of the recovery process, and fear of not being able to be the same as before	Hopelessness

Maintaining A Safe Environment

Nursing diagnosis 1: "Risk of injury" due to loss of function in the extremities caused by neurological involvement, dependence on in-bed movement, and weakness.

Aim: Non-occurrence of physical trauma and injury in the patient.

Nursing interventions

1. The patient is oriented to the environment during hospitalisation (introduction of the ward and the room, use of the call bell, etc.), and the fall risk is identified using the ITAKI Fall Risk Scale.
2. Safety measures are taken while mobilising the patient. Safety of the patient's room and bed surroundings is ensured.
3. The patient bed is set to the lowest level. The patient's cabinet/shelves are placed near the bed so that he can easily reach the items he may need.
4. The bed barriers are fixed while the patient is lying down.
5. To ensure patient safety, at least two people accompany him during care delivery.
6. It is ensured that the valuable equipment (wheelchair) used by the patient during mobilisation is intact. It is necessary to make sure that equipment is safe to be used for the patient.
7. Since high-dose anticoagulant drugs may increase bleeding during trauma, sharp objects are kept away from the patient, and unnecessary invasive procedures are avoided.

Evaluation: The patient's safety was ensured during treatment, and no injury occurred. The fall risk was determined as "high."

Nursing diagnosis 2: "Infection risk" due to frequent urinary catheter change, neurogenic bladder, and invasive procedures.

Aim: Decrease in signs and symptoms of infection in the patient.

Nursing interventions:

1. The patient is encouraged to take 2-3 litres of fluid daily.
2. Urinary retention and negative conditions caused by the urinary catheter are evaluated by following up on what the patient has taken and excreted during the day.
3. Patient caregivers are trained in perineum care and hand hygiene.
4. Laboratory findings are evaluated (urinary analysis, such as hematuria, pyuria, and amount of bacteria in urine, causing microorganisms with urine culture).
5. Attention is paid to aseptic techniques during urinary catheter insertion.
6. Signs and symptoms of urinary tract infection (such as pain in the lower abdomen, burning, blurred urine colour, and sharp odour of the urine) are followed up.
7. Attention is paid to the administration times of the ordered antibiotic (IV cephalosporin), and the effectiveness of the treatment is checked.

*Evaluation:*The frequency of recurring urinary tract infections decreased gradually in the first 1-1.5 months of treatment, and urinary tract infections did not develop in the last 3-4 months. The patient's intake and excretion were approximately +250 mL in 24 hours.

Communication

Nursing diagnosis 3: "Anxiety" due to the inability to accept the disease, having to receive treatment for a long time, being away from the family and work, and fearing death.

Aim: Not observing the signs and symptoms of anxiety and the patient's ability to use coping methods effectively.

Nursing interventions:

1. The patient is accompanied during his acute, stressful period and not left alone.
2. All treatment methods are explained to the patient, and his questions are answered.
3. Care is delivered in a calm, supportive, and safe manner.
4. The patient's justification is accepted, not disputed, and he can express 124 his thoughts without being judged.
5. Unnecessary assurances are avoided since they may increase the patient's concerns.
6. Interview is planned with the spiritual support unit of the hospital, providing active services and followed up.
7. Depending on the doctor's request, sedative drugs are given, and their effectiveness is checked during distress.
8. His relationships with other anxious patients are limited.

9. The patient is taught relaxation exercises and assisted in doing them.

10. Information is given about reducing nervousness, such as music.

Evaluation: The patient reported that his level of anxiety decreased significantly compared to the past, and his level of coping increased.

Respiration

Nursing diagnosis 4: "Ineffective respiratory pattern" due to permanent dysfunction in the right lung following the embolectomy procedure.

Aim: Ensuring that the patient breathes effectively and adequately.

Nursing interventions:

1. The patient's respiratory rate and blood oxygen saturation (SpO2) value are measured during the day, and the doctor is informed about changes related to the respiratory parameter.

2. The patient is given deep breathing and coughing exercises. If necessary, respiratory physiotherapy is provided.

3. The importance of the TriFlo exercise is explained, and the patient is helped to do the exercise.

4. The patient is enabled to lie down in Semi-147 Fowler's/Fowler's position.

5. Lung sounds are checked during the day, and the doctor is informed in case of a negative situation.

6. Tapotement is performed and taught to the patient and the patient's relatives. They are told to perform it when secretion increases.

