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Port-site hernia after laparoscopic cholecystectomy: retrospective clinical experience

Laparoskopik kolesistektomi sonrasi port yeri fıtığı: retrospektif klinik deneyim

Fatih Büyüker, Mehmet Acar, Mehmet Sait Özsoy, Medeni Sermet, Hakan Baysal

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Abstract

Purpose: Laparoscopic cholecystectomy is the gold standard in patients scheduled for cholecystectomy. Complications related to laparoscopy may occur during or after laparoscopic cholecystectomy. This study is aimed to examine the incidence of port-site hernia and its predisposing factors.

Materials and methods: Laparoscopic cholecystectomy operations performed in the general surgery clinic of our hospital between January 2016 and March 2021 were reviewed retrospectively. The pneumoperitoneum was created by entering the abdomen with a mini-incision from the umbilicus using the Hasson technique. All cholecystectomies were performed using the 4-port technique. The umbilical trocar fascia was closed in all patients. Demographic data were evaluated retrospectively.

Result: The incidence of port-site hernia was determined as 0.5%. The umbilical hernia was detected in 15 patients: 11 male and four female. The mean age was 55.4 years. The mean hernia detection time was 14.3 months. The mean body mass index [BMI] was found to be 30.11. Four patients had a chronic disease. Fourteen of the patients underwent surgery. One of the patients was operated on a mini-incision urgently due to the development of strangulation. Recurrence was detected in three patients. No mortality was observed.

Conclusion: Obesity, age, and female gender are considered important risk factors. In our series, fascial closure was performed instead of the umbilical port in all cases, but most of the port site hernias originate from the umbilicus port.

Key words: Port-site hernia, fascial closure, risk factor, laparoscopic cholecystectomy.

Buyuker F, Acar M, Ozsoy MS, Sermet M, Baysal H. Port-site hernia after laparoscopic cholecystectomy: retrospective clinical experience. Pam Med J 2023;16:362-367.

Öz

Amaç: Kolesistektomi planlanan hastalarda laparoskopik kolesistektomi altın standarttır. Laparoskopik kolesistektomi esnasında veya sonrasında laparoskopiye bağlı komplikasyonlar görülebilir. Bu çalısmada port yeri hernisi insidansı ve predispozan faktörlerinin incelenmesi amaçlanmaktadır.

Gereç ve yöntem: Ocak 2016-Mart 2021 tarihleri arasında hastanemiz genel cerrahi kliniğinde yapılan laparoskopik kolesistektomi operasyonları retrospektif olarak incelendi. Pnömoperitoneum oluşturmak için hasson tekniği kullanıldı. Tüm kolesistektomiler 4 port tekniği ile yapıldı. Tüm hastalarda umbilical trokar fasyası kapatıldı. Demografik veriler retrospektif olarak değerlendirildi.

Bulgular: Port yeri hernisi insidansı %0,5 olarak bulundu. 15 hastada umblikal herni saptandı. 11 hasta erkek 4 hasta kadın idi. Ortalama yaş 55,4 idi. Ortalama herni tespit süresi 14,3 ay idi. Ortalama BMI 30,11 olarak bulundu. 4 hastada kronik hastalık mevcut idi. 14 hasta opere edildi. 1 hasta acil strangülasyon gelişmesi üzerine acil opere edildi. 3 hastada nüks saptandı. Mortalite gözlenmedi.

Sonuç: Obezite, yaş kadın cinsiyet önemli risk faktörleri olarak degerlendirilmektedir. Serimizde umblikal port yerine tüm olgularda fasiyal kapama yapılmakta ancak en çok port hernisi umblikus portundan kaynaklanmaktadır.

Anahtar kelimeler: Port yeri hernisi, fasiyal kapama, risk faktörleri, laparoskopik kolesistektomi.

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Introduction

In 1985, surgeon Erich Mühe was the first to perform the laparoscopic cholecystectomy operation [1, 2]. It was later applied by Philippe Mouret in 1987 in France [3]. Although laparoscopic cholecystectomy received great criticism at first, it has spread rapidly worldwide due to less postoperative pain, better cosmetic result, faster recovery, les hospital stays, and fast return to work [4, 5]. Complications (trocar injury, hypercapnia due to pneumoperitoneum, port-site hernia, etc.) started to be seen due to the widespread use of laparoscopy [6]. The type of hernia developed by laparoscopy was called port-site hernia. In different studies, the incidence of port-site hernia was given at different intervals (0.5-23.7%) [7-9].

The gallbladder is removed using the location of one of the 10 mm ports. Publications are stating that both 10 mm port sites can be used, and the general approach is to leave it to the surgeon's opinion [10, 11].

Old age, female gender, chronic disease (diabetes mellitus (DM), pulmonary disease etc.), obesity, trocar blade type, trocar size, trocar incision enlargement, surgical site infection and increased intra-abdominal pressure are shown as factors that increase the development of port site hernia [12-14].

This study presents the incidence and risk factors of port-site hernia after laparoscopic cholecystectomy.

Material and method

The data of 2,978 patients who underwent laparoscopic cholecystectomy between January 2016 and March 2021 in the Department of General Surgery at the Istanbul Medeniyet University Goztepe Prof. Dr. Suleyman Yalcin City Hospital were retrospectively analyzed. Excluded from the study were patients with primary umbilical hernia or recurrent hernia, and patients who were switched from laparoscopic to open surgery. Port-site hernia was detected in 15 patients. It was determined that 14 patients underwent surgery with the diagnosis of port site hernia.

Ethical approval was obtained from the Ethics Committee of our hospital.

This study used demographic analysis for statistics due to the small number of patients.

The Laparoscopic cholecystectomy operation was performed with the same technique in all patients. Under endotracheal general anesthesia, a mini-incision was made from the umbilicus, and the abdomen was entered with the open method [Hasson technique]. It was inserted with a 10 mm trocar. Carbon dioxide [CO2] was insufflated. After the pneumoperitoneum (12 mmHg) was created, the camera was entered into the abdomen through the 10 mm port, and exploration was achieved. The abdomen was entered with two 5 mm trocars from the right subcostal region and one 10 mm trocar from the epigastric region under the xiphoid. Facial closure suture was applied only to the umbilical port area.

Results

A laparoscopic cholecystectomy procedure was performed in 2.978 patients between January 2016 and March 2021 in the general surgery clinic. In the retrospective data scan from the records, port-site hernia was detected in 15 patients, and 14 patients were operated on. Eleven of the patients were female (73.33%) and four were male (26.67%). The mean age was 55.4 (34-84), and the median age was 53. Four of the patients had a chronic disease (26.67%). DM was found in two patients, asthma in one patient, and asthma and DM in one patient. Three of the operated patients had a history of acute cholecystitis before the operation. One of the patients with a history of acute cholecystitis had a history of Endoscopic Retrograde Cholangiopancreatography (ERCP). The mean hospital stay after cholecystectomy was 1.15 (1-2) days. The mean BMI was 30.11 (22.22-41.62). Of the patients, one was morbidly obese, two moderately obese, and four mildly obese. Eight patients had a normal BMI. Mean port-site hernia development time was 14.3 (0-37) months. Hernia developed at the umbilical port site in 13 (86.67%) patients and at the epigastric port site in 2 (13.33%) patients. Five patients underwent primary hernia repair, and nine patients underwent mesh hernia repair. After cholecystectomy, one patient presented to the emergency service with the development of umbilical port site hernia on the sixth postoperative day. The patient was hospitalized with a preliminary diagnosis

of strangulated hernia. The patient was taken into an emergency operation. In the operation, the intestines were evaluated as viable, and resection was not performed. The hernia defect was repaired primarily. The other 13 patients were operated on electively. Recurrence was observed in three (21.4%) patients during follow-up. The mean recurrence time in patients with hernia repair was 19 (12-29) months. No mortality was observed during the follow-up. No complications requiring hospitalization were observed in patients who followed up for port-site hernia. The clinical features are detailed in Table 1.

Table 1. Clinical features of cohort

		N	%
Sex	Male	4	26.67
	Female	11	73.33
Age		55.4 (34-84)	
Cause Of Cholecystectomy	Chronic Stone Cholecystitis	12	80
	AcuteStone Cholecystitis	3	20
Complaint	NO	1	6.67
	Swelling at the Incision or pain	13	86.67
	Acute Pain	1	6.67
Surgical Treatment	YES	14	93.33
	NO	1	6.67
Operation Type	Emergency	1	7.14
	Elective	13	92.86
Hernia Site	Umbilical	13	86.67
	Epigastric	2	13.33
	5 mm port	0	
Chronic Disease	Diabetes	2	13.33
	Asthma	1	6.67
	Diabetes + Asthma	1	6.67
BMİ	BMI <30	8	53.33
(Body Mass Index)	BMI 30-34.)	4	26.67
	BMI 35-39.9	2	13.33
	BMI>40	1	6.67
Hernia Repair	NO	1	6.67
	Mesh	9	60
	Primary	5	33.33
Mortality	Totally	0	

Discussion

The incidence of a port-site hernia developing after laparoscopic procedure is found to be less than normal. Because sometimes port site hernias may not show any symptoms. Publications are reporting different incidences in the literature due to reasons such as lack of follow-up and absence of symptoms [15]. Comajuncosas et al. [16] found the incidence of port-site hernia to be 25.9% in their 2011 study. Again, in a study by Uslu et al. [17], the incidence was reported as 5.2%, and in another series, a rate of 0.08% was reported [18]. In our study, the rate was 0.5%.

There are literature reports that strangulated port-site hernia develops after laparoscopic surgery. In a study conducted by Nacef et al. [19], five patients were operated on urgently for strangulated hernia in a series of 19 patients. Again, in a published case report, a strangulated hernia was detected on the second post-op day after laparoscopic cholecystectomy, and it was operated on [20]. In our series, one patient was operated on for strangulated hernia on the seventh postoperative day. It was observed that the small intestine was compressed into the hernia defect. No organ resection was required.

In the series performed by Nacef et al. [19], recurrence was observed in two (10.5%) patients. In our study, recurrence developed in three (21.43%) of 14 patients who were operated on.

Age, obesity, gender, chronic disease, incision size, surgical site infection development, trocar size, a trocar with or without a blade, cholecystitis status, etc., are shown as predisposing factors in the development of port-site hernia [14, 16, 21, 22]. In our series, the standard open-entry method was used for all cholecystectomy procedures. All trocars used had a disposable blade. In all patients, the gallbladder was removed from the abdomen at the epigastric port location.

In the study of Uslu et al. [17], age (mean age 60 years) and female gender were found to be risk factors. In our series, the patients who developed port-site hernia were female (73.33%). The mean age was 55.4.

In a single-center, 10-year series conducted by Chatzimavroudis et al. [21], BMI greater than 30, development of surgical site infection, and enlargement of the incision were determined as important risk factors. In our series, the mean BMI was found to be 30.11 in patients with trocar site hernia. The BMI was greater than 30.0 in 46.67% of the patients. However, surgical site infection was not detected in cases with port hernia in our series.

It has been reported in the literature that port-site hernia develops mostly from the umbilical port site [15]. In our study, it developed from the umbilical port site in 13 patients (86.67%).

In the literature, it is generally recommended to study 10 mm port locations; however, there is no consensus. Mayol et al. [23] found no difference between fascia closure and non-closure in their study with 403 patients. Again, Singal et al. [24], in their study of 200 people in 2016, argued that fascia closure is not necessary. In our series, umbilical port sites were closed with 1.0 vicryl in all patients, and facial closure was not performed at other port sites. The facial closure procedure was performed with the same procedure in all patients with the single suture method. During the operation, fascial closure was performed by a novice doctor (Assistant doctor with 1 to 2 years of experience) on the surgical team.

The gallbladder can be taken out of the abdomen from the port in the umbilical or epigastric regions. In the meta-analysis of Kulkarni et al. [25], a significant rate of port-site hernia development was reported when the gallbladder was removed from the umbilical port. In a meta-analysis by Sood et al. [26], trocar hernia development was not found to be statistically significant in removing the gallbladder from either the epigastric or umbilical trocar sites. In our series, the gallbladder was removed from the abdomen using the epigastric port in all patients.

Limitations

This study is retrospective. Cholecystectomy operation was performed by different surgical teams. Radiologic control of the patients who were asymptomatic and did not show any symptoms on physical examination was not performed. Fascia closure in operation was performed by novice doctors. Due to the COVID-19 pandemic, some checks are missing or done by teleconference.

In our series, the incidence of port-site hernia after laparoscopic cholecystectomy is found to be low. Obesity, age, and the female gender are considered important risk factors. In our series, fascial closure is performed in all cases instead of the umbilical port, but most port-site hernias originate from the umbilicus port. Although there is no complete information in the literature on the relationship between the experience of surgical assistants and the development of port site hernia, we think that a research plan with a large number of prospective cases will clarify this issue. Long-term results of a prospective, well-designed study will give more reliable results about port-site hernia occurrence.

Conflict of interest: No conflict of interest was declared by the authors.

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Ethics committee approval: Permission was obtained from Istanbul Medeniyet University Goztepe Prof. Dr. Suleyman Yalcin City Hospital Ethics Committee Clinical Research for the study (date of permission 08.12.2021, file/ permission number 2021/0575).

Authors' contributions to the article

F.B. and M.A. have constructed the main idea and hypothesis of the study. F.B., H.B., M.A. and M.S.O. They developed the theory and arranged the material and method section. F.B., M.S. and H.B. have evaluated the data in the Results section. Discussion section of the article Written by M.A. and F.B.

F.B., H.B., M.S. and M.S.O. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

Research Article

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Determination of the relationship between radiographic parameters and patient-reported outcomes in Lenke type-1 adolescent idiopathic scoliosis

Lenke tip-1 adolesan idiyopatik skolyozda radyografik parametreler ile hasta tarafından bildirilen sonuçlar arasındaki ilişkinin belirlenmesi

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Abstract

Purpose: This study aims to examine sagittal alignment and spinopelvic parameters in patients with surgically treated Lenke type-1 AIS and to determine the relationship between radiographic outcomes and body image, self-esteem, disability and anxiety.

Materials and methods: Twenty-five patients who underwent posterior spinal fusion surgery and followed up for more than 1 years were eveluated (mean age 14.20±1.63 years). Radiographic analysis of A/P and lateral full spine standing radiographs was carried out with the Surgimap software. The patient-reported outcomes were evaluated with Walter Reed Visual Assessment Scale, Rosenberg Self-Esteem Scale, Oswestry Disability Index and Beck Anxiety Inventory. Correlations between deformity measures and patient-reported outcomes were evaluated by the Pearson's correlation test.

Results: There was a significant decrease in Cobb angle, AVT, trunk shift, T1 tilt and pelvic incidence at early postoperative and final follow up compared with the preoperative measurement (p<0.005). Oswestry disability index was moderately negatively correlated with major curve Cobb angle (r=-0.545, p=0.007), and moderately positively correlated with pelvic tilt (r=0.478, p=0.021). There was no significant correlation between all other radiographic and patient reported outcomes (p>0.05).

Conclusion: Patient-reported outcomes are important in terms of evaluating the physical and psychosocial effects of scoliosis-related deformity from the patient's perspective. However, low or no correlation was found between radiographic evaluation and patient-reported outcomes. This result indicates that objective and patient-reported results should be interpreted separately.

Key words: Scoliosis, patient reported outcome measures, surgery.

Arik I, Buker N, Savkin R, Ok N, Kiter AE. Determination of the relationship between radiographic parameters and patient-reported outcomes in Lenke type-1 adolescent idiopathic scoliosis. Pam Med J 2023;16:368-375.

Öz

Amaç: Bu çalışma, cerrahi olarak tedavi edilen Lenke tip-1 AIS'li hastalarda sagital dizilim ve spinopelvik parametreleri incelemeyi ve radyografik sonuçlar ile vücut imajı, benlik saygısı, disabilite ve anksiyete arasındaki ilişkiyi belirlemeyi amaçlamaktadır.

Gereç ve yöntem: Posterior spinal füzyon cerrahisi uygulanan ve 1 yıldan fazla takip edilen 25 hasta (ortalama yaş 14,20±1,63 yıl) retrospektif olarak değerlendirildi. A/P ve tam lateral omurga ayakta radyografilerin radyografik analizi Surgimap yazılımı ile yapıldı. Hasta tarafından bildirilen sonuçlar Walter Reed Görsel Değerlendirme Skalası, Rosenberg Benlik Saygısı Ölçeği, Oswestry Disabilite İndeksi ve Beck Anksiyete Envanteri ile değerlendirildi. Deformite ölçümleri ile hasta tarafından bildirilen sonuçlar arasındaki korelasyonlar Pearson korelasyon testi ile incelendi.

Bulgular: Erken postoperatif ve son takip değerlendirmelerinde Cobb açısı, AVT, gövde kayması, T1 tilt ve pelvik insidansta ameliyat öncesi ölçüme göre anlamlı azalma vardı (p<0,005). Oswestry disabilite indeksi, majör eğri Cobb açısı ile orta derecede negatif korelasyon (r=-0,545, p=0,007), pelvik tilt ile orta derecede pozitif korelasyon gösterdi (r=0,478, p=0,021). Diğer tüm radyografik ve hasta tarafından bildirilen sonuçlar arasında anlamlı bir ilişki yoktu (p>0,05).