7. The patient is recommended not to be in an environment with air pollution. The room is ventilated frequently, and the patient is kept away from damp and humid environments.

8. It is ensured that the patient does not use tobacco derivative products such as cigarettes.

Evaluation: No respiratory distress was observed in the patient who regularly performed TriFlo exercise 3 times a day. In his vital follow-up, the patient's SpO2 value was 95-96%, and his respiratory rate was 20-21 per minute.

Excretion

Nursing diagnosis 5: "Constipation" due to neurological involvement, inactivity, and stress.

Aim: Regular excretion of the patient.

Nursing interventions:

1. Distension, pain in the abdomen, and defecation are questioned and written on the daily follow-up form.

2. The mobility of the patient is increased within his in-bed capacity.

3. If not contraindicated, fluid intake is increased, and the patient is given fibrous foods during the day (such as fresh fruits, vegetables, and cereals).

4. Current drugs (such as those that cause constipation) are checked.

5. The patient is warned about consuming beverages such as soda, coffee and tea, which cause loss of fluid in the body.

6. The patient is informed about eating regularly, not skipping meals, 170 and eating slowly.

7. The patient and his relatives are taught abdominal exercises and massage, which help accelerate bowel movements.

8. Non-narcotic analgesics are preferred in pain control.

9. Patient privacy is given importance during bottom cleaning.

Evaluation: It was observed that the defecation frequency of the patient, whose defecation frequency was once a week before the nursing interventions, increased to 3 times a week after the interventions.

Individual Cleaning and Dressing

Nursing diagnosis 6: "Risk of deterioration in skin integrity" due to dependence on the family in personal care, lying down continuously without moving, and weight gain.

Aim: Identification of factors that may lead to pressure ulcers and prevention of their formation.

Nursing interventions:

1. Skin, clothes, and bedding are kept clean and dry, and the patient is informed about the necessity to prefer clothes made of cotton.

2. The patient's position is changed frequently, and pressure areas are checked for redness.

3. The importance of using barrier cream during the patient's body care is explained to the patient and his relatives.

4. Light massage is applied around the pressure areas. It is ensured that bedsheets and clothes are not wrinkled.

5. If needed, air or anti-decubitus mattresses are used. Precautions are taken to keep the skin away from the rubbed surface.

6. The patient is provided with adequate fluid intake and protein-rich nutrition.

7. When the patient lies down in the supine position, the back of the waist is supported 193 with a towel or a small pillow not to impair the body posture.

Evaluation: The patient did not develop any pressure ulcers, and no redness and tenderness were observed in the pressure areas.

Movement

Nursing diagnosis 7: "Impairment of physical movement" due to immobility caused by quadriplegia, weakness in extremities, and loss of function.

Aim: Enhancing the strength and durability of the individual's extremities and reaching and supporting the maximum body functions.

Interventions:

1. The patient's compliance with physical therapy is evaluated, and the patient is encouraged to receive treatment.

2. The patient's position is changed every 2-4 hours, and it is checked whether a pressure ulcer has occurred.

3. The patient is encouraged and assisted in using extremity-strengthening equipment.

4. During the day, the patient is mobilised with a wheelchair to ensure his safety.

5. It is ensured that the bed brakes are off when the patient is taken to the bed, and the patient is prevented from falling by keeping the bed barriers up while lying on the bed.

6. Areas with reduced sensitivity in the extremities are protected against excessive heat, cold and impacts.

7. The patient and his relatives are informed about in-bed passive exercises, ensuring that he continues his daily activities.

8. The movement tolerance of the individual is evaluated (such as vital signs, duration, pain control, patient's strength, and hunger-satiety state).

Evaluation: While the patient received treatment in the ward, significant progress was observed regarding increasing extremity range of motion, sensation, and strength. The patient can lift his arms without help and hold light objects with his hands for a short time.

Nursing diagnosis 8: "Acute pain" due to involuntary contractions in different muscle groups caused by neurological involvement and intense physical exercises.

Aim: Relieve the patient's pain and ensure his comfort.

Nursing interventions:

1. The pain characteristics are determined (such as severity, region, type of pain, initial features, and duration).

2. Factors that increase and decrease pain are identified.

3. The patient's pain is accepted, and the patient is kept away from stress and additional sources of stress as much as possible.