Sonuç: Hasta tarafından bildirilen sonuçlar, skolyoza bağlı deformitenin fiziksel ve psikososyal etkilerinin hasta açısından değerlendirilmesi için önemlidir. Ancak, radyografik değerlendirme ile hasta tarafından bildirilen sonuçlar arasında düşük korelasyon bulundu veya hiç korelasyon bulunmadı. Bu sonuç, objektif ve hasta tarafından bildirilen sonuçların ayrı ayrı yorumlanması gerektiğini göstermektedir.

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Introduction

Adolescent idiopathic scoliosis (AIS) is a three-dimensional spinal deformity that shows changes in the axial rotations of the vertebrae and pelvis in the coronal and sagittal planes, with a prevalence of 0.47-5.2% [1, 2]. The relationship between sagittal pelvic parameters and thoracic hypokyphosis and lumbar lordosis requires the evaluation of sagittal and spinopelvic parameters as well as coronal in AIS [3, 4].

In recent years, although remarkable advances have been made in the treatment of AIS in the correction of spinal deformity psychosocial problems may persist even after surgical correction [5, 6]. Quality of life can be affected by physical symptoms such as back pain, psychosocial problems such as low self-esteem and negative body image [7, 8]. Especially aesthetic concerns are given more importance nowadays than in the past decades [9]. Improvements in radiographic deformities, general cosmetic status, and self-perception of health of patients are expected to be closely related [10]. However, the finding of a poor correlation between the radiographic and self-reported findings is challenging in the sense that it leads to the misinterpretation of the physical and functional outcomes [11, 12].

A limited number of studies have investigated psychosocial variables such as body image, self-esteem, and anxiety in surgically treated AIS patients [13-15]. However, the relationship between radiographic and physical/psychosocial patient-reported variables has not been clarified yet. This study aims to examine sagittal alignment and spinopelvic parameters in patients with surgically treated Lenke type-1 AIS and to determine the relationship between radiographic outcomes and body image, self-esteem, disability and anxiety.

Materials and methods

Study design and participants

This single-center, retrospective cohort study carried out in a university hospital. Patients who underwent surgery for AIS between 2008 and 2015 were screened. This study was approved by Pamukkale University, Non-Invasive Clinical Research Ethics Committee, and written informed consent was obtained from legal guardians.

The inclusion criteria were as follows: ages between 10 to 16, diagnosed with Lenke type-1 AIS, underwent posterior spinal fusion surgery by the same experienced orthopedic surgeon (AEK) and team, at least 1-year follow-up. Exclusion criteria were as follows: revision surgery, previous spinal infection, luminal pathologies as detected by magnetic resonance imaging, neurological, muscular, or rheumatic diseases, and lack of postoperative follow-up examinations.

In the present study, data of 71 patients with AIS were scanned through the hospital registry system. 46 patients were excluded from the study: Lenke type 2-6 (n=9), revision surgery (n=4), previous spinal infections (n=3), luminal pathologies as detected by magnetic resonance imaging (n=5), neurological, muscular, or rheumatic diseases (n=6), incomplete data (n=12), and inability to maintain contact because of a change in telephone number (n=7). The final study sample consisted of 25 patients.

Measurements

Data were obtained from the hospital information management system and patients' medical records. Demographic variables, clinical characteristics, and operative findings of the patients were recorded.

Radiological evaluations

All radiographic measurements (EIDOS 3000 Multifunctional Radiographic Unit Mecall s.r.l. X-Ray Equipment Lissone Milan-Italy) were analyzed using the image archiving and communication system and the measurements were performed using the Surgimap software (Nemaris Inc., New York, USA). Standing full-length anteroposterior and lateral radiographs were taken before surgery, early postoperative period and at the last follow-up. The coronal

Cobb angle, apical vertebral translation (AVT), trunk shift, T1 and L4 tilt, pelvic tilt, pelvic incidence, sacral slope, lumbar lordosis, thoracic kyphosis, sagittal and coronal balance were measured by the same investigator (İA).

Patient-reported outcomes

Walter Reed Visual Assessment Scale [16], Rosenberg Self-Esteem Scale [17], Oswestry Disability Index [18] and Beck Anxiety Inventory measurements [19], which were filled in at the last follow-up under the supervision of a physiotherapist (RS, NB), were obtained from patient records.

Walter Reed Visual Assessment The subjective perception of the deformity is evaluated with a group of figures representing the seven aspects of the deformity. Total score ranges from 0 to 35, with higher scores indicating maximum deformity [16].

The Rosenberg Self-Esteem Scale is a 10-item scale that measures overall feelings about self-esteem. Total score ranges from 0 to 30, with higher scores indicate higher self-esteem [17].

Oswestry Disability index is most widely used condition-specific outcome measures used in the assessment of spinal conditions. It consists of 10 items that examine how much the pain affects patients' ability to manage everyday life. The final score ranges from 0-100, and higher scores represents higher disability [18].

The Beck Anxiety Inventory measures the severity of anxiety symptoms and consists of 21 items. The total score ranges from 0 to 63, and higher scores indicate higher anxiety. Scores above 15 are considered a clinical cutoff and the scale interpreted as follows: minimal (1–5 points), mild (6–15), moderate (16–30) and severe (31–63) anxiety [19].

Statistical analysis

IBM SPSS Statistics for Windows version 24.0 software (IBM Corp., Armonk, NY, USA) was used for data analysis. Continuous variables were defined by mean±standard deviation, minimum and maximum values and categorical variable values as absolute numbers and percentages. Data distribution was evaluated using the Shapiro-Wilk test. Radiographic outcomes were evaluated by repeated-measures ANOVA. Relationship between the last follow up radiographic measurements and patient-reported outcomes were evaluated with Pearson's correlation coefficient. Statistical significance was set at $p \leq 0.05$.

Results

A total of 25 patients (24 female and 1 male; mean age 14.20±1.63 years) participated in the study. The mean last follow-up period of the patients was 39.08±19.88 months. Distribution of Risser stages was as follows: 6 patients were classified as having grade 1; 4 as grade 2, 4 as grade 3, 7 as grade 4 and 4 as grade 5 (Table 1).

Table 1. Demographic and clinical characteristics of the study group

	Mean±SD
Age (year)	14.20±1.63
Follow up (month)	39.08±19.88
	n (%)
Gender	
Female	24 (96)
Male	1 (4)
Risser stage	
1	6 (24)
2	4 (16)
3	4 (16)
4	7 (28)
5	4 (16)

SD, standard deviation, n, number; %, percent

Radiographic measurement outcomes are shown in Table 2. Cobb angle was 48.16±9.21 before surgery, 13.08±6.41 in the early postoperative period, 14.88±4.96 at the last follow-up. There was a significant decrease in Cobb angle, AVT, trunk shift, T1 tilt and pelvic incidence at early postoperative and final follow up compared with the preoperative measurement (p<0.005).

Patient-reported outcomes scores are presented in Table 3. Walter Reed Visual Assessment Scale score was 10.14±3.15, Rosenberg Self-esteem Scale was 41.74±10.71, Oswestry Functional Disability Scale was 9.61±8.49 and Beck Anxiety Inventory was 10.32±10.18.

The relationship between the last follow-up radiographic measurements and patient-reported outcomes were presented in Table 4. Oswestry disability index was moderately negatively correlated with major curve Cobb angle (r=-0.545, p=0.007), and moderately positively correlated with pelvic tilt (r=0.478, p=0.021). There was no significant correlation between all other radiographic and patient reported outcomes (p>0.05) (Table 4).

Table 2. Radiographic measurement outcomes

	Before surgery	Early postoperative	Last follow-up	f	*p* value
Deformity measures					
Major curve Cobb angle (degree)	48.16±9.21	13.08±6.41	14.88±4.96	390.573	**<0.001** [1-2, 1-3]
AVT (mm)	24.78±32.04	-1.57±13.11	-0.53±12.95	17.612	**<0.001** [1-2, 1-3]
Trunk shift (cm)	6.70±17.97	-9.27±12.53	-8.54±9.61	15.233	**0.001** [1-2, 1-3]
T1 tilt (degrees)	-0.32±5.87	2.92±4.05	3.47±4.08	7.891	**0.001**[1-2, 1-3]
L4 tilt (degrees)	-4.55±9.23	-2.66±5.66	-3.43±6.84	1.189	0.307
Pelvic parameters					
Pelvic tilt	10.76±5.67	8.96±5.87	7.80±5.52	4.655	**0.019**[1-3]
Pelvic incidence	48.24±8.96	45.28±7.29	44.08±7.59	8.787	**0.002**[1-2, 1-3]
Sacral slope	37.48±5.13	35.88±4.91	36.32±4.71	3.230	0.052
Spinal parameters					
Lumbar lordosis (degrees)	47.30± 7.12	49.53±10.28	50.92±8.00	1.446	0.246
Thoracic kyphosis (degrees)	28.62±10.91	31.92±5.94	30.28±6.48	1.417	0.252
Sagittal balance (mm)	-25.53±27.00	-22.58±36.84	-31.25±35.84	0.509	0.605
Coronal balance (mm)	-10.51±16.79	-10.95±15.74	-8.90±12.40	0.192	0.826

AVT, apical vertebral translation; [1-2], Before surgery vs Early postoperative; [1-3], Before surgery vs Last follow-up

Table 3. Patient-reported outcomes

	Patients (n=25)	
	Min-Max	**Mean±SD**
Walter Reed Visual Assessment Scale	7-16	10.14±3.15
Rosenberg Self-esteem Scale	8-30	20.87±5.35
Oswestry Functional Disability Scale	0-30	9.61±8.49
Beck Anxiety Inventory	0-34	10.32±10.18

AVT, apical vertebral translation

Table 4. Relationship between the last follow up radiographic measurements and patient-reported outcomes

	Walter Reed visual assessment scale		Rosenberg self-esteem scale		Oswestry disability index		Beck anxiety inventory	
	r	*p*	r	*p*	r	*p*	r	*p*
Deformity measures								
Major curve Cobb angle (degrees)	0.219	0.328	0.267	0.219	-0.545	**0.007**	-0.285	0.198
AVT (mm)	0.238	0.285	-0.097	0.661	-0.067	0.761	-0.105	0.641
Trunk shift (cm)	-0.059	0.793	0.026	0.905	0.229	0.292	0.002	0.993
T1 tilt (degrees)	0.085	0.706	-0.116	0.599	0.068	0.760	-0.065	0.774
L4 tilt (degrees)	-0.015	0.947	0.069	0.756	-0.221	0.311	-0.197	0.378
Pelvic parameters								
Pelvic tilt	0.249	0.263	-0.077	0.726	0.478	**0.021**	0.045	0.842
Pelvic incidence	-0.016	0.945	-0.027	0.902	0.380	0.074	0.067	0.767
Sacral slope	-0.288	0.194	0.001	0.995	0.068	0.758	0.057	0.801
Spinal parameters								
Lumbar lordosis (degrees)	-0.139	0.538	0.091	0.681	0.036	0.871	-0.004	0.988
Thoracic kyphosis (degrees)	-0.010	0.966	0.085	0.700	-0.201	0.357	0.087	0.700
Sagittal balance (mm)	-0.025	0.911	0.053	0.811	0.201	0.359	0.028	0.901
Coronal balance (mm)	0.222	0.320	-0.125	0.570	0.077	0.727	-0.004	0.986

AVT, apical vertebral translation

Discussion

This study was planned to examine the sagittal alignment and spinopelvic parameters in patients with surgically treated Lenke type-1 AIS and to determine the relationship between radiographic and patient-reported outcomes. A significant improvement was found in Cobb angle, AVT, trunk deviation, T1 and L4 tilt, pelvic incidence in the early postoperative and last follow-up. Although there was a moderate relationship between the Oswestry disability index and Cobb angle and pelvic tilt at the last follow-up, there was no significant relationship between all other radiographic measurements and body image, self-esteem, disability, and anxiety outcomes.

The spine is a complex structure that is balanced by multiple forces in the sagittal and coronal vertical axis, and proper alignment of the spine and pelvis, including appropriate physiological sagittal curves, is important to maintain as stable posture and balance as possible [20, 21]. Surgical correction aims to correct postural imbalances in the coronal and sagittal planes. Understanding spinopelvic parameters in AIS is important for preoperative planning and minimizing degenerative changes in the long term [21]. In this study, we found that the mean of the main curve Cobb thoracic angle decreased by 33.28 at the last follow-up compared to the preoperative period, and from mean of pelvic parameter there is a decrease of pelvic tilt by 2.96, of pelvic incidence by 4.16 and of sacral slope by 1.16.

Low self-esteem and deterioration in perceived body image are often associated with physical disorders and can have emotional and psychological effects in individuals [22]. In particular, patients with AIS tend to worry that their bodies will become more and more different from normal/ordinary individuals as the disease progresses. In addition, factors such as dissatisfaction with physical appearance, low body image, lack of self-confidence, pessimism, anxiety may cause deterioration in social adaptability and isolation [23]. Corrective surgeries can improve body image, self-esteem, life satisfaction and quality of life in patients with AIS [23-26]. We found that patients with Lenke type-1 AIS had good perceived body image, high self-esteem, and mild anxiety after surgical correction. This may be due to the improvement in the physical appearance of the patients with an average 3-year follow-up, resulting in an increase in their ability to tolerate and manage psychosocial stressors. In the early period of AIS surgery, there may be a decrease in the tendency to participate in physical activity due to fear of injury [27]. However, we found that patients had minimal disability in the late

postoperative period. A detailed examination of the Oswestry disability index scores revealed that only 3 patients (12%) had moderate disability. All the other patients were at a level at which no treatment was indicated except for the recommendations to lifting, sitting and exercise. Our study results revealed that back pain after scoliosis surgery can generally be mild and may not cause disability in most patients.

The primary clinical assessment and management of AIS is based on radiographic measurements. In recent years, disease-specific and patient-reported outcomes have become an important tool to measure the impact of scoliosis on patient health. However, questionnaires developed to assess patients' subjective perceptions of their spinal deformities had low or no correlation with radiological findings [12, 28-31]. In our study, except for a moderate relationship between Oswestry disability index and Cobb angle and pelvic tilt, there was no significant relationship between all other radiographic measurements and patient-reported scales. Therefore, we think that radiographic and clinical outcome data should be analyzed and interpreted separately when evaluating postoperative outcomes.

Some limitations might be considered when interpreting the findings of this study. The small number of patients in this retrospective study may have resulted in low statistical significance. Due to the lack of preoperative patient-reported outcomes, we could not determine the effect of surgery on these outcomes. Another limitation was that the study results could not be generalized to other curve patterns. Further studies can be performed in a larger sample with different curve patterns and preoperative mesurements. Since the main purpose of surgery is to correct curvature and restore spinal balance, surgeons tend to evaluate clinical results radiologically. However, our study results showed low or no correlation between self-reported outcomes such as adolescent body image, self-esteem, disability, and anxiety, and radiographic outcomes. In this sense, it can be a guide in terms of revealing the necessity of comprehensive clinical evaluation after surgery in patients with AIS.

In conclusion, significant improvements were detected in the postoperative radiographic evaluation of patients with Lenke type 1 AIS who underwent posterior corrective surgery. However, low or no correlation was found between radiographic evaluation and patient-reported outcomes. Patient-reported outcomes are important in terms of evaluating the physical and psychosocial effects of scoliosis-related deformity from the patient's perspective. However, the lack of correlation with radiographic data indicates that the results should be interpreted separately.

Conflict of interest: No conflict of interest was declared by the authors.

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Authors' contributions

Surgical and Medical Practices: I.A., N.O. and A.E.K., Concept: I.A., N.B., R.S., N.O. and A.E.K., Design: I.A., N.B., N.O. and A.E.K., Data Collection or Processing: I.A. and R.S., Analysis or Interpretation: I.A., N.B., R.S. and A.E.K., Literature Search: I.A., N.B., R.S. and N.O., Writing: I.A., N.B. and R.S.

Research Article

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Evaluation of the presence of SARS-CoV-2 in the aqueous humor and vitreous in patients undergoing combined phaco-vitrectomy surgery

Kombine fako-vitrektomi ameliyatı geçiren hastalarda aköz hümör ve vitreusta SARS-CoV-2 varlığının değerlendirilmesi

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Abstract

Purpose: To investigate the presence of virus in the aqueous humor and vitreous of patients undergoing elective combined cataract and pars plana vitrectomy during the Coronavirus disease 2019 (COVID-19) pandemic.

Materials and methods: In this prospective cross-sectional study, of the patients to undergo elective surgery, those who had a negative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nasal swab test 24-72 hours prior to the surgery and who were asymptomatic were included. SARS-CoV-2 IgG antibodies were evaluated in blood samples taken 24-72 hours before the operation. 0.1 cc of aqueous humor and 0.1 cc of vitreous fluid were aspirated at the beginning of the surgery. The presence of SARS-CoV-2 viral ribonucleic acid (RNA) was evaluated by real-time reverse transcriptase polymerase chain reaction (RT-PCR).