4. When the severity of the pain increases during exercise, a break is taken, and the patient rests in bed.

5. When the severity of the pain increases, analgesic therapy is applied upon the doctor's request, and its effectiveness is evaluated.

6. Analgesics suitable for the pharmacological management of the pain are selected (nonopioids, opioids, local analgesics).

7. The doctor is informed when pharmacological interventions are ineffective.

8. Relaxation techniques (such as breathing exercises, diverting attention, massage, and listening to music) that will help the patient cope with the pain are taught.

Evaluation: The patient's pain continues after exercise, but pain can be controlled with relaxation and breathing exercises without needing analgesics. When the patient was requested to rate his pain, he described the severity of his pain as 6, among the parameters from 1 to 10.

Work and Entertainment

Nursing diagnosis 9: "Ineffective role performance" due to the inability to work and transition from active social life to a dependent isolated life.

Aim: Preventing the individual from feeling incompetent and helping him have realistic expectations about himself.

Nursing interventions:

1. The patient is allowed to express his feelings and thoughts.
2. The patient's stress and anxiety levels are minimised.
3. The patient's communication with family members is kept uninterrupted, and he can see his children by complying with infection and hospital rules.
4. Exercises are planned in line with the patient's capacity to prevent a decrease in his physical activity levels.
5. The patient is not allowed to neglect himself.
6. The patient's capacity is determined, and his roles are re-determined accordingly.
7. To avoid regression in the patient's physical activities, appropriate activity programs are organised.

Evaluation: As the patient's muscle strength and performance increased, his belief in himself and his future was also observed to increase.

Death

Nursing diagnosis 10: "Hopelessness" due to uncertainties about the disease process, plodding recovery progress, and fear of being unable to be the same as before.

Aim: Ensuring that the patient verbally states he is not hopeless.

Nursing interventions:

1. The patient is informed about people who had the same disease and recovered.
2. Positive feedback is given about the patient's achievements during treatment.
3. The patient is reminded that the treatment process is long, but his motivation is the best treatment during this period.
4. Upon the patient's request, he can benefit from support units such as a psychological counsellor and spiritual support unit.
5. The role of the disease in the patient's hopelessness is assessed.
6. The effect of hopelessness on the patient's physical condition is evaluated (such as appearance, nutrition, cleaning and sleeping habits).
7. It is revealed whether the patient needs information about the procedures.
8. Patient uncertainty is eliminated by providing sufficient information about tests or procedures.

Evaluation: In the last interview, the patient stated that he was not as hopeless as in the beginning, thanks to his progress during the treatment process, and his belief in himself increased with each passing day.

Discussion

Studies on COVID-19 show that the virus can be associated with numerous neurological complications, as seen in the case.[5,10] In a patient with weakness in the extremities, a lesion was detected in the cervical MRI, as stated in the case report, and SARS-CoV-2 was seen in the CSF examination of the patient.[11] In another case involving neurological symptoms, acute cerebrovascular disease, confusion, movement disorders and involuntary twitching were reported, and these symptoms are similar to those stated in the case report.[12]

In a study conducted in our country, neurological findings were reported by 34.7% of 239 patients infected with COVID-19. The most common neurological symptom was headache (27.6%).[13] In a study on the psychological effects of COVID-19 in our country, 1026 patients were examined. As a result of the study, it was reported that one out of every four participants exhibited moderate-severe anxiety symptoms, and about one out of every three participants exhibited moderate-severe hopelessness symptoms.[14] In the patient, anxiety, hopelessness, and uncertainty about the future were the most prominent psychological symptoms. Therefore, the approach to individuals infected with COVID-19 should be multifactorial, and it should be kept in mind that psychological and spiritual support and medical treatment are essential.

The patient in the case report had a person

with quadriplegia and a depressive picture in the initial days of treatment in the palliative care clinic. When the patient's treatment was completed, sensation and strength increased in his hands and arms, and he started to have a mild sensation in the lower extremities. The safe bond established with the patient and psychological and spiritual support reduced his anxiety and helped him think more positively about himself. Nursing interventions contributed to the acceleration of the recovery process of the patient suffering from a disease whose treatment and care process were not yet fully known. With effective and safe nursing care, the patient's quality of life was improved, existing problems were alleviated, and the patient was protected against complications. This also contributed to nurses working in the palliative care clinic and providing care for patients diagnosed with COVID-19.

There is a need for more nursing care plans and care models to determine the effective nursing care in permanent damages caused by the COVID-19 infection. Planning case reports within the scope of nursing models are critical in guiding the nursing care of cases diagnosed with COVID-19. The pandemic's effect continues worldwide, and nursing studies on effective patient care during this period are critical due to their contribution to the field.

Conflict of Interests

The authors declare that there is no conflict of interest about this manuscript.

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Authors' Contribution

Literature Review, Critical Review, and Manuscript preparing held by all authors.

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Case Report

Primary Hyperparathyroidism Due to Mediastinal Parathyroid Adenoma, Our Point of View

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ABSTRACT

Primary hyperparathyroidism is defined by elevated parathyroid hormone and calcium levels, most usually caused by a parathyroid adenoma. Parathyroid adenomas are most commonly detected in the neck or an ectopic site, seldom in the mediastinum. The parathyroid adenoma can occur in ectopic locations such as the mediastinum, thymus, or retro oesophagal area in 6-16% of cases. We presented the example of a 73-year-old woman who was found to have hypercalcemia during a regular test. The patient's serum calcium (3.11 mmol/L), alkaline phosphatase (162 U/L), parathyroid hormone (PTH: 379 pg/mL) and creatinine (111.6 umol/L) levels were higher than the reference values. A chest computerized tomography scan revealed an anterior mediastinal mass, and nuclear scintigraphy revealed functioning parathyroid tissue in the mediastinum. The mediastinal parathyroid adenoma was effectively removed surgically, and the PTH level began to fall. Any hypercalcemia and high PTH levels in the absence of a parathyroid adenoma in the neck should prompt clinicians to look for ectopic sites using a mix of imaging modalities.

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Introduction

Primary hyperparathyroidism is a common endocrine condition characterised by hypercalcemia and increased or abnormally normal serum parathyroid hormone levels. Primary hyperparathyroidism is most commonly asymptomatic in places where serum calcium levels are frequently tested. The parathyroid adenoma can occur in ectopic locations such as the mediastinum, thymus, or retro oesophagal area in 6-16% of cases. A combination of imaging modalities, including nuclear scintigraphy and high-resolution computerised tomography (CT), can aid in detecting an ectopic parathyroid adenoma. Many people without symptoms are followed without surgery. However, some patients progress to symptomatic hyperparathyroidism and require surgery, while others remain asymptomatic. Here we presented primary hyperparathyroidism caused by an ectopic parathyroid gland in the anterior mediastinum.

Case Report

A 73-year-old woman patient who was found to have hypercalcemia and elevated alkaline phosphatase (ALP) in her routine checkup was admitted to our department. Laboratory testing as part of a hypercalcemia workup revealed elevated serum calcium (3.11 mmol/L, reference range [RR]: 2.10-2.55), ALP (162 U/L, RR: 35-120), parathyroid hormone (PTH; 379 pg/mL, RR: 12.0-65.0), phosphorus (0.73 mmol/L, RR: 0.74-1.52) and vitamin D (53.14 nmol/L, RR: 75-250) levels. The serum creatinine concentration was 111.6 µmol/L (RR: 45-109), and the estimated glomerular filtration rate (eGFR) was 42 mL/min. The total T score for femoral bone mineral density, excluding osteoporosis, was –0.7. A single tracer, dual-phase anterior planar 99mTc-MIBI scintigraphy scan showed enhanced tracer uptake in the front of the sternum, and findings were interpreted as an ectopic parathyroid gland (*Figure 1*). A non-contrast CT of the chest revealed a well-defined soft tissue mass measuring 1.0x1.0x0.7