Results: Of 66 participants, 39 were male (59.1%) while 27 were female (40.9%). Twenty-five patients (37.8%) had a history of COVID-19 between 20 days-60 days (mean 49 days) before the surgery. There were 58 patients (87.9%) with a history of vaccination before the operation and 8 patients (12.1%) without a history of vaccination. No SARS CoV 2 RNA was detected in the aqueous humor and vitreous samples of any patient. IgG against SARSCoV-2 was detected in 3 patients who had not been vaccinated against COVID-19 before and had no known history of COVID-19.

Conclusion: We did not find any SARS-CoV-2 viral genetic material in the aqueous and vitreous fluids of asymptomatic participants whose nasal swab test results were negative, even if they recently had COVID-19. There is a need for more comprehensive studies investigating the latency of the virus in immune-privileged areas such as the eye, how long it remains in the eye even if it is withdrawn from the circulation, and possible eye diseases that it may cause during the convalescence period.

Key words: Aqueous humor, COVID-19, SARS-CoV-2, vitreous.

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Öz

Amaç: Coronavirus 2019 (COVID-19) pandemisi döneminde elektif kombine katarakt ve pars plana vitrektomi cerrahisi uygulanan hastaların aköz ve vitreus sıvısında virus varlığının araştırılması amaçlandı.

Gereç ve yöntem: Bu prospektif kesitsel çalışmaya elektif kombine katarakt ve pars plana vitrektomi ameliyatı yapılacak hastalardan preoperatif 24-72 saat önceki SARS-CoV-2 nazal sürüntü testi negatif çıkan, COVID-19 bakımından asemptomatik olanlar dahil edildi. Preoperatif 24-72 saat önce alınan kan numunelerinde SARS-CoV-2 IgG antikoru değerlendirildi. Katarakt cerrahisinin başlangıcında 0.1 cc aköz hümör, vitrektominin başlangıcında ise 0.1 cc vitreus sıvısı aspire edildi. SARS-CoV-2 viral ribonucleic acid (RNA) varlığı real-time reverse transcriptase polymerase chain reaction (RT-PCR) ile değerlendirildi.

Bulgular: Otuz dokuzu erkek (%59,1), 27'si kadın (%40,9) olmak üzere 66 katılımcının göz içi sıvı örnekleri başarıyla analiz edildi. 25 hastada (%37,8) operasyondan 20 gün-60 gün önce (ortalama 49 gün) COVID-19 geçirme öyküsü mevcuttu. Operasyondan önce aşı öyküsü bulunan 58 hasta (%87,9), aşı öyküsü bulunmayan 8 hasta (%12,1) mevcut idi. Hiçbir hastanın aköz hümör ve vitreus örneklerinde SARS-CoV-2 RNA'sına rastlanmadı. Daha önce COVID-19 aşısı yapılmamış ve bilinen COVID-19 geçirme öyküsü olmayan 3 hastada SARSCoV-2'ye karşı gelişen IgG tespit edildi.

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Sonuç: Bu çalışmada COVID-19 bakımından asemptomatik, nazal sürüntü testi negatif katılımcıların aköz ve vitreus sıvılarında SARS-CoV-2 viral genetik materyaline rastlamadık. Virüsün göz gibi immün ayrıcalıklı alanlarda latent kalma durumunu, dolaşımdan çekilse bile gözde ne kadar süre kaldığını ve nekahat döneminde neden olabileceği olası göz hastalıklarını araştıran daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Aköz hümör, COVID-19, SARS-CoV-2, vitreus.

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Introduction

Coronavirus disease 2019 (COVID-19), first reported in December 2019 in Wuhan, China's Hubei province, is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. It was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020. The virus can lead to clinical pictures ranging from asymptomatic infection to serious illness and death. The respiratory system is the most frequently affected system, but the virus shows neurotropism and endothelial tropism, causing a cytokine storm by creating a general inflammatory reaction [1, 2]. Conjunctivitis and keratoconjunctivitis are the most common ocular symptoms. Conjunctival irritation is the most common ophthalmologic finding (50.8%), followed by diplopia (27.8%) and cotton wool patches (27.8%) [3].

As of 6 January 2023, 657.977.736 cases of COVID-19 were reported to WHO, including 6.681.433 deaths. As of 21 December 2022, a total of 13.073.712.554 vaccine doses have been administered. Accordingly, it is thought that approximately 15 million people have died in the last two years, either due to the coronavirus or the negative effect of the virus on systems. In studies conducted during that period, it was emphasized that the different modes of spread of SARS-CoV-2, systemic organ involvement, and the possibility of the viral reservoir in humans should be comprehensively investigated.

The eye is a recognized immune-privileged location that harbors viruses. Previously, Varkey et al. [4] and Gonzales et al. [5] detected live Ebola and Rubella viruses in the aqueous humor, respectively. Considering the high number of cases in ophthalmology practice and the physical close contact of the ophthalmologist with the patient during eye examination and interventions, the presence of SARS-CoV-2 in the eye has also been investigated in various studies in order to take measures to reduce pathogen contamination. Most of these studies have been conducted either with postmortem tissues from people who died due to the disease or on a limited number of patients with COVID-19. Koo et al. [6], on the other hand, demonstrated the presence of the virus for the first time in the aqueous fluid of elective anterior segment surgery patients who were asymptomatic for COVID-19 and had a negative SARS-CoV-2 nasal swab test. This suggests that the virus can stay in asymptomatic individuals beyond the blood-ocular barrier, raising the possibility that it could persist in immune-privileged environments despite the lack of symptoms [3, 6]. To date, many studies have been conducted on SARS-CoV-2 in aqueous humor and vitreous samples. These were done on a small number of case samples, usually in patients known to have COVID-19. Although it is seen that the COVID-19 pandemic has started to regress and the number of deaths is rapidly decreasing, no studies investigating the simultaneous presence of the virus in both the anterior chamber and vitreous in asymptomatic individuals with negative nasal swab test have not been conducted to date.

In this study, we aimed to investigate the presence of SARS-CoV-2 viral material in both aqueous humor and vitreous samples in elective surgery patients and to evaluate their relationship with serum immunity level.

Materials and methods

This prospective cross sectional study was conducted from Dec 2021 to March 2022 in Adana City Training and Research Hospital which is a tertiary hospital attached to a COVID-19 facility. The Institutional Research and Ethics Committee granted ethical clearance for the study (95/1686), which was carried out in accordance with the Declaration of Helsinki's principles. Informed consent was obtained from

all individual participants included in the study.

Patients who were planned to undergo elective combined phaco-vitrectomy surgery, over 18 years of age, of both genders, who gave consent to participate in the study, whose data were fully accessible, and whose nasal swab was negative for SARS-CoV-2 real-time reverse transcriptase polymerase chain reaction (RT-PCR) Test performed 24-72 hours before the operation were included in the study. Those who did not consent to participate, under the age of 18, with possible COVID-19 symptoms such as fever, cough, absence of smell and taste immediately before surgery, with positive SARS-CoV-2 PCR test, with incomplete data, and from whom sufficient volume of aqueous or vitreous samples could not be obtained were excluded from the study.

The COVID-19 dates, the vaccination dates, and the names of the vaccines were recorded from the patients' electronic files. The operations were performed by the same senior surgeon (E.Ç.) under topical or general anesthesia. Using a 1-cc syringe and a 30-G cannula, approximately 0.1 cc of aqueous humor was collected at the beginning of combined phacoemulsification- pars plana vitrectomy. At the beginning of the vitrectomy, 0.1 cc of vitreous was aspirated from the 25-G trocar inlet 4 mm behind the pars plana, before the infusion was opened with the help of a cannula.

Viral RNA was extracted with the QIAamp Viral RNA Mini kit Cat: 52906 (QIAGEN) according to the protocols. After viral RNA extraction, RNA quality was assured via nanodrop measurement, determined using Thermo Scientific ND8000 Uv/vis spectrophotometer [7]. The viral RNA amplification was performed using the One Step PrimeScript III RT-qPCR Kit (Takara). All reactions were conducted ~~out~~ on a CFX96 Touch instrument with the following Real-Time-PCR conditions: 52°C for 5 min, 95°C for 10 sec, followed by 44 cycles at 95°C for 5 sec and 55°C for 30 sec. The primer and probe sequences used for RT-PCR are targeted against the Nucleocapsid (NC) gene of SARS-CoV-2 with the following primers and probes: N1 Forward: 5'-GAC CCC AAA ATC AGC GAA AT-3', N1 Reverse: 5'-TCT GGT TAC TGC CAG TTG AAT CTG-3' N1 Probe: 5'-FAM-ACC CCG CAT TAC GTT TGG TGG ACC-BHQ1-3 N2 Forward: 5'-TTA CAA ACA TTG GCC GCA AA-3' N2 Revers: 5'-GCG CGA CAT TCC GAA GAA-3' N2 Probe: 5'-FAM-ACA ATT TGC CCC CAG CGC TTC AG-BHQ1-3 [7, 8]. For inhibition control, another primer and probe set targeted against the human RNase P gene was used as: RP-F RNase P Forward Primer AGA TTT GGA CCT GCG AGC G, RP-R RNase P Reverse Primer GAG CGG CTG TCT CCA CAA GT, RP-P RNase P Probe FAM – TTC TGA CCT GAA GGC TCT GCG CG – BHQ-1.

In the samples, the IDT nCoV-N Positive Control (1/10 diluted) included in the CDC Primer kit gave a CT value between 25-27. On the other hand, human samples have the same result as the negative control used in the experiment. The positive and negative control in the experiment worked, so the experiment worked.

IgG developed against SARS-CoV-2 was examined in serum samples taken 24-72 hours before the operation. The binding activity of antibodies in the serum of each patient against SARS-CoV2 Spike Protein receptor binding domain (RBD) was measured with an in-house indirect ELISA test. Briefly, 50 ng of a purified recombinant protein RBD were coated into a 96-well ELISA plate (nuncMaxisorp) overnight at 4°C. Wells were blocked with milk powder in PBS for 1 hour at 37°C, followed by incubation with diluted antisera and positive and negative control serum for 1 hour at 37°C. A diluted horseradish peroxidase (HRP)-conjugated rabbit anti-human IgG antibody was added for 1 hour at room temperature. Wells were washed three times between each step and five times for the last step with Tween-20 buffer in PBS. Wells were developed using 3,3,5,5-tetramethylbenzidine (TMB) and read at 450 nm after terminated with 2M H_2SO_4.

Statistical analysis

We used IBM SPSS statistics version 26 for Windows to analyse the data obtained from the study. Numerical data were given as mean, minimum, and maximum while categorical data were expressed as numbers (n) and percentages (%).

Results

Of the 66 patients included in the study, 39 (59.1%) were male and 27 (40.9%) were female, with a mean age of 60.1±9.14 (28-75) years.

Tractional retinal detachment was present in 36 patients, vitreous hemorrhage in 17 patients, epiretinal membrane in 9 patients, macular hole in 4 patients, and cataract in all patients. 25 patients (37.8%) had a history of COVID-19 between 20 days and 60 days (mean 49 days) before the operation. Eight patients who had never been vaccinated before the operation, 3 patients with a single dose, 22 patients with 2 doses, 20 patients with 3 doses, and 13 patients with 4 doses. It was known that six patients had previously been vaccinated with Sinovac (CoronaVac), 31 patients with Pfizer–BioNTech, and 21 patients with both Sinovac (CoronaVac) and Pfizer–BioNTech. The last vaccine dose of 58 patients (87.9%) who had a history of vaccination before the surgery was administered an average of 90 days (7-270 days) before the surgery. The flow chart showing the immune status of 8 patients (12.1%) who had no previous vaccination history is given in Figure 1.

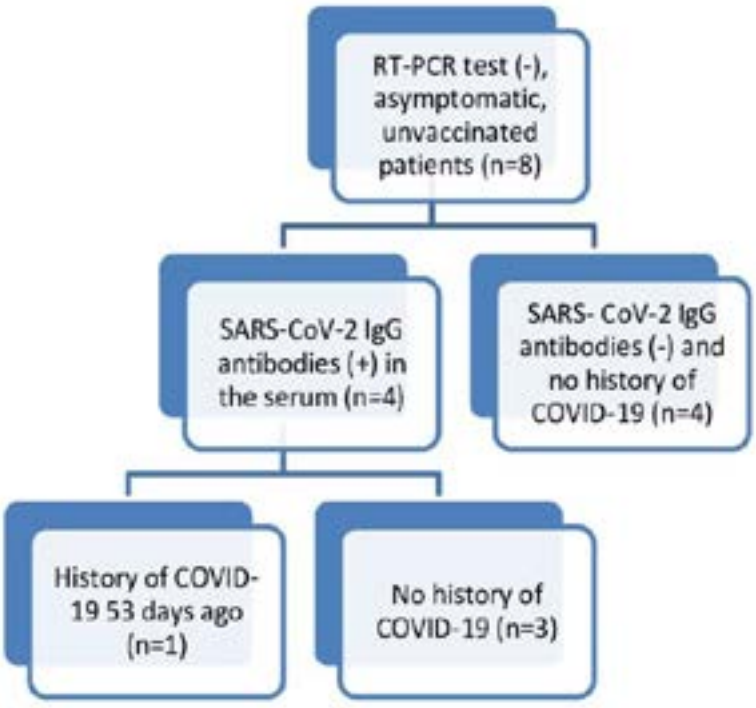

Figure 1. Flowchart demonstrating the immune status of unvaccinated patients

Fifty patients were operated on under topical anesthesia whereas 16 patients were operated on under general anesthesia. The mean surgery duration was 105 minutes (90-125 minutes). Intraocular fluid samples taken from the right eye of 37 patients and the left eye of 29 patients were analyzed. No SARS-CoV-2 RNA was detected in the aqueous humor and vitreous samples of any patient. No COVID-19 symptoms were observed in any of the patients in the 72-hour period after the operation. No ocular complications were encountered in the postoperative follow-up of the patients. IgG against SARS-CoV-2 was detected in the serum of 3 patients who had not been vaccinated against COVID-19 before and had no known history of COVID-19 disease.

Discussion

This study was conducted to determine the presence of SARS-CoV-2 in the aqueous humor and vitreous in patients undergoing combined phaco-vitrectomy surgery. We did not find any SARS-CoV-2 viral genetic material in asymptomatic participants whose nasal swab test was negative, even if they recently had COVID-19.

During the COVID-19 pandemic, outpatient and inpatient surgeries were limited and the number of ophthalmologic cases fell sharply. With the decrease in the number of COVID-19 cases and the abandonment of the pandemic rules, the number of ophthalmic surgeries has increased rapidly. In this study, SARS-

CoV-2 viral genetic material in aqueous humor and vitreous samples and SARS-CoV-2 IgG antibody levels in the serum of asymptomatic individuals with negative nasal swab test who presented for elective combined phaco and pars plana vitrectomy surgery were evaluated.

Ocular symptoms and signs are frequently encountered in COVID-19 patients. In these cases, either the haematogenous route to the posterior segment or direct implantation of viral load in conjunctival mucosa can result in ocular symptoms [9, 10]. Sometimes ocular symptoms may precede respiratory or other symptoms. Adults most frequently experience follicular conjunctivitis, conjunctival hyperemia, chemosis, and epiphora. Patients with COVID-19 have been documented to develop uveitis, optic neuritis, disc edema, retinal artery occlusions, intraretinal hemorrhages and cotton wool spots. Signs and symptoms of neuro-ophthalmology include myasthenia gravis, diplopia, and ocular discomfort. Whether these symptoms result from direct infection of the eye, immunologic reactions, or ischemic damage to the visual system is not clear [11].

The presence of SARS-CoV-2 has previously been described on the ocular surface, including the tears, conjunctiva and nasolacrimal duct [12, 13]. Studies investigating the presence of SARS-CoV-2 genetic material or proteins in intraocular fluids or tissues have generally been conducted on people known to be infected with the virus or on postmortem tissues. In the first study evaluating the presence of the intraocular virus, the SARS-CoV-2 PCR test was found to be negative in postmortem aqueous humor and vitreous samples of 16 patients whose nasopharyngeal swab tests were positive and the cause of death was respiratory failure due to SARS-CoV-2. It was considered that the amount of time between a person's passing and their autopsy had no bearing on the virus' detectability because SARS-CoV-2 was still detectable after 14 days at +4°C and 7 days at +22°C in a virus transit environment [14], and it was argued that due to the small sample size, intraocular involvement cannot be completely excluded with these results [15].

In another study conducted in 10 eyes of 5 patients who died from COVID-19, SARS-CoV-2-RNA was not detected in any of the human vitreous and retinal samples. Histopathological examinations revealed no signs of viral damage to the retinal vasculature or tissues. It was emphasized that SARS-CoV-2 infection of human retinal tissue and/or vitreous fluid, if viral replication is possible, is extremely rare in COVID-19 postmortem donors, therefore retinal histopathology was normal in a small patient cohort. In addition, negative results have been explained by the view that pathological changes may not be permanent in individuals succumbing to COVID-19 [16]. In a larger study evaluating 28 conjunctiva, 30 aqueous humor, and 30 vitreous fluid, SARS-CoV-2 RNA was evaluated in postmortem ocular specimens, and positive results were found in 1 conjunctival and 2 vitreous specimens in 3 different patients [17]. Compared to the aforementioned studies, the higher number of samples in this study may have resulted in positive results.