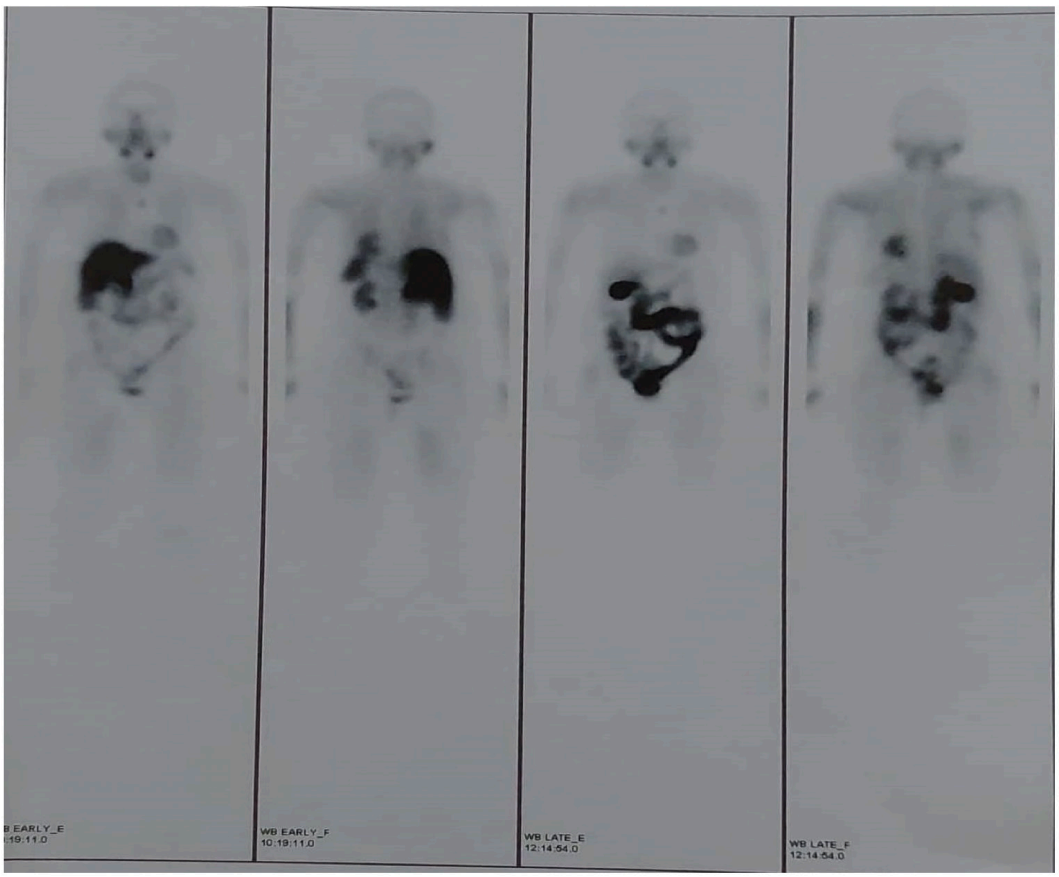

Figure 1. 99mTc-MIBI parathyroid scintigraphy, the early (1,2) and the late (3,4) planer images.

cm that was located retrosternal (*Figure 2*). The patient was treated effectively by surgically removing 3x3x1 cm parathyroid tissue and 1.2 cm parathyroid adenoma. The histopathological investigation revealed an adenoma composed of homogeneous cells with eosinophilic and lighter cytoplasm and spherical nuclei. The surgical material changes described confirmed an adenoma in an ectopically located parathyroid gland. PTH levels and serum calcium levels gradually drop after surgery.

Discussion

Primary hyperparathyroidism is an uncommon condition characterised by elevated parathyroid levels and hypercalcemia, usually caused by a parathyroid adenoma. Parathyroid adenomas are typically found in the neck in the juxta thyroid position, but earlier research has shown that 6-16% of parathyroid adenomas can present in an ectopic location. According to Roy et al.[4], parathyroid adenomas in the anterior mediastinum are one of the rarest areas, occurring in only 4% of affected patients. Recurrent kidney stones, bone pain, and gastrointestinal symptoms are the hallmarks of hyperparathyroidism. However, this type of presentation in clinical practice is becoming less common, owing to increasingly frequent routine checks that allow for early diagnosis, even in the asymptomatic phase.[5] Our patient is an example of this, as she has no symptoms, and the condition was discovered via routine laboratory tests. Ultrasonography, radionuclide scintigraphy, CT, and magnetic resonance imaging are all diagnostic modalities for imaging parathyroid adenomas.[1] The combination of a 99mTc-MIBI sestamibi scan with a CT scan offers 100% sensitivity and 97.4% positive predictive value for diagnosing ectopic parathyroid adenoma. At the 2013 Fourth International Workshop, surgical indications for operative treatment of an asymptomatic case were strictly specified. Age under 50 years, serum calcium level greater than 1 mg above normal, DEXA scan, osteoporosis, and renal problems (creatinine clearance less than 60 mL/min) are all examples. At the same time, surgery is the sole option for such patients.