Sanjay et al. [18] isolated SARS-CoV-2 in the vitreous sample of a case with endogenous endophthalmitis and conducted the first study demonstrating the presence of intraocular virus in a live case. In another study, 7 posttraumatic patients with positive nasal swab test who were asymptomatic or had moderate COVID-19 were evaluated, and RT-PCR tests were found to be negative in 7 aqueous fluid samples and 5 vitreous fluid samples [19].

In the study conducted by Yan et al. [20], despite the date, 2 months after the reported infection, viral proteins were observed. The study revealed the possibility that SARS-CoV-2 proteins could be discovered inside of the eye and continue to exist even after the virus has appeared to have cleared up in the bloodstream. However, in our study, no genetic material was found in the intraocular fluids of 25 patients who were known to have had COVID-19 on average 49 days (20-60) ago, and in a patient who was unvaccinated but had SARS-CoV-2 IgG antibodies in the serum who was known to have had COVID-19 53 days ago. Additionally, there was no genetic material in the intraocular fluids of 3 patients who were unvaccinated and had SARS-CoV-2 IgG antibodies in the blood and had no history of COVID-19, possibly asymptomatic.

Jin et al. [21] reported a case who had acute graft rejection and tested positive for SARS-CoV-2 by PCR 5 days after the onset of ocular symptoms. This suggests that aqueous humor

may play a role in corneal endothelial rejection in some patients infected with SARS-CoV-2. Based on this study, Dr. Koo et al. [6] conducted the first study investigating SARS-CoV-2 in the aqueous humors of living individuals with a negative nasal swab test. PCR results were positive in aqueous humor in 6 of 31 samples with no symptoms and a negative nasal swab test. Information about the immunity level and vaccination status of the patients is not available in this study. We think that this positivity rate is quite high for these patients with a negative COVID-19 swab test and no symptoms.

In our study, in which we evaluated both anterior chamber and vitreous samples with a larger patient population, we did not find any genetic material belonging to the virus in either the aqueous or vitreous in any of the participants. In our study, the COVID-19 histories of the patients were determined not only according to their statements but also according to electronic records. We also evaluated the serum Ig G levels of our patients and found that there were 3 patients developed immunity in the serum, even if they were unvaccinated and had no known history of COVID-19. We think that these patients had the infection asymptomatically and gained immunity. One immunized patient who was unvaccinated and had a history of COVID-19 was COVID-19 positive 53 days before the operation. Although it has been previously shown that the SARS-CoV-2 antigen is present in a patient with a history of COVID-19 30 days prior [20], we think that the time of infection of these 4 patients who were unvaccinated and had Ig in their blood, long before the operation date, may have negatively affected the possible presence of virus in the intraocular fluid samples.

The presence of SARS-CoV-2 in body fluids including tears has been predicted to be associated with viral load and disease severity, as indicated by the Ct values of naso-oropharyngeal RT-PCR [22]. Contrary to the previous studies, no virus was found in the vitreous and aqueous fluid samples of any of the patients, suggesting that this may be related to the viral load and the increasing rate of vaccination today. In addition, as a limitation of the study, it may not be appropriate to investigate the possibility of latent virus in the vaccinated participant group.

In conclusion, in this study, we did not detect SARS-CoV-2 viral genetic material in the aqueous and vitreous of asymptomatic patients with negative nasal swab test for COVID-19. There is a need for more comprehensive studies investigating the latency of the virus in immune-privileged areas such as the eye and how long it remains in the eye even if it is withdrawn from circulation. In addition, more comprehensive studies are needed to investigate possible eye diseases that may be caused in the convalescent phase.

Conflict of interest: The authors declare that they have no conflict of interest.

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Ethics committee approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Adana City Training and Research Hospital Ethics Committee (95/1686, 16.12.2021) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by G.H.N.S., E.C., N.U., H.P., E.A. The first draft of the manuscript was written by G.H.N.S. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Research Article

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Evaluation of quality of life and post-operative complications of our radical prostatectomy series for 5 years

Beş yıllık radikal prostatektomi serimizin postoperatif komplikasyon ve yaşam kalitelerinin değerlendirilmesi

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Abstract

Purpose: The aim of this study is to evaluate health status, erectile function, continence status and mental status of the patients. We also analyze demographic features and post-operative complications. We want to detect changings in surgical techniques and complication rates, so we will obtain accurate knowledges for the patients who will undergo radical prostatectomy in the future.

Materials and methods: 67 patient included to this study with permission of Pamukkale University ethic commission. We phoned patients and ask to come hospital to filling out forms and to ask few questiones. We suggest them to fill out generel health quality, IIEF, ICIQ and MMT forms. We also asked them how they decide to undergo operation, their satisfaction with the treatment and whether they would accept the same treatment again. We record demographic and follow-up informations of patient from database of our hospital.

Results: We found that the number of the patients who undergone radical prostatectomy increased over the years and the lenght of stay in hospital and the risk of additional operation for urethral stricture decreased.

Conclusion: Data from our study were compatible with the existing literature.

Key words: Radical prostatectomy, quality of life, complications.

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Öz

Amaç: Çalışmamızın amacı kliniğimizde son 5 yılda yapılan radikal prostatektomi ameliyatlarının hastaların genel sağlık durumları, erektil fonksiyonları, kontinans durumları ve mental durumlarını değerlendirmek ayrıca hastaların demografik özellikleri ile post-operastif takiplerini retrospektif olarak değerlendirmektir. Bu değerlendirmeler sonucunda kliniğimizde yapılan radikal prostatektomi ameliyatlarının yıllar içinde teknik ve sonuçlar açısından değişimi saptanacak ayrıca önümüzdeki yıllarda bu ameliyatın önerileceği hasta grubuna sunulabilecek somut verilere ulaşılabilecektir.

Gereç ve yöntem: Çalışmaya Pamukkale Üniversitesi Tıbbi Etik kuruldan alınan izinle toplam 67 hasta dahil edildi. Hastalar telefonla aranarak hastaneye çağrıldı. Hastalara genel sağlık durumu, 11EF, ICIQ ve MMT sorgu formları uygulandı. Ayrıca hastalara operasyona karar aşamasındaki tutumları, tedavi memnuniyetleri ve aynı tedaviyi tekrar kabul edip etmeyecekleri soruldu. Ardından hastaların operasyon ve operasyon sonrası takip bilgileri hastane hasta takip sisteminden kaydedildi.

Bulgular: Çalışma kliniğimizin son 2 yılda radikal prostatektomi sayısında artış olduğu ayrıca vaka sayısında artışla birlikte hastaların hastanede kalış sürelerinin ve darlık nedeniyle ek girişim riskinin azaldığı saptanmıştır.

Sonuç: Çalışmamızdan elde edilen veriler mevcut literatür ile uyumlu saptanmıştır.

Anahtar kelimeler: Radikal prostatektomi, yaşam kalitesi, komplikasyon.

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Introduction

PSA (prostate-specific antigen) and DRE (rectal examination) are often used for prostate cancer screening. Younger patients are diagnosed with PCa (prostate cancer), and more patients are undergoing RP (radical prostatectomy) surgery. However, RP can cause long-term urinary and sexual problems in some patients. In addition to the survival rates, the effect of the surgery on the quality of life of the patients should be carefully examined in each case separately and in a unique way. Many parameters affect patients' satisfaction with the treatment and their perceptions about the treatment. These are briefly; long-term cancer control, side effects of treatment, complications that may develop and quality of life after treatment.

The aim of this study is to evaluate the general health status, erectile function, continence, mental aspects of the patients who underwent RP in our clinic and to determine the changes over the years. As a result of this study, the technical development of RP surgeries performed in our clinic over the years and the results of the procedures will be determined. In addition, it is to provide concrete data that can be presented to patients for whom we recommend this surgery in the future.

This study was produced from the Medicine Specialization Thesis by Cihan Toktas MD.

Materials and methods

This study was performed at the Department of Urology, Pamukkale University Faculty of Medicine Hospital clinic. Of the 87 patients (N) who underwent RP surgery and knew that they had been diagnosed with cancer, the data of 67 patients (n) who agreed to participate in the study were included.

Detailed information about the study was given to the patients included in the study, information was given to the volunteers and their written consent was obtained. Ethics Committee approval was obtained for the study.

Inclusion Criteria:

1- Patients who underwent RP with Pca diagnosis in our clinic

Exclusion Criteria:

1- Those who underwent another intraabdominal / urinary surgery after RP.

2- Those whose quality of life changes for another reason after RP

Questionnaire filling method

Patients who met the criteria sought were contacted by phone and invited to the hospital after being given a brief information about the study. Patients who came to the hospital and agreed to participate in the study were informed in detail about the study. Then, the patients were given 4 query forms by a medical doctor who was not involved in the study and asked to fill out these forms. These forms are IIEF (International Index of Erectile Function), ICIQ (International Consultation on Incontinence Questionnaire, mini mental test and EQ-5D (also to benefit from general health care). After filling out the forms, the patient's name and an identification mark were not written on any of the inquiry forms. In the forms, the age and comorbidity, clinical stage, prostate biopsy Gleason score of all patients, the Gleason score of the surgery, prostatectomy material from the hospital information tracking system, the duration of hospital stay of the patients in the postoperative period, and the intervention status due to anastomotic stricture in the post-discharge period were recorded.

SPSS 15 (Statistical Package for Social Sciences) package program was used for statistical evaluations. In the analysis of the obtained data, Mann Whitney U test, significance test of the difference between the two averages and chi-square test were used. In statistical analysis, $p>0.05$ was accepted as significant value.

Results

The 67 patients included in the study had a mean age of 61.57 years. When we examine the total number by years, the number of surgeries performed in the last 2 years (34-Dark columns) was higher compared to the number of surgeries in the first 3 years (33-Light columns) (Figure 1).

The distribution of patients according to their clinical stages is as shown in Figure 2.

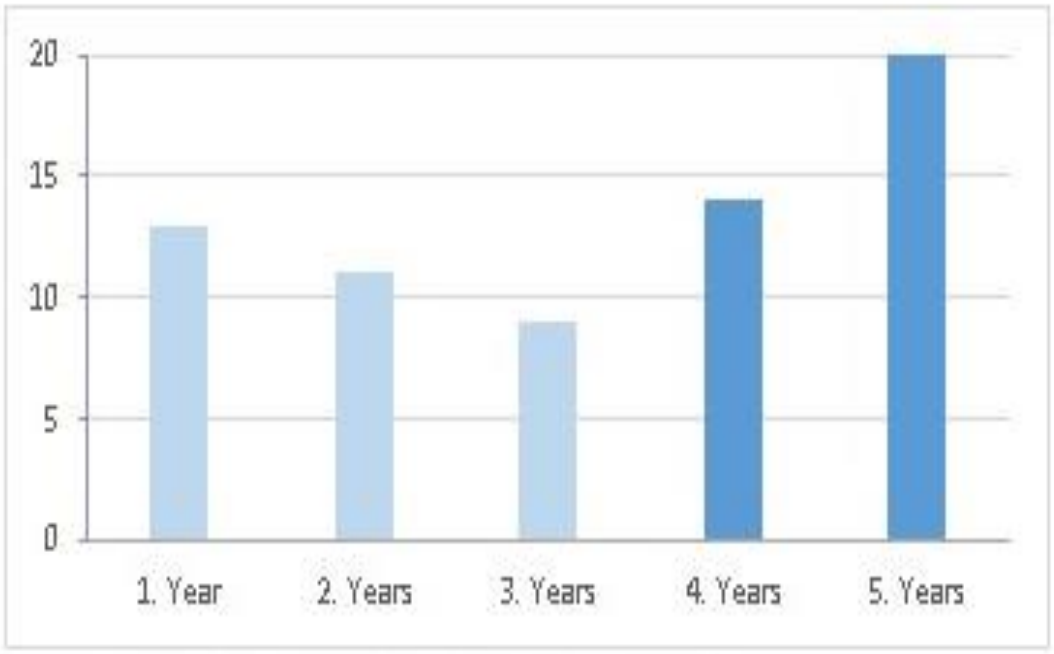

Figure 1. Number of RP by years

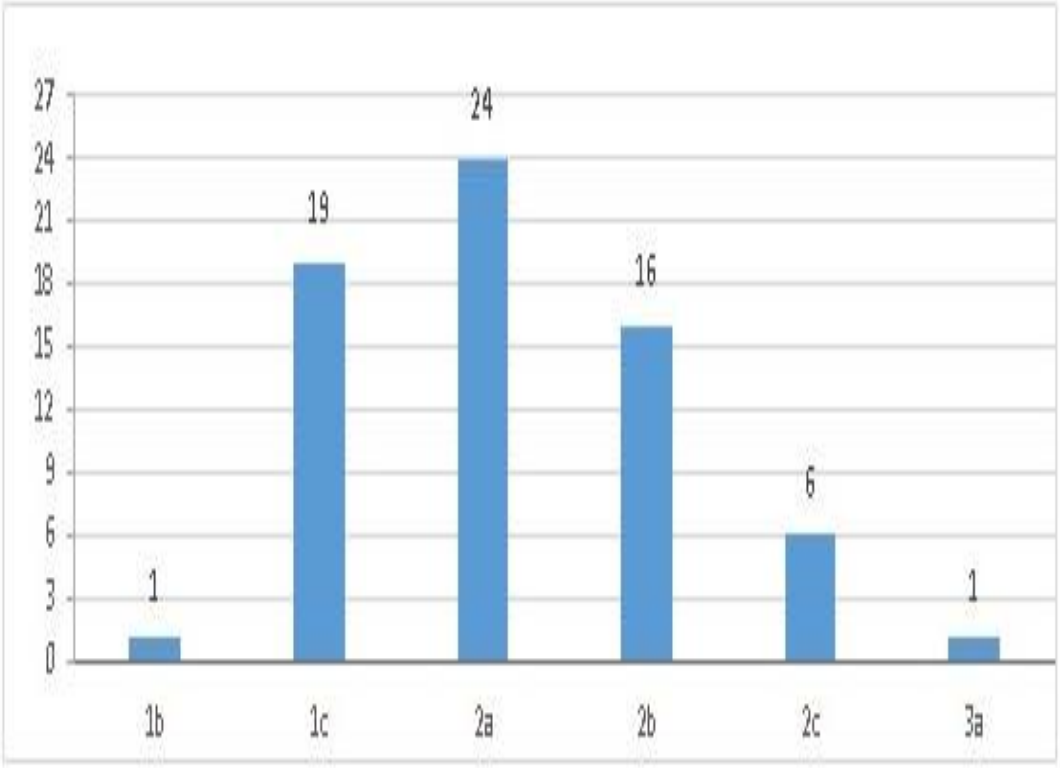

Figure 2. The clinical stages of the patients

The mean hospitalization period of the patients was calculated as 5.67 (±2.6) days. When the duration of hospitalization was analyzed according to the groups: Group 1 (first 3 years) average was 7.03 days, group 2 (last 2 years) average was 4.35 days, and there was a statistically significant difference between the groups (p=0.001) (Table 1).

Age, PSA value and biopsy Gleason score according to the groups are given in Table 2. There was a statistically significant difference in PSA values between the groups (p=0.034).

Table 1. The length of hospitalization of the two groups

	n	Duration of hospitalization	
Group 1	33	7.03 days	***p*=0.001**
Group 2	34	4.35 days	

Table 2. Age, PSA value and biopsy Gleason scores of the groups

	Group 1	Group 2	*p*
Age	60.30	62.76	>0.05
PSA	8.40	12.66	**0.034**
Biopsy Gleason Scores	6.4	6.5	>0.05

In the general evaluation of the patients, 18 (26.9%) of 67 patients were operated due to anastomotic stricture. We did not find a statistically significant difference in the comparison of the groups according to the years of operation and under/over the age of 60 (p>0.05).

When vesicourethral anastomotic stricture was examined, the number of procedures per patient was 0.57 (19/33) in Group 1 and 0.23 (8/34) in Group 2, and there was a statistically significant difference (p<0.05).

When patients are asked to evaluate their health status; The median of the scores they gave out of 100 ranged from 75 to 100 and the mean was 91.87 (±6.7). In the evaluation of the mini mental test scores of the patients, the mean score was found to be 25.9 (±1.85). When the patients were evaluated according to their ICIQ scores, it was found that 15 patients (22.4%) had no urinary incontinence. Of the 52 patients with urinary incontinence, 16 had severe scores of 8 and above, defined as the ICIQ score. With these results, severe urinary incontinence was observed in 23% of the entire patient group. There was no statistically significant difference between the incontinence rates of groups 1 and 2 (p>0.05).

When the IIEF values of the patients in group 1 and group 2 were compared, there was no statistically significant difference (p>0.05).

The satisfaction rate of our patients was 97%, and the rate of re-accepting the same treatment was 98%. The prostate cancer specific survival rate was 100% after a mean follow-up of 30 months, and these results are consistent with the literature.

In the interviews about the decision process, 9 (13%) of 67 patients followed the recommendations of the responsible doctor without questioning in the decision process, 32 (48%) decided in line with the doctor's recommendations together with the responsible doctor, and 26 (39%) patients stated that they chose surgery after doing research on PCA treatment after diagnosis.

Discussion

Prostate cancer is the 2nd most common cancer type in men and the 5th deadliest cancer type in 2020 [1]. Worldwide, 1.4 million new cases and 375,000 deaths are predicted annually [1, 2]. The use of PSA is gradually increasing and patients can be diagnosed at earlier stages in this way [3]. In the locally/ locally advanced group, which constitutes as high as 87% of the patients, the 5-year relative survival rates are 100% [4].

Although the results of treatment options for localized PCa are close to each other, the risks they carry differ. While sexual and urinary problems are seen in RP patients, intestinal

problems are more common in radiotherapy patients [5-10]. However, in a study in which patients were followed for approximately 30 years, it was found that RP contributed approximately 3 years to life expectancy compared to untreated patients [11].

One of the indicators that determine the success in localized PCa treatment is patient satisfaction [12]. Therefore, it is recommended that patients be informed about the treatment process [13].

While there were only 86 studies on quality of life in prostate cancer between 1990 and 2000, this number was 243 in 2010 and 2011 alone [14].

Clear differences in favor of RP were reported in a study involving a total of 695 patients in which the non-procedure active surveillance and RP groups were compared [15]. The fact that radical prostatectomy is the only effective treatment method for localized PCa treatment, despite monitoring, has made this surgery more popular. Because the feeling of getting rid of the cancerous organ at the end of this surgery increases the quality of life of patients after surgery [16-19].

In patients with localized PCA, as well as in patients locally advanced with lymph node dissection, the recommendation for radical prostatectomy surgery is ‘strong’ in the European Association of Urology 2022 Pca guidelines [13].

The effect of patients’ feelings of being completely free of cancerous tissues on their quality of life was shown in a study of 223 patients in 2000. It has been reported that patients receiving maximum androgen blockade (MAB) as primary treatment had higher depression scores than the RP group [20]. Similar results were found by Johansson et al. [21].

Studies have shown that prostate cancer patients’ satisfaction with treatment with RP and the rate of re-admission to the same treatment are quite high (77-97%) [22-25]. As a result of our study, we noticed that patients prioritize cancer control above all else, and complaints of incontinence and erectile dysfunction remain in the background.

Studies show that the decision-making process for treatment also affects satisfaction. Miles et al. [26] reported that those who were dissatisfied with the treatment thought that the choice of treatment was rushed and that they did not make a second opinion decision on their own. It was also found that a significant portion of the patients were between the ages of 60 and 69. The results of the patients in our study are consistent with the literature.

Davison et al. [27] 155 patients who underwent RP were evaluated in the 1st year after surgery. Of these patients, 30% received opinions from at least 2 urologists before deciding on surgery, 32% received a consultation from a radiation oncologist before deciding on surgery, 84% (109 patients) negotiated with their doctor before deciding on surgery, 5% of them (7 patients) said that they took a collaborative role in line with the physician’s recommendations. A study that published in 2008 shows that 19,4% of the patients had no enough information about the surgery they were going to undergo [28]. These results were similar to the results in our study.

The results of these studies highlight the necessity of adequately informing patients about all treatment options after the diagnosis of PcA. Similarly, as stated in the quality of life study according to cystectomy and urinary diversion in patients with bladder cancer performed by Baser et al. [29] in our clinic, it is important to inform patients preoperatively without compromising oncological principles.

After radical prostatectomy, approximately half of the patients describe a decrease in sexual desire, and 80% of them describe a decrease in the frequency of sexual intercourse. 56.5% of patients say that their partner’s satisfaction with sexual intercourse decreases [30]. These factors are reported to increase patient satisfaction as the surgical experience of the health center where RP surgery is performed and the surgical team that performs the surgery increases.

It has been reported that vesicourethral anastomotic stricture is in the range of 24-45% in patients with post-surgical urethroscopic examination of patients with stress incontinence, and the anastomotic stricture occurs in the first 6 months [31-33]. The rate of 26% obtained in our study was similar to the studies in the literature.

In our study, anastomotic stricture developed in 16 of 18 patients (88%) who developed anastomotic stricture in the first 3 months.

Predictive factors for anastomotic stricture developing after radical prostatectomy were associated with patient age, operation time, and blood loss [34-36].

More complications and mortality are seen in clinics with a small number of operations compared to clinics with larger series [37].

As a result; as the number of patients undergoing RP surgery and their surgical experience increase, the length of hospital stay of the patients shortens significantly. In addition, the rate of additional interventions per patient for vesicourethral anastomotic stricture is significantly reduced. Informing patients about complications before surgery increases their satisfaction. Patients' satisfaction with radical prostatectomy surgery and our readmission rates are high. Radical prostatectomy surgery is a surgery with low per-op and post-op mortality rates.

Conflict of interest: No conflict of interest was declared by the authors.

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Ethics commite approval: Permission was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committee for the study (date: 17-5-2011 and permission number: 9).

Authors' contributions to the article

All authors have constructed main idea of the study. C.T. arranged the material also has done the evaluation of the data in the results. Discussion section written by C.A. and C.T.; L.T. reviewed and corrected the study. In addition, all authors discussed the entire study and approved the final version.

Research Article

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The psychometric properties of the general phubbing scale in adolescents

Ergen yaş grubunda genel phubbing ölçeği'nin psikometrik özelliklerinin incelenmesi

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Abstract

Purpose: Numerous studies indicate that the use of smartphones among adolescents has increased recently. Studies on phubbing generally focus on how parental phubbing affects adolescents. This study aims to contribute to the literature by revealing the validity and reliability of the scale measuring phubbing behavior in adolescents.

Material and methods: The sample included 206 adolescents aged 12-17 who applied to Pamukkale University Medical Faculty Hospital Child and Adolescent Psychiatry Outpatient Clinics and Kırıkkale Yüksek İhtisas Hospital Child and Adolescent Psychiatry Outpatient Clinic.

Results: To evaluate the construct validity of the General Phubbing Scale (GPS) in adolescents, first and second level confirmatory factor analyses were performed. The data model fit was shown to be at an acceptable level. The general phubbing was negatively related to social connectedness and positively related to internet addiction. Test-retest analysis indicated that the subdimensions nomophobia, interpersonal conflict, self-isolation, problem acknowledgment, and total score were 0.82, 0.80, 0.71, 0.66 and 0.81, respectively. The coefficients of internal consistency for the subdimensions of nomophobia, interpersonal conflict, self-isolation, problem acknowledgment, and total score were 0.78, 0.85, 0.92, 0.77, and 0.94. Furthermore, it has been shown that the GPS structure was identical for both genders.

Conclusion: This study demonstrated that the GPS can be used as a valid and reliable measurement tool for determining general phubbing levels for the clinical adolescent sample.

Key words: Phubbing, adolescent, smartphone.

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Öz

Amaç: Birçok çalışmada son yıllarda ergenler arasında akıllı telefon kullanımının arttığı gösterilmektedir. Phubbing ile ilgili yapılan çalışmalarda, genellikle ebeveyn phubbing davranışının ergenler üzerindeki etkilerine yoğunlaşıldığı görülmektedir. Phubbing davranışını ölçen ve ergenlerdeki geçerlik ve güvenilirliği yapılmış bir ölçeği ortaya koyarak literatüre katkı sunulması amaçlanmıştır.

Gereç ve yöntem: Çalışmanın örneklemini, Pamukkale Üniversitesi Tıp Fakültesi Hastanesi Çocuk ve Ergen Ruh Sağlığı ve Hastalıkları Poliklinikleri'ne ve Kırıkkale Yüksek İhtisas Hastanesi Çocuk ve Ergen Ruh Sağlığı ve Hastalıkları Polikliniği'ne başvuran 12-17 yaş arası 206 ergen oluşturmaktadır.

Bulgular: Genel Phubbing Ölçeğinin (GPÖ) ergenler için yapı geçerliği test etmek amacıyla birinci ve ikinci düzey doğrulayıcı faktör analizi yapılmış ve veri model uyumunun kabul edilebilir düzeyde olduğu gösterilmiştir. Genel phubbingin, sosyal bağlılık ile olumsuz yönde ve internet bağımlılığı ile olumlu yönde ilişkili olduğu ortaya koyulmuştur. Test tekrar test analizleri korelasyon sonuçları; nomofobi, kişiler arası çatışma, kişisel izolasyon, problem kabulü alt boyutları ve toplam puan için sırasıyla 0,82, 0,80, 0,71, 0,66 ve 0,81 olduğu gösterilmiştir. Ölçeğin iç tutarlılık katsayısıları ise; nomofobi, kişiler arası çatışma, kişisel izolasyon, problem kabulü alt boyutları ve toplam puan için sırasıyla 0,78, 0,85, 0,92, 0,77 ve 0,94 olarak saptanmıştır. Ayrıca, GPÖ'nün her iki cinsiyet için de aynı yapıya sahip olduğunu gösterilmiştir.

Sonuç: Bu çalışmanın bulguları GPÖ'nün klinik ergen örneklemi için Genel Phubbing düzeylerini belirlemede geçerli ve güvenilir bir ölçme aracı olarak kullanılabileceğini göstermektedir.

Anahtar kelimeler: Phubbing, ergen, akıllı telefon.

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Introduction

The role and quality of communication has gained great significance in the modern world. Moreover, with the development of technology, the quality of communication and the speed of communication have also increased [1]. The production of personal devices, such as smartphones, has also expanded the area of communication technology by facilitating human interaction [2]. Smartphones not only provide easy communication, but also allow people to connect with family and friends throughout the day, wherever and whenever they want [3]. In addition, they also allow access to entertainment [4] and online games [5].

These developments in information technology have also led to some undesirable results. According to the study conducted by the Savci and Aysan [6], the most sensitive group to smartphone or internet addiction is youth. Pew Research (2018) report revealed that 95% of youths have attainment to a smartphone, and 45% of youths are online almost constantly [7]. It was found that smartphone addiction among adolescents in India ranged from 39% to 44% in a meta-analysis study [8]. Another review study revealed that problematic smartphone use among children and adolescents ranged from 5% [9] to 50% [10, 11]. With the presence of many technological devices in smartphone models in the last 15 years [12], many addictions such as Short Message/Messaging Service (SMS) addiction [13], internet addiction [14], and game addiction [15] are gathered under a single focal object [1]. Due to all of these reasons, phubbing occurs in the area where these addictions meet and enter our daily lives as a multidimensional phenomenon that can seriously affect daily communication [16].

With the widespread introduction of smartphones into our lives, the concept of phubbing emerged in 2007 in Australia [17] and was included in an advertising campaign in the dictionary of Macquarie [2]. Phubbing is when a person suddenly gets lost in his/her phone during a social interaction and focuses on it [18]. The word phubbing is formed by the combination of the words “phone” and “snubbing”. It is described as the act of belittling the person in social environment by focusing on the phone/smartphone during communication, in place of talking to the person directly [19]. Nazir and Piskin [17] define phubbing as the act of disregarding one or more people during social activities, controlling or using WhatsApp, Facebook, WhatsApp or other social media applications using smartphones. According to Aagaard [18], phubbing is an act in which a person suddenly turns their gaze down in the middle of a social interaction and gets lost in their smartphone. Blanca and Bendayan [20] describe phubbing as using smartphone in social environment with two or more people and interacting with the phone instead of communicating with other persons. The concept of phubbing received worldwide media coverage and became popular with the ‘Stop Phubbing’ campaign [21]. The definition of phubbing shows that there is a behavior pattern that can affect social interaction. Some studies have shown that high levels of phubbing are associated with depressive mood [22]. In other studies, it was found that high social anxiety increased phubbing during peer communication [23], and loneliness played a mediating role between adolescents’ problematic smartphone use and parents’ phubbing behaviors [24]. In a study conducted in Turkey, it was shown that aggression was one of the predictors of phubbing behavior [25].

Recent studies have investigated the antecedents of phubbing behavior. It has been observed that the most important determinant is smartphone addiction [16, 26]. Studies about phubbing revealed that people perceive their interactions to be of poorer quality [27], be less satisfied with their interactions [28], trust their interaction partners less [29], and feel less close to their interaction partners in the presence of the phone [19, 30]. The results of a study that included 2407 adolescents in China showed that there was a relationship between the level of parental phubbing and depressive symptoms in adolescents [31]. It was found that parent phubbing behavior was positively associated with adolescent mobile phone addiction in another study, which included 726 adolescents in China. This association was mediated by the parent-child relationship [32].

Karadag et al. [16] found that smartphone addiction, SMS addiction, social media addiction and internet addiction predicted phubbing behavior. In addition, Chotpitayasunondh and Douglas [33] found that internet addiction, fear

of missing out and lack of self-control predict smartphone addiction, which in turn predicts the extent to which people phub [26]. It is seen that internet addiction is effective on phubbing behavior both directly and through smartphone addiction. On the other hand, as can be understood from the definition of phubbing behavior, it can be considered as a behavior pattern that may cause problems in social relationships. When previous studies on the relationship between social commitment and phubbing behavior are examined, it is seen that there is a negative relationship between social commitment and phubbing behavior [34].

It is evident that there are studies examining phubbing behavior in the literature. The studies conducted on adolescents are mostly related to the effects of parent phubbing behavior on adolescents. Moreover, the scales used to evaluate phubbing behavior were designed to be used in adults. We found no scale designed for adolescents measuring phubbing behavior in our literature review. In our study, it was aimed to contribute to the literature by performing the validity and reliability of the phubbing scale in the adolescent age group.

Materials and methods

Our research is methodological and cross-sectional study. This study, includes adolescents between the ages of 12 and 17, who applied to Pamukkale University Faculty of Medicine Hospital Child and Adolescent Psychiatry Department and Pamukkale Hospital Child and Adolescent Psychiatry Outpatient Services. The data were collected between August and December 2022. Ethics committee approval of the study was obtained with Pamukkale University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee meeting dated 26.07.2022 and numbered 11. The study contained adolescents aged 12-17 years, whose parents agreed to participate and who completed the scales and did not include adolescents with autism spectrum disorder, mental retardation, psychotic disorder, or who did not agree to participate. Written informed consent was obtained from the participants and their parents before participation in the study.

Dr. Chotpitayasunondh, the co-author of the study who developed the scale, was contacted via e-mail and required permissions were obtained to use the scale. Dr. Naif Ergun, the responsible author of the study that examined the Turkish validity and reliability (TVR) of the scale in adults, was contacted by e-mail and permissions were obtained to use the Turkish version of the scale in adolescents.

In methodological studies, sample size can be calculated by different methods. In terms of sample size, Comrey and Lee [35] evaluated sample sizes between 50 and 1000. 50 is very weak, 100 is weak, 200 is mild, 300 is good, 500 is very good, and 1000 is excellent for determining the sample size in their scale studies. The sample size recommended by Kline [36] was ten times the number of items, while Bryman and Cramer [37] recommended five or ten times the number of items. In this study, a total of 206 adolescents participated, and scales were re-administered to 34 adolescents 4 weeks later for the test-retest.

Statistical analysis

Data analysis was applied in three stages using SPSS 22 and AMOS 22. First process, Confirmatory Factor Analysis (CFA) was conducted to test the construct validity (CV) of the GPS. The fit indexes recommended by Kline [38] were used to test the Data-Model fit (DMF). These are: Root Mean Square of Error Approximation (RMSEA), Chi-Square (X2), Standardized Root of Mean Errors (SRMR), Chi-Square/Degree of Freedom (X2/Sd). As fit indices; Comparative Goodness of Fit Index (CFI), Tucker Levis Index (TLI), Goodness of Fit Index (GFI), Relative Goodness of Fit Index (RFI) and Normized Goodness of Fit Index (NFI) were used.

Testing the latent structure is an important step in validating a measurement instrument or construct. Latent structures refer to the underlying theoretical constructs or dimensions that a set of observed variables are intended to measure. In addition, to test the latent structure because it helps to confirm whether the observed variables are actually measuring what they are intended to measure. In other words, it helps to determine whether the observed variables are good indicators of the underlying construct or dimension.

The second process, Cronbach's Alpha (CA) and test-retest coefficient were calculated to calculate the internal consistency coefficient of the variable. In the third process, the convergent and criterion-related validity (CRV) of the scale was calculated. For convergent validity, the Pearson correlation coefficient was calculated to calculate its relationship with the Internet Addiction scale. For criterion-dependent validity, correlation analysis was used to calculate the relationship between phubbing and social commitment based on the theoretical explanations in the literature. Also, we analyzed the average variance extracted (AVE) value for convergent validity. In the fourth stage, measurement invariance was used to measure whether there was a similarity in terms of male and female gender.

Data collection tools

Sociodemographic Data Form (SDF): SDF was composed by the researchers.

General Phubbing Scale (GPS): Scale developed by Chotpitayasunondh and Douglas [33] in 2018. It was formed as a 7-point Likert scale for phubbing in adults. The scale consists of 15 questions and 4 subdimensions. These subdimensions are nomophobia (NP), self-isolation (SI), interpersonal-conflict (IC), problem-acknowledgment (PA). Low score from GPS defines low level of phubbing, and high score defines a high level of phubbing. The TVR of the scale for adults were performed by Ergun et al. in 2019 [39].