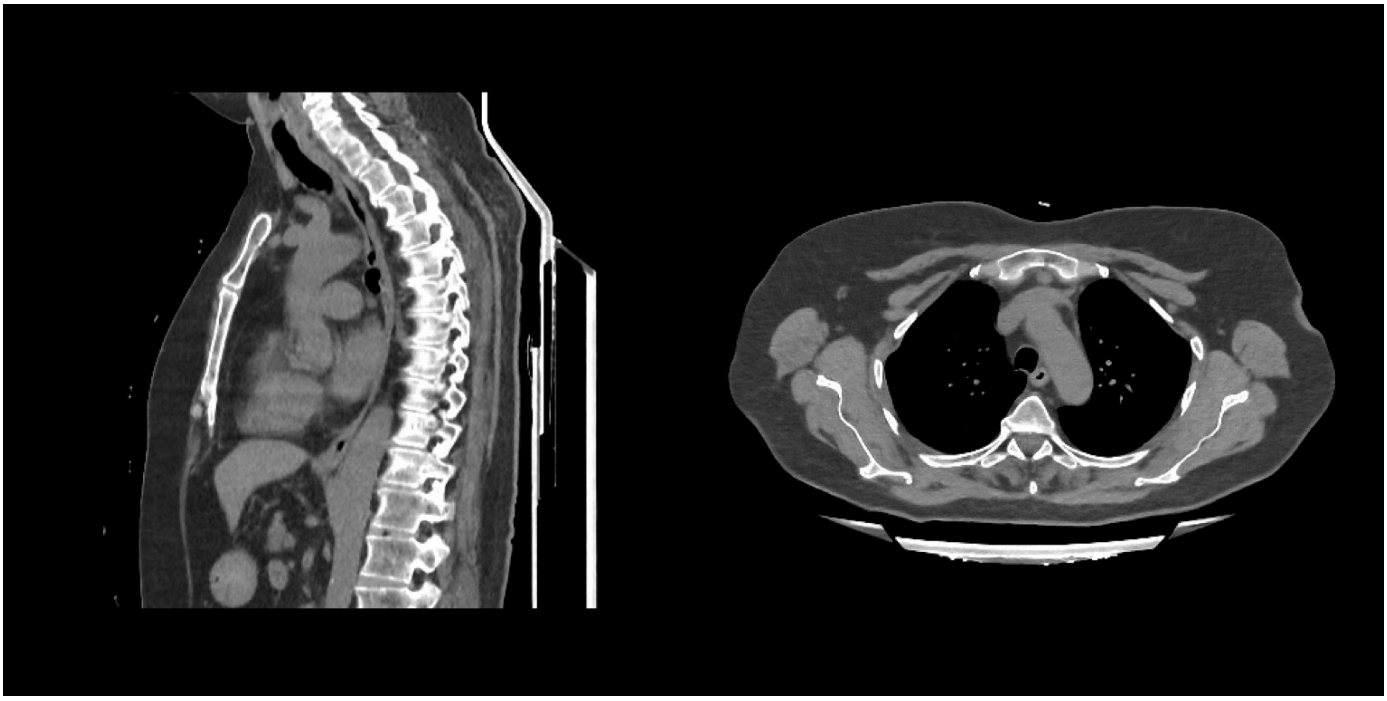

Figure 2. Computerised tomography scan of the thorax.

Concluisons

Any hypercalcemia and elevated PTH levels in the absence of a parathyroid adenoma in the neck should alert clinicians to look for ectopic sites using a mix of imaging modalities. This example highlights the need for you to consider the diagnosis of an ectopic parathyroid adenoma in the absence of neck swelling and prolonged hypercalcemia. This instance case was reported due to its rarity and odd presentation.

Conflict of Interests

The authors declare that there is no conflict of interest about this manuscript.

Informed Consent

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Authors' Contribution

Literature Review, Critical Review, and Manuscript preparing held by all authors.

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