Young's Internet Addiction Test (Y-IAT) short version: Developed by Young [40] and transformed into a short form by Pawlikowski et al. [41]. The scale occurs twelve items, and it is a five-point Likert scale. The outcomes of the validity and reliability studies indicated that the validity and reliability of Y-IAT Short Version was provided. High scores acquired from the scale define that the level of internet addiction is high. The Turkish adaptation of Y-IAT was made by Kutlu et al. in 2016 [42].

Social Connectedness Scale: The scale, developed by Lee and Robbins [43], consists of 8 items that evaluate the level of social connectedness, which is an important part of individuals' sense of belonging, especially during and after adolescence. The scale is a six-point likert type. High scores acquired from the scale, which does not have a reverse scored item, defines high social connectedness. Turkish adaptation of the scale was made by Duru [44].

Results

Sociodemographic Data

Among the patients included in the study, 61.2% were female and 38.8% were male. The mean age of the cases was 15.13±1.5 years (min:12, max:17). Regarding the family structure of the participants, it was found that 78.2% had nuclear families, 8.3% had extended families, 11.2% had divorced parents, and 2.3% had deceased parents. The income levels of the cases were found to be 7.8% low, 67.5% middle and 24.7% high income.

Validity analysis

The CV and CRV were analyzed inside of content of the validity analysis of the GPS.

Construct Validity (CV)

To test the CV of the GPS for adolescent population, first and second level CFA were performed (Figure 1 and Figure 2). First level CFA results indicated that the DMF was at an acceptable level [X2(Sd=84, N=206)=187.062, p<.001, X2/Sd=2.227, RMSEA=.08 (.06-.09), SRMR=.05, CFI=.95, TLI=.94, NFI=.91 ve IFI=.95)]. In the second stage, second-level CFA was applied to test whether latent structure was confirmed or not. Our findings of the second-level CFA indicated that the DMF was at an acceptable level [X2(Sd=86, N=206)=198.109, p<.001, X2/Sd=2.304, RMSEA=.08 (.07-.09), SRMR=.05, CFI=.94, TLI=.93, NFI=.91 ve IFI=.94)].

Convergent Validity

The convergent validity of General Phubing Scale was examined in two stages. In the first step, the composite (CR) value and of General Phubing Scale were tested. The findings indicated that The AVE values for nomophobia, interpersonal conflict, self-isolation, and problem acknowledgment are 0.49, 0.58, 0.75, and 0.54, respectively. According to Fornell and Larcker's [45] standards, AVE values greater than or equal to 0.5 indicate good convergent validity.

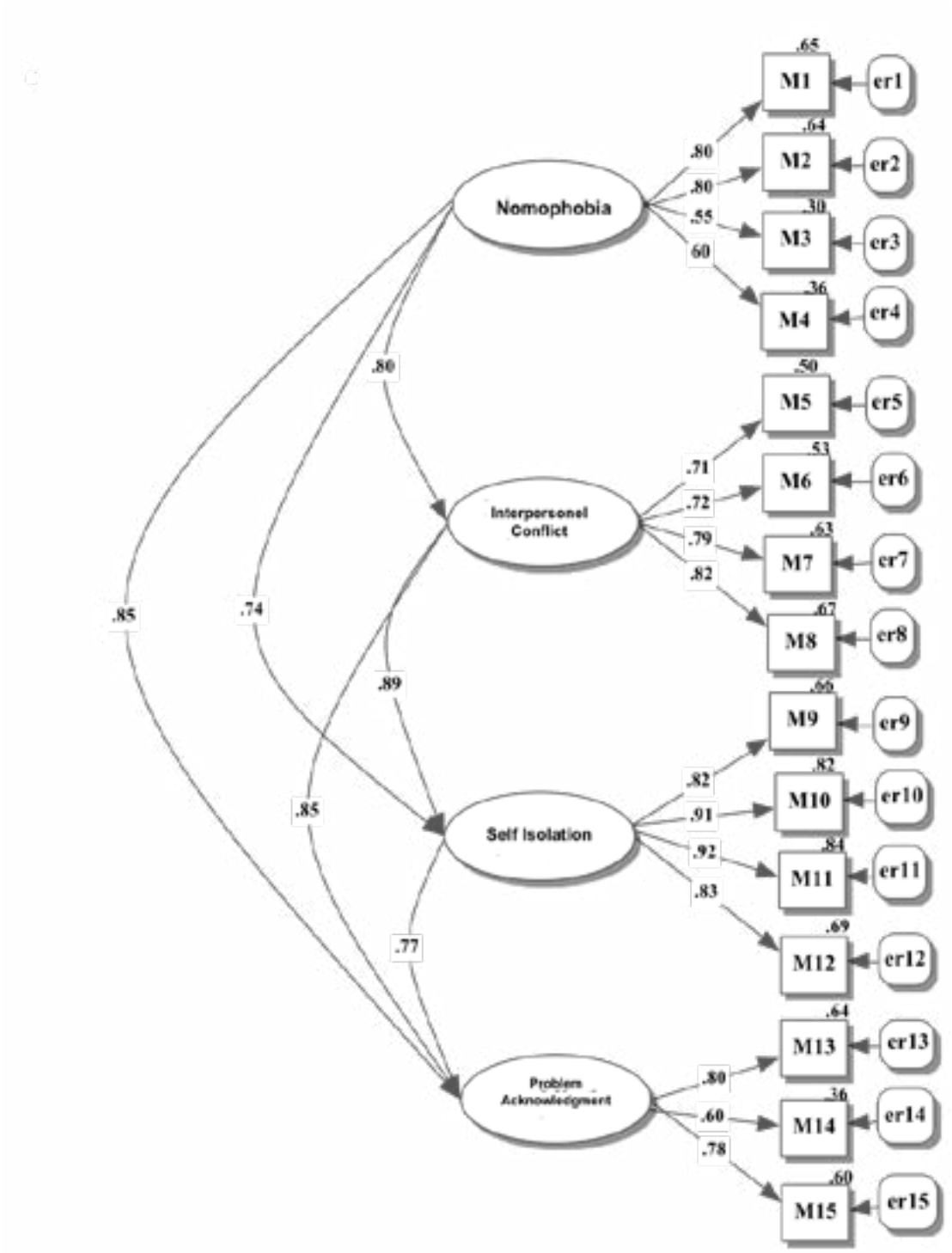

Figure 1. First level confirmatory factor analysis graph

Figure 2. Second level factor analysis graph

The composite reliability values for nomophobia, interpersonal conflict, self-isolation, and problem acknowledgment are 0.79, 0.85, 0.92, and 0.77, respectively. These values suggest good internal consistency reliability for the measures. In the second step, the Pearson correlation coefficient was calculated to calculate its relationship with the Internet Addiction scale. The finding from correlational analysis indicated that genaral phubbing was positively related to internet addiction (r=.77, *p*<.001)

Criterion Relevant Validity (CRV)

For the CRV of the GPS, the relationships between adolescents' general phubbing mean scores and social connectedness and internet addiction mean scores were calculated through correlation analysis. Our study results indicated that general phubbing was negatively involved to social connectedness (r=-.65, *p*<.001) and positively involved to internet addiction and this relationship was statistically significant (r=.77, *p*<.001) (Table 1).

Reliability analysis

To ensure evidence for the reliability of the GPS, a test-retest application was applied with an interval of four weeks. Pearson product-moment correlation analysis was applied to determine the relationships between the subdimensions and total scores obtained from the first and second application of the scale. In addition, CA reliability coefficients were calculated for the scale and its subdimensions.

Test-retest analyzes, r=.82, *p*<0.001 for nomophobia subdimension, r=.80, *p*<0.001 for interpersonal conflict subdimension, r=.71, *p*<0.001 for self-isolation subdimension, and problem acknowledgement subdimension for r=.66, *p*<0.001. In the first and second applications, it was shown that there was high positive correlation with r=.81, *p*<0.001 in terms of total scores.

In the second process, the CA internal consistency coefficient of the GPS was calculated. Our findings revealed that the internal consistency coefficient of the scale was α=.78 for the nomophobia subdimension, α=.85 for the interpersonal conflict subdimension, α=.92 for the self-isolation subdimension, α=.77 for the problem acceptance subdimension. For the whole scale, it was revealed as α=.94.

Measurement invariance

To test whether the measurement model of the GPS is similar for boy and girl adolescents, configurational, metric and scalar invariance were tested, respectively. First, the formal invariance was tested for both sexes separately via CFA. CFA results indicated that DMF was acceptable for both genders (For boys: X^2(83, N=80)=138.892, X^2/df=1.673, *p*<0.001, RMSEA=.09 (0.07-.12); SRMR=.06; CFI=.93; TLI=.91, NFI=.84 ve IFI=.93; For girls: X^2(83, N=126)=156.088, X^2/df=1.881, *p*<0.001, RMSEA=.08 (.06-.10); SRMR=.06; CFI=.94; TLI=.92, NFI=.88 ve IFI=.94). Then, Metric and Scale invariance were tested via Multiple Group Confirmatory Factor Analysis (MGCFA) (Table 2).

Table 1. Descriptive and correlation analysis results

Variables	1	2	3	4	5	6	7
1-Nomophobia	-	.66**	.66**	.66**	.85**	.60**	-.50**
2-Interpersonal Conflict		-	.78**	.71**	.90**	.74**	-.60**
3-Self-Isolation			-	.67**	.90**	.65**	-.62**
4-Problem Acknowledgment				-	.84**	.75**	-.54**
5-General Phubbing					-	.78**	-.65**
6-Internet Addiction						-	-.60**
7-Social Commitment							
Arithmetic means	15.39	11.97	12.20	10.98	50.55	31.83	31.81
Standard deviation	6.37	6.89	7.67	5.12	22.88	11.13	11.64

***p*<.001

Table 2. Fit indices for MGCFA

	X^2 (df)	*p*	X^2 / df	ΔX^2 (df)	*p*
Configurational	312.081 (168)	.001	1.858		
Metric	321.876 (183)	.001	1.759	9.795 (15)	.83
Scalar	324.368 (189)	.001	1.716	2.492 (6)	.87

Discussion

New concepts related to smartphone use have begun to appear, as smartphone using is increasing. Phubbing can also be considered as one of the concepts that may be related to smartphone using. We believe that it is important to measure phubbing, a concept that includes also social relations depending on the use of smartphones, and to investigate its possible effects on children and adolescents. There are scales that measure the phubbing behavior of individuals in adulthood. However, there was no scale measuring the concept of phubbing in the adolescents, where smartphone use is intense. For this reason, in our study, we planned to make a new contribution to the literature by aiming to investigate the psychometric properties of the GPS in adolescents.

In this study, the psychometric properties of the GPS were tested for adolescents in a clinical sample. The construct and criterion validity of the scale were analyzed, respectively, and then the test-retest and internal consistency coefficients were calculated to determine the reliability of the scale.

Validity of the GPS in adolescent age group

TVR of the scale was conducted by Ergun et al. [39]. In our study, CV analysis was used as a method to define the validity of the scale. In the broadest sense, function of CV is to test the relationships between constructs. For this purpose, CFA is used [46]. This method measures whether there is a sufficient level of relationship between the determined factors, whether they are independent of each other, which variables are related to which factors, and whether they are sufficient to explain the model [47]. According to Kline [38], a value of X2/s.d below 3 definites a perfect fit, while values equal to or less than 0.05 for RMSEA and SRMR indicate a perfect fit. Values below 0.08 define an acceptable fit. TLI, RFI, GFI, NFI and CFI take values from 0 to 1. Values of 0.95 and above correspond to perfect fit, while values between 0.90 and 0.94 indicate acceptable fit. To test the CV, first and second level CFA were performed, respectively. First level CFA results indicated that the DMF was excellent and the four-factor structure of the scale was valid for the clinical adolescent sample. The findings of the second level CFA defined that the items and subdimensions of the scale represented general phubbing latent variable at a statistically significant level (Figure 1 and Figure 2).

The CRV was also tested within the extent of the validity analyses of scale. In this context, relationship between the general phubbing mean scores of adolescents and the mean scores of social connectedness and internet addiction were examined. We found that general phubbing was negatively related to social connectedness and positively related to internet addiction. The internet addiction scale [40-42], was used for the convergent validity of the scale, and the social commitment scale [43, 44] was used for the criterion-related reality. We found that the correlation coefficient of GPS with internet addiction in the adolescents was statistically significant as +0.77 (p<.001). The correlation coefficient of GPS with the social commitment scale was -0.65 (p<.001), which is statistically significant. The findings are consistent with research findings showing positive relationships [20, 33, 39] between phubbing and internet addiction, whereas there are negative relationships with social commitment [48, 49]. AVE values for nomophobia, interpersonal conflict, self-isolation, and problem acknowledgment are 0.49, 0.58, 0.75, and 0.54, respectively. Therefore, all of these findings demonstrate that the GPS has both construct and criterion validity for the clinical adolescent sample.

Reliability of the GPS in the adolescent age group

The reliability of the scale is defined as the fact that the results correctly reveal the phenomenon regarding the conceptual structure, and that similar results are obtained when the measurement tool is applied at different times, in different places, and in different sample groups selected from the same population [50]. The alpha coefficient was developed by Lee CA as an evaluation of the internal consistency of a test and a scale. It is stated as a number between 0 and 1 [51, 52]. According to the generally accepted classification; ≥0.9 CA is excellent, 0.7≤CA<0.9 is good, 0.6≤CA<0.7 is acceptable, 0.5≤CA<0.6 is weak, and CA less than 0.5 is unacceptable [53]. The study in which the GPS was developed found that the CA were 0.84, 0.87, 0.83, 0.82, 0.93 for respectively NP, IC, SI, PA and the whole of scale [33]. In the TVR of the GPS in adults, the CA were 0.82, 0.84, 0.86, 0.74, 0.91 for respectively NP, IC, SI, PA and the whole of scale [39]. The reliability of the scale for adoleslescent was determined CA were 0.78, 0.85, 0.92, 0.77, 0.94 for respectively NP, IC, SI, PA and the whole of scale. Based on findings, it can be said that GPS and its subdimensions have sufficient reliability for the clinical sample of adolescents.

To investigate the invariance of the scale in terms of time factor, we examined test-retest reliability. For this purpose, 34 adolescents who filled out the scales were asked to complete the same scales 4 weeks later. The correlation coefficient obtained as a result of the test-retest reliability analysis provides information about the level and direction of the relationship between the two variables. The correlation coefficient ranges from -1 to +1, and as it gets closer to 1 on the minus and plus sides, it means that the relationship is perfect. If the obtained value is (-), the relationship is negative, and (+) indicates that the relationship is positive. In test-retest analyses, the correlation coefficient is required to be positive and close to 1. This situation reveals that the scale is stable and unchanging over time [54]. A correlation analysis was applied to determine the relationships between the first and second application of the scale, subdimensions, and total scores. The results indicate that there are high positive correlations between the subdimensions in both applications, varying between 0.66 and 0.82.

Measurement invariance aims to show that the structure of a measurement tool is similar in different groups [55]. Formal invariance was tested by CFA, and metric and scale invariance was tested separately for both genders by MDFA. Findings from the MDFA based on the chi-square difference proposed by Chen [56] showed that formal, metric and scale invariances can be accepted for the measurement model of the GPS. Our findings indicated that the GPS had the same structure for both genders.

The limitations of this study should be considered when evaluating the findings. The psychometric properties of the GPS were only investigated for the clinical adolescent sample in the current study. This may limit the generalizability of the present findings to all adolescents. Investigating the psychometric properties of the scale in population based sample may provide important contributions to the validity and usefulness of the scale.

In summary, the findings of this study demonstrate that the GPS can be used as a valid and reliable measurement tool to determine the general phubbing levels for the clinical adolescent sample. This study revealed the measurement invariance of the scale according to gender. With this result, it made a significant contribution to GPS validity by providing evidence that the scale can be used in gender comparisons.

Conflict of interest: No conflict of interest was declared by the authors.

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Contributions of the authors to the article

E.G.G., A.B. designed the research study. E.G.G., A.B., C.S. collected the data. M.B. analyzed the data. E.G.G. wrote the manuscript. A.B. and M.B. assisted in writing and editing the manuscript. E.G.G., A.B., M.B. and C.S. read and approved the final manuscript.

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Factors associated with frequency and severity of COVID-19 in patients with axial spondyloarthritis

Aksiyel spondiloartritli hastalarda COVİD-19 sıklığı ve ilişkili faktörler

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Abstract

Purpose: The severe course of COVID-19 in individuals with chronic diseases has led to concerns in managing rheumatic diseases during the pandemic; therefore, we aimed to define the factors associated with the frequency and severity of COVID-19 in patients with axial spondyloarthritis (axSpa) in this study.

Materials and methods: Patients with axSpa who were followed up in three tertiary hospitals and used their treatment regularly for at least six months were included. We assessed the relationship between axSpa-associated variables such as disease duration time, radiological severity, treatment and COVID-19 outcomes.

Results: A total of 833 patients with a mean disease duration of 109 months were analyzed; 64.5% of them had ankylosing spondylitis, 35.5% had non-radiographic axSpa, and 59.4% of patients were treated with a biologic agent. The frequency of COVID-19 was 23% (n:192); only five patients (0.5%) had a history of intensive care unit. Advanced age, hypertension (HT), and diabetes mellitus (DM) were found to be significantly more common in those with involvement in high-resolution computed tomography (HRCT) (*p*:0.02, *p*:0.01, and *p*<0.001). In hospitalized individuals, female gender, HT, DM, and disease lasting longer than 10 years were significantly higher (*p*:0.03, *p*:0.011, *p*<0.001, and *p*:0.014). Only DM was found as an independent risk factor for both pulmonary involvement in HRCT (*p*:0.029) and hospitalization (*p*:0.001).

Conclusion: We conducted our study with a homogenous study population and our results suggested that biological agents did not affect poor COVID-19 outcomes; only DM was associated with a more severe COVID-19 course in patients with axSpa.

Key words: COVID-19, axial spondyloarthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, diabetes mellitus.

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Öz

Amaç: Kronik hastalığa sahip bireylerde COVİD-19'un ağır seyri romatolojik hastalıkların tedavisinde endişeye yol açmıştır. Bu yüzden çalışmamızda aksiyel spondiloartritli (aSpa) hastalarda COVİD-19 sıklığı ve şiddeti ile ilişkili faktörleri tanımlamayı amaçladık.

Gereç ve yöntem: Üç tersiyer merkezde izlenen ve en az altı aydır tedavilerini düzenli kullanan aSpa'lı hastalar çalışmaya dahil edildi. Hastalık süresi, radyolojik şiddet ve tedavi gibi aSpa ilişkili değişkenler ile COVİD-19 sonuçları arasındaki ilişkiyi değerlendirdik.

Bulgular: Ortalama hastalık süresi 109 ay olan toplam 833 hasta analiz edildi; %64,5'inde ankilozan spondilit ve %35,5'inde non-radyografik aSpa tanısı mevcutken hastaların %59,4'ü biyolojik ajanlarla tedavi edilmekteydi. Çalışma grubumuzda COVİD-19 sıklığı %23 (n:192) olup sadece beş olguda (%0,5) yoğun bakım ünitesi öyküsü vardı. İleri yaş, hipertansiyon (HT) ve diabetes mellitus (DM) yüksek çözünürlüklü bilgisayarlı tomografisinde (YÇBT) tutulum olan hastalarda anlamlı olarak daha fazlaydı (*p*:0,02, *p*:0,01 ve *p*<0,001). Hastaneye yatış gerektiren hastalarda ise ileri yaş, HT, DM ve 10 yıldan uzun hastalık süresi anlamlı olarak daha fazlaydı (*p*:0,03, *p*:0,011, *p*<0,001 ve *p*:0,014). Çok değişkenli regresyon analizinde sadece DM hem YÇBT'de akciğer tutulumu (*p*:0,029) hem de hospitalizasyon (*p*:0,001) için bağımsız bir risk faktörü olarak bulundu.

Sonuç: Homojen bir hasta grubu ile yaptığımız çalışmamızın sonuçları biyolojik ajanların COVİD-19 ilişkili kötü sonuçlar üzerine etkisini olmadığını göstermiştir; çalışmamızda sadece DM, aSpa'lı hastalarda daha ciddi COVİD-19 sonuçları ile ilişkiliydi.

Anahtar kelimeler: COVID-19, aksiyel spondiloartrit, ankilozan spondilit, radyografik olmayan aksiyel spondiloartrit, şeker hastalığı.

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Introduction

The COVID-19 pandemic which is caused by SARS-CoV-2 virus affected over 500 million people, and approximately 6.5 million patients died. Advanced age and having comorbidity or cancer are the risk factors for serious COVID-19 disease [1]. Rheumatic diseases are immune-mediated chronic diseases; conventional and biological disease-modifying anti-rheumatic drugs (c/bDMARDs) act on the immune system. Therefore, rheumatologists could be undecided about anti-rheumatic treatment, especially bDMARDS, during the pandemic.

Ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpa) are common diseases in daily rheumatologic practice; sacroiliac joints, vertebral column, peripheral joints, and enthesis are the most targeted sites. Axial spondyloarthritis (axSpa) has a prevalence higher than 1% in selected areas [2, 3]. Biological agents such as tumor necrosis factor inhibitors (anti-TNF) and interleukin inhibitors (ILi) are recommended for the treatment of patients with axSpa who has high disease activity [4]. Five licensed anti-TNF agents have different molecular structures for treating axSpa; their first approvals for AS and nr-axSpa were in 2003 and 2012, respectively [5]. Secukinumab (SEC), which demonstrates long-term efficacy and safety for axSpa, is a fully human monoclonal antibody blocking IL-17A; approved for AS and nr-axSpa in 2016 and 2020, respectively [6].

Both anti-TNF agents and SEC are associated with increased infections (but not serious infections) in patients with axSpa [7] so patients or rheumatologists could avoid biological agents during the COVID-19 pandemic. Do comorbidities, radiological severity or biological agents have a negative impact on COVID-19 in patients with axSpa? Which biologic agent is safer in patients with axSpa during the pandemic? These questions are still unclear.

Over the past two years, most published data on COVID-19 and rheumatic diseases consisted of different rheumatic disease groups, so the results of a homogenous study group with axSpA are rare. In our study, we tried to investigate the answers to the above questions. We hope that our real-life results will provide more confidencely follow-up and treatment protocols in patients with axSpa during the COVID-19 pandemic.

Materials and methods

Patients

We analyzed patients with axSpa who were following up in three central tertiary hospitals, which were localized in three different geographic regions of Turkey. The study started in March 2020, as the first COVID-19 case detection date; the study finished in March 2021, as the first cycle of the COVID-19 vaccination completion date. The patients' electronic files were evaluated retrospectively for demographic, clinical, and treatment data. Inclusion criteria of patients were; aged 18 years or older, diagnosed with AS according to Modified New York Criteria or nr-axSpa according to Assessment of Spondyloarthritis International Society (ASAS) criteria [8, 9], regularly using cDMARD or bDMARD at least six months. Exclusion criteria were; aged 65 years or older, concomitantly immunosuppressive drug therapy (such as >7.5 mg/day prednisolone, azathioprine, mycophenolate mofetil, cyclophosphamide or any chemotherapeutic agent), having an immunosuppressive disease/status such as active cancer (solid or hematologic), transplantation history, HIV infection, chronic pulmonary disease (CPD: chronic obstructive pulmonary disease, COPD or interstitial lung disease, ILD), and liver cirrhosis. Comorbidities such as hypertension (HT), diabetes mellitus (DM), and chronic kidney disease (CKD: defined as glomerular filtration rate <60 [min/1.73m^2 and lasting at least three months) were noted if there was.

Definition of COVID-19

We identified the SARS-CoV-2 infection according to diagnosis guideline of the Turkish Ministry of Health [10]. We noted the results of polymerase chain reaction (PCR) from the nasopharyngeal swab, which is regarded as the gold standard laboratory technique diagnosing SARS-CoV-2 infection [11]. We noted the high-resolution chest computed tomography (HRCT) results as positive if a patient had Coronavirus Disease 2019 Reporting and Data System (CO-RADS) Score ≥3. In asymptomatic individuals, a CO-RADS score of 3 or greater detects SARS-CoV-2 infection with low sensitivity but high specificity [12]. A confirmed diagnosis was defined as a positive test result from nasopharyngeal swab or chest CT. We divided patients with a positive history of SARS-CoV-2 into three groups according to treatment completing area; home isolation, hospitalization at service, or hospitalization at the intensive care unit (ICU).

Statistical analysis

Data were assessed using SPSS 21.0 (Statistical Package for the Social Science, version 21.0). Descriptive statistics were frequency (n) and percentage (%). The chi-square test was used to determine whether the difference between the observed and expected frequencies was significant. Univariate and multivariate regression analyses assessed the relationship between demographic data and COVID-19. A p-value less than 0.05 was considered statistically significant. The Ethics Committee of the University where the study was conducted approved our study.

Results

We analyzed 833 patients with axSpA; 54.3% of patients were male, and the mean age was 42 years. In the study population, 64.5% of patients had been diagnosed with AS, and the mean disease duration was nearly 10 years. Biologic agent use was 59.4%; adalimumab was the most commonly chosen with a rate of 20.8%. COVID-19 history in patients with axSpA was 23%, and 2.5% were hospitalized. Twelve patients with COVID-19 had negative PCR test results, and four of them had positive CT results, so 184 (95.8%) patients had confirmed diagnosis. Demographic, comorbidity, diagnosis, and treatment characteristics shown in Table 1.

We didn't find any relationship between variables and the frequency of COVID-19. COVID-19 frequency was 22.1% and 23.9% in smoker and non-smoker group respectively; 22.8% and 23.4% in biological agent user and non-user group respectively, but differences were not statistically significant.

Advanced age, HT, and DM were significantly higher in patients with pulmonary involvement in HRCT (p:0.02, p:0.01, and p<0.001, respectively). Pulmonary involvement in HRCT was 20.4% and 24.1% in biological agent user and non-user groups respectively; 27.5% and 17.9% in disease duration time ≥10 years and <10 years respectively, differences were not statistically significant. Female sex, HT, DM, and disease duration time ≥10 years were significantly higher in the hospitalized patients (p:0.03, p:0.011, p<0.001 ve p:0.014, respectively). The hospitalization rate was 15.8% and 8% in biological agent user and non-user groups respectively, but the difference was not statistically significant. Univariate analysis between variables and COVID-19 outcomes was given in Table 2. In multivariate analysis, only DM was found as an independent risk factor of pulmonary involvement in HRCT (p:0.029) and hospitalization (p:0.001).

COVID-19 frequency was statistically higher in non-steroidal anti-inflammatory drugs (NSAID) users than drug-free group (p:0.016) in univariate analyses but pulmonary involvement and hospitalization rates were similar. The frequency, pulmonary involvement, and hospitalization rates were similar between sulfasalazine and NSAID groups. There were no significantly differences in COVID-19 outcomes between biological agents; results were shown in Table 3.

Table 1. Demographic, comorbidity, diagnosis and treatment characteristics

Patient, (n)	833
Male sex %, (n)	54.3 (452)
Female sex %, (n)	45.7 (381)
Age, mean, years (range)	42 (23-82)
Body-mass index, mean, (kg/m^2), (range)	26.4 (16-46)
Smoking, %, (n)	45.1 (376)
Diabetes mellitus, %, (n)	9.2 (77)
Hypertension, %, (n)	16.3 (136)
Chronic kidney disease, %, (n)	2.3 (19)
Ankylosing spondylitis, %, (n)	64.5 (537)
Non-radyographic axial spondyloarthritis, %, (n)	35.5 (296)
Disease duration time, mean, month, (range)	109 (1-504)
Non-biological treatment %, (n)	40.6 (337)
***Drug-free follow-up**	14.8 (123)
***Non-steroidal anti-inflammatory drugs**	15.5 (129)
***Sulfasalazine**	9.7 (81)
***Methotrexate**	0.6 (5)
Biological treatment, %, (n)	59.4 (495)
***Adalimumab**	20.8 (173)
***Infliximab**	10 (83)
***Etanercept**	9 (75)
***Golimumab**	8.5 (71)
***Certolizumab pegol**	4.9 (41)
***Secukinumab**	6.2 (52)
COVID-19 history, %, (n)	23 (192)
***Home isolation**	20.5 (171)
***Hospitalization at service**	1.9 (16)
***Hospitalization at intesive care unit**	0.6 (5)
PCR positivity in COVID-19 cases %, (n)	93.8 (180)
Pulmonary involvement on HRCT in COVID-19 cases %, (n)	21.9 (42)

PCR: polymerase chain reaction (PCR) from nasopharangeal swab, HRCT: high-resolution computed tomography of lungs

Table 2. Univariate analysis between variables and COVID-19 outcomes

Variable	**Frequency of COVID-19**	**Pulmonary involvement on HRCT**	**Hospitalization**
Age, years (≥50, <50)	-	**+**	-
Gender	-	-	**+**
BMI, kg/m^2 (>25, ≤25)	-	-	-
Smoking	-	-	-
Hypertension	-	**+**	+
Diabetes mellitus	-	**+**	+
Diagnosis (AS, nr-axSpA)	-	-	-
Disease duration time, years (≥10, <10)	-	-	+
Biologic agent use	-	-	-

BMI: body-mass index; AS: ankylosing spondylitis; nr-axSpA: non-radyographic axial spondyloarthritis
HRCT: high-resolution computed tomography of the lungs; '-', $p>0.05$; '+', $p\leq0.05$

Table 3. Comparison of biologic agents and COVID-19 outcomes HRCT, high- resolution computed tomography of lungs

Biologic agent	COVID-19 frequency (%), (n/total patient)	Hospitalization (%), (n/total patient)	Pulmonary involvement on HRCT (%), (n/total patient)
Adalimumab	25.4 (44/173)	9.0 (4/44)	15.9 (7/44)
Infliximab	15.7 (13/83)	15.4 (2/13)	53.8 (7/13)
Etanercept	18.7 (14/75)	7.1 (1/14)	21.4 (3/14)
Golimumab	31.0 (22/71)	0 (0/22)	13.6 (3/22)
Certolizumab pegol	22.0 (9/41)	11.1 (1/9)	11.1 (1/9)
Secukinumab	21.2 (11/52)	9.1 (1/11)	18.2 (2/11)
Total	22.8 (113/495)	8 (9/113)	20.4 (23/113)

Discussion

Previous studies usually included patients with a pooled inflammatory rheumatic disease (IRD) groups. However, in this multi-centric study, we defined the COVID-19 outcomes in a homogenous axSpA study group; 23% of patients had SARS-CoV-2 infection in an one-year period, but variables did not affect the frequency of infection. Advanced age, HT, and DM were statistically higher in patients with pulmonary involvement in HRCT; female sex, HT, DM, and disease duration time ≥10 years were statistically higher in hospitalized patients in univariate analysis. In multivariate analysis, we found that only DM was the independent risk factor of pulmonary involvement in HRCT and hospitalization. Biologic agent use did not affect the frequency or severity of COVID-19. Serious complications such as venous thromboembolism, cerebral or myocardial infarction, acute renal failure, or mechanical ventilation were not observed in hospitalized patients.

Raiker et al. [13] showed that patients with axSpa had better COVID-19 outcomes such as severity, hospitalization, and mortality but worsened results for venous thromboembolism (VTE) and cerebral infarction than propensity score matched controls, but we didn't observe these complications; anti-TNF agents did not affect poor COVID-19 outcomes as our study. Rosenbaum et al. [14] reported that both Spa and its treatment, including cDMARDs or bDMARDs (anti-TNF agents and IL-17 inhibitors), had no unfavourable impact on COVID-19 frequency and severity; 83.5% of study patients were AS and 7% were nr-axSpa, but results didn't include subgroup analysis. Turk et al. [15] performed a study with AS patients before the vaccination against SARS-CoV-2 infection as our study (77 were TNFi users, 49 were non-users; age, sex, and comorbidities were similar between the two groups) and defined that anti-TNF agents weren't associated with frequency and severity of COVID-19; our results supported that small sample sized study.

In a study from Spain which included 820 patients with IRDs (25% was of them were AS) between 1st December 2019 and 1st December 2020, COVID-19 frequency was 4.3% in patients with AS, and bDMARDs (except for rituximab) weren't associated with frequency of SaRS-CoV-2 infection and serious COVID-19 manifestations also AS-specific results were absent [16]. The COVID-19 Global Rheumatology Alliance reported that axSpa, biologic agents, NSAIDs, and csDMARDs were not associated with increased hospitalization; age >65 years, DM, HT, and lung disease were associated with higher hospitalization ratio, but only 8% of the study population had diagnose with axSpA. Their hospitalization rate was (33%) higher than our study, which could be a result of exclusion criteria of our study, such as older age and chronic lung disease [17]. In a study from Turkey which included 535 patients with IRDs (35% was of them Spa, and 61.6% of patients achieved bDMARDs) between June 2020-March 2021, adalimumab (ADA), etanercept (ETA), and golimumab (GOL) were associated with lower SARS-CoV-2 infection rates than non-bDMARD group and ADA reduced the hospitalization ratio; but results weren't specific to axSpa [18]. Favalli et al. [19] showed that the incidence and severity of COVID-19 in patients with IRDs who were treated with csDMARDs or bDMARDs were not significantly different from the general population in the same region; the study population was heterogeneous, and only 19% was of them were AS.

A meta-analysis from China reported that anti-TNF agents had lower hospitalization risk and older age was associated with worse clinical outcomes in patients with IRDs during pandemic [20]. In a multi-centric study from Germany which included 468 patients with IRDs who had confirmed COVID-19 diagnosis between March 2020-November 2020, advanced age (especially >75 years), rheumatic disease activity, cardiovascular disease, ILD/COPD, glucocorticoid treatment (GC) >5 mg/day were the independent risk factors of hospitalization as the general population. Regarding the IRD diagnosis, RA was the most common with a rate of 48%, and axSpa was the third as 12%. The hospitalization rate was 16% in patients with Spa, which was lower than RA. Unlike our study, DM does not affect poor prognosis [21]. The hospitalization risk of COVID-19 in patients with immune-mediated inflammatory diseases (IMID) is higher than in the general population, but the hospitalization risk varies between IMIDs; iritis, multiple sclerosis, RA, and vasculitis have an increased risk but is not applicable for AS so we believe that each IMID should be assessed separately with a homogenous study group for the evaluation of COVID-19 outcomes [22]. In a prospective study with 103 COVID-19 patients who had a diagnosis with AS (54%) and RA (46%), hospitalized patients had a higher ratio of advanced age, HT, COPD, and GC use, but anti-cytokine therapy wasn't associated with worse COVID-19 outcomes [23].

Some predictive factors of acute respiratory distress syndrome (ARDS) in patients with rheumatic diseases such as age, daily glucocorticoid dose, pulmonary hypertension, interstitial lung disease, CKD, rituximab (RTX), DM, HT, active rheumatic disease, and morbid obesity existed in our exclusion criteria so it may be the reason why we didn't encounter the ARDS [24]. Obesity, male sex, HT, DM, and CKD are associated with poor prognosis in COVID-19. Still, we defined only DM, which could be a result of study design because other poor prognostic factors such as advanced age (>65 years), cardiovascular disease, CLD, transplantation or cancer were replaced in exclusion criteria [25]. Pablos et al. [26] showed that connective tissue disease had worsened outcomes than inflammatory arthritis during COVID-19 pandemic so rheumatologists should keep in mind both of disease type and comorbidities [26].

Pulmonary involvement in HRCT and hospitalization rates were 20.4% versus 24.1%, and 8% versus 15.2% in biological agent user and non-user groups, but the differences were not statistically significant. In patients with severe SARS-CoV-2 infection, the serum level of TNF-α is elevated, which causes cytokine storm and lung injury [27, 28]; potential beneficial effects of TNF-α blocking may be a result of this mechanism. Systemic GC and RTX use have harmful effects on COVID-19 in patients with IRD, but GC is not widely used, and RTX is not licensed for the treatment of axSpa [16, 17, 21, 23, 24, 29]. Thus, the treatment of axSpa is safe during COVID-19 pandemic.

There were some limitations in our study. First, we didn't perform SARS-CoV-2 antibody testing because of technical insufficiency, so that we couldn't detected the asymptomatic COVID-19 cases; a serologic study, which was based on anti-SARS-CoV-2 antibodies, demonstrated that COVID-19 cases were higher than reported based on symptoms or PCR test form nasopharyngeal swabs [30]. Second, we didn't had mortality results because the study included the patients who visited to the hospital. Third, we didn't had disease activity indexes during the pandemic because of the communal isolation rules. Four, biological agent users were more isolated than the non-biologic group in daily life because they had legal permission to work.

In conclusion, we performed a study with a homogenous study group including only patients with axSpa (not including other IRDs). Only DM was an independent predictor of pulmonary involvement in HRCT and hospitalization in patients with axSpa. During an one-year period, hospitalization and ICU requirement rate was 2.5% and 0.6%, respectively; serious complications were absent. We didn't detect a red flag for the treatment of axSpa during COVID-19 pandemic; cDMARDs or bDMARDS showed a good safety profile. No differences existed between biological agents but larger studies were needed comparing head-to-head results.

Conflict of interest: The authors declared no conflict of interest.

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Authors' contributions to the article

M.P. and M.K. constructed the main idea and hypothesis of the study. G.K. and E.K. developed the theory and arranged the material and method section. M.P., M.K., E.K. and G.K. have done the evaluation of the data in the results section. Discussion section of the article written by M.P. and E.K., M.K. and G.K. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

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Using small size grafts in live donor liver transplantation: is size important?

Canlı vericili karaciğer naklinde küçük boyutlu greft kullanımı: boyut önemli mi?

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Abstract

Purpose: In living donor liver transplantation, it is preferred that the ratio of the weight of the graft to the weight of the recipient (GRWR) be higher than 0.8%. We aimed to compare recipients with a GRWR greater than 0.8% and those with a small GRWR regarding post-transplant complications and outcomes.

Materials and methods: Data of the patients who had undergone living donor liver transplant surgery in İstinye University Hospital Liver Transplant Unit between January 2017 and July 2022 were reviewed. The study group patients were classified as GRWR<0.8% (Group 1), GRWR 0.8-1% (Group 2), and GRWR>1% (Group 3) and compared regarding clinical data, complications, and mortality rates.

Results: Liver transplant recipients from 220 living donors were included. The mean recipient age was 53.6 (18-79). The comparative analysis between Group 1 (n=29), Group 2 (n=70), and Group 3 (n=121) revealed significant differences concerning the rates of bile leak and the length of hospital stay (p=0.033, p<0.05). Bile leak rates were 7.4% in Group 1, 6% in Group 2, and 0.8% in Group 3. The bile leakage rate was significantly lower in Group 3 than in Groups 1 and 2 (p=0.041, p<0.05).

The medians of hospitalization periods were 18 (7-40) days, 15 (5-46) days, and 16 (1-130) days in groups 1, 2, and 3. In addition, the median length of stay was higher in Group 1 than in groups 2 and 3 (p=0.033). In terms of other parameters, the three groups gave similar results.

Conclusion: Although a GRWR value of lower than 0.8 seems as a factor causing prolonged hospital stay, and a GRWR value of higher than 1 seems to lower the risk of biliary complications after a live donor liver transplantation, these changes are not associated with the changes in total complication and acute rejection rates and patient survival.

Key words: Graft recipient weight ratio, liver transplantation, live donor.

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Öz

Amaç: Canlı vericili karaciğer naklinde greft ağırlığının alıcı ağırlığına (GRWR) oranının %0,8'den yüksek olması tercih edilir. GRWR'si %0,8'in üzerinde olan alıcılar ile küçük GRWR'si olan alıcıları nakil sonrası komplikasyonlar ve sonuçlar açısından karşılaştırmayı amaçladık.

Gereç ve yöntem: Ocak 2017-Temmuz 2022 tarihleri arasında İstinye Üniversitesi Hastanesi Karaciğer Nakli Ünitesi'nde canlı vericili karaciğer nakli yapılan hastaların verileri incelendi. Çalışma grubu hastaları GRWR<0,8% (Grup 1), GRWR %0,8-1 (Grup 2) ve GRWR>%1 (Grup 3) olarak sınıflandırıldı ve klinik veriler, komplikasyonlar ve mortalite oranları açısından karşılaştırıldı.

Bulgular: 220 canlı donörden alınan karaciğer nakli alıcıları dahil edildi. Ortalama alıcı yaşı 53,6 (18-79) idi. Grup 1 (n=29), Grup 2 (n=70) ve Grup 3 (n=121) arasındaki karşılaştırmalı analiz, safra kaçağı oranları ve hastanede kalış süresi (p=0,033, p<0,05) açısından anlamlı farklılıklar ortaya koydu. Safra kaçağı oranları Grup 1'de %7,4, Grup 2'de %6, Grup 3'te %0,8 idi. Safra kaçağı oranı Grup 3'te Grup 1 ve Grup 2'ye göre anlamlı derecede düşüktü (p=0,041, p<0,05). Hastanede kalış sürelerinin ortancaları grup 1, 2 ve 3'te 18 (7-40) gün, 15 (5-46) gün ve 16 (1-130) gündü (p=0,033). Diğer parametreler açısından, üç grup benzer sonuçlar verdi.

Sonuç: Canlı vericili karaciğer nakli sonrası GRWR değerinin 0,8'den düşük olması hastanede kalış süresini uzatan bir faktör, GRWR değerinin 1'den büyük olması ise biliyer komplikasyon riskini azaltan bir faktör gibi görünse de, bu farklılıklar toplam komplikasyon, akut rejeksiyon ve hasta sağkalımı oranlarını etkilememektedir.

Anahtar kelimeler: Greft alıcı ağırlık oranı, karaciğer nakli, canlı vericili.

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Introduction

In living donor liver transplantation, it is traditionally preferred that the ratio of the weight of the graft to the weight of the recipient (GRWR) be higher than 0.8% [1]. The most important reason for this preference is the belief that in case of lower rates, parenchymal damage will occur in the recipient due to portal hypertension, and therefore the metabolic and synthetic capacities of the graft will decrease [2, 3]. This liver dysfunction picture, which can present itself with cholestasis, coagulopathy, ascites, and/or encephalopathy in the absence of immunological, technical, or infectious causes, is called “small size syndrome” (SSS) [4, 5]. However, as a result of advances in surgical techniques, such as modulation techniques and a better understanding of the pathophysiology compared to the past, the validity of this threshold value has been questioned in recent years [6]. Therefore, it is crucial to determine the most appropriate lower limit of GRWR for donors and living donor liver transplant recipients because if lower threshold values are accepted, donors will have a more limited chance of performing hepatectomy [1]. In addition, in this case, potential liver donors will be more encouraged to donate [7, 8].

Based on these considerations, we aimed to compare recipients with a GRWR greater than 0.8% and those with a small GRWR in our living donor liver transplant series regarding post-transplant complications and outcomes.

Materials and methods

The target population of this study was the patients who had undergone living donor liver transplant surgery in İstinye University Hospital Liver Transplant Unit between January 2017 and July 2022. After the study was approved by the clinical studies ethics committee of the same hospital, patient data were reviewed retrospectively through the electronic file system of our hospital. However, patients who had liver transplantation due to acute liver failure, patients with blood group incompatibility with their donor, patients who had left lobe graft transplantation, and patients with missing data were excluded.

After applying the inclusion and exclusion criteria, the remaining study group patients were classified as GRWR<0.8% (Group 1), GRWR 0.8-1% (Group 2), and GRWR>1% (Group 3), based on the graft-recipient weight ratio. Data, including age, gender, body mass index (BMI), duration of follow-up, MELD (Model for End-stage Liver Disease) score, the etiological factor causing liver failure, donor age, gender, and graft weight, were obtained from electronic files. These data were saved in a database. In addition to these parameters, information related to surgical complications, length of stay, length of stay in the intensive care unit, early rejection, and mortality were also transferred to the same database.

Three patient groups were compared regarding demographic and clinical data, complications, and mortality rates.

Living donor liver transplantation protocol

In the liver transplantation unit of our hospital, donor and recipient evaluations are made according to the AASLD (American Association for the Study of Liver Diseases) guidelines [9]. The transplant surgery was performed in patients with alcoholic liver cirrhosis after an abstinence period of at least six months. In addition, the University of California San Francisco (UCSF) criteria were considered in patients who underwent liver transplantation for hepatocellular carcinoma [10].

A threshold of 0.6% was accepted as the minimum acceptable GRWR. All grafts were right lobe grafts with or without the middle hepatic vein. This approach aimed to leave a liver remnant with good segment IV venous drainage. The removed liver was immediately washed with histidine-tryptophan-ketoglutarate solution (Custodiol; Köhler Chemie, Alsbach-Hähnlein, Germany) at 4°C. After the solution was completely drained from the liver, the graft weight was measured in grams with an automatic weighing machine. When calculating the graft-recipient weight ratio, the recipient weight was taken as the basis for the recipient’s dry weight. Therefore, 5%, 10%, or 15% were subtracted from the recipient’s measured weight, respectively, according to the presence of mild, moderate, or severe ascites. In addition, the weight was reduced by 5% in the presence of pedal edema. In cases where the graft did not include the middle hepatic vein, middle hepatic vein reconstruction was performed using a polytetrafluoroethylene (PTFE) graft in cases where the recipient’s portal vein or portal vein

was not suitable due to hepatocellular carcinoma or poor wall quality. Portal vein pressures were not measured routinely, and portal venous flow modulation was not performed in any patient.

Statistical analysis

SPSS (Statistical Package for Social Sciences, IBM SPSS Statistics v24, Armonk, New York, US) program was used for statistical analysis. First, the conformity of continuous quantitative data to normal distribution was evaluated with the Shapiro-Wilk test. Then, since continuous quantitative data did not follow a normal distribution, variances between groups were evaluated with the Kruskal-Wallis test. The relevant data were given as medians, minimum and maximum values. Finally, in the evaluation of nominal data, differences between groups were evaluated with Chi-square or Fisher's exact test and given with percentages. The difference between the groups was considered significant if the *p* value was less than 0.05.

Results

After applying the inclusion and exclusion criteria, liver transplant recipients from 220 living donors were included in the study. The mean age of the entire group was calculated as 53.6 (18-79). Approximately 70% (69.1%, n=152) of the patients were male, and 30.1% (n=68) were female. Follow-up periods ranged from 3 months to 51 months. The GRWR values of the patients ranged from 0.67% to 3%. When the whole group was divided into three according to GRWR values, there were 29 patients in Group 1, 70 in Group 2, and 121 in Group 3 (Table 1).

Comparison of three gorups concerning recipient and donor demographic data, recipient BMI, MELD scores revealed significant differences in terms of BMI (χ^2 (2)=51.201, p=0.000, p<0.05) and graft weight (χ^2 (2)=34.218, p=0.000, p<0.05). The BMI median of Group 1 (32.792 [22.9-44.4] kg/m^2) was higher than the median BMI values of both Group 2 (29.207 [19.1-45] kg/m^2) and Group 3 (24.913 [17-46.8) kg/m^2] (p=0.032, p=0.000).

In addition, Group 2 BMI median was calculated to be higher than Group 3 BMI median (p=0.000). The median graft weights were determined as 750 (525-1020), 800 (370-1260), and 922 (540-1500) grams in Group 1, Group 2, and Group 3, respectively. While no statistically significant difference was detected between Groups 1 and 2 (p=1.000), the median graft weight of Group 3 was higher than both Group 2 (p=0.000) and Group 1 (p=0.000). However, the three groups were similar regarding the other parameters examined.

The comparative analysis of three groups regarding the rates of bile leak, stricture, all complications, surgical (i.e., early) mortality, late mortality, length of hospital stay, and acute rejection revealed significant differences concerning the rates of bile leak and the length of hospital stay between the three groups (χ^2 (2)=6.843, p=0.033, p<0.05) (Table 2).

Table 1. Comparative analysis of the groups regarding demographic and clinical data

	Group 1 n:29	**Group 2 n:70**	**Group 3 n:121**	***p* value**
Recipient age (year)	52 (22-68)	53.5 (18-75)	54 (19-79)	0.975
Recipient gender	Male: 25 (86.2%)	Male: 47 (67.1%)	Male: 80 (66.1%)	0.108*
	Female: 4 (13.8%)	Female: 23 (32.9%)	Female: 41 (33.9%)	
Recipient BMI (kg/m^2)	32.792 (22.9-44.4)	29.207 (19.1-45)	24.913 (17-46.8)	**0.000**
Duration of follow-up (month)	27 (3-49)	16 (3-51)	19 (3-50)	0.94
MELD score	17 (6-37)	17 (7-34)	17 (6-36)	0.541
Donor age (year)	31 (18-46)	30 (12-48)	32 (18-55)	0.221
Donor gender	Male: 21 (72.4%)	Male: 43 (61.4%)	Male: 78 (65%)	0.596*
	Female: 8 (27.6)	Female: 27 (38.6%)	Female: 42 (35%)	
Graft weight (gr)	750 (525-1020)	800 (370-1260)	922 (540-1500)	**0.000**

Kruskal Wallis test was performed, *Chi-square test, BMI: Body-mass index, MELD: Model for end-stage liver disease

Table 2. Comparison regarding complications and outcomes

	Group 1 n:29	Group 2 n:70	Group 3 n:121	*p* value
Bile leak	Present: 2 (7.4%) Absent: 25 (92.6%)	Present: 4 (6%) Absent: 63 (94%)	Present: 1 (0.8%) Absent: 117 (99.2%)	**0.041****
Stricture	Present: 5 (18.5%) Absent: 22 (81.5%)	Present: 6 (9%) Absent: 61 (91%)	Present: 10 (8.5%) Absent: 107 (91.5%)	0.309*
Other complications	Present: 9 (32.1%) Absent: 19 (67.9)	Present: 21 (30.9%) Absent: 47 (69.1%)	Present: 36 (30.8%) Absent: 81 (69.2%)	1.0*
Surgical mortality	Present: 2 (6.9%) Absent: 27 (93.1%)	Present: 3 (4.3%) Absent: 67 (95.7%)	Present: 12 (9.9%) Absent: 109 (90.1%)	0.376*
Late mortality	Present: 0 (0%) Absent: 29 (100%)	Present: 6 (8.6%) Absent: 64 (91.4%)	Present: 9 (7.4%) Absent: 112 (92.4%)	0.329**
Length of hospital stay (days)	18 (7-40)	15 (5-46)	16 (1-130)	**0.033**
Length of icu stay (days)	2 (1-11)	1 (1-12)	1 (1-26)	0.328
Acute rejection	Present: 12 (41.4%) Absent: 17 (58.6%)	Present: 18 (25.7%) Absent: 52 (74.3%)	Present: 37 (30.6%) Absent: 84 (61.4%)	0.299*
Rejection Time (days)	8 (4-21)	7.5 (3-13)	6.5 (3-16)	0.406

Kruskal Wallis test was performed. *Chi-square testi **Fisher's exact test

Bile leak rates in recipients were calculated as 7.4% in Group 1, 6% in Group 2, and 0.8% in Group 3. Bile leakage was observed at a lower rate in Group 3 than in Groups 1 and 2, and the difference was statistically significant (p=0.041, p<0.05).

The medians of hospitalization periods were determined as 18 (7-40) days, 15 (5-46) days, and 16 (1-130) days in Group 1, Group 2, and Group 3, respectively. The median length of stay in Group 1 was higher than in both groups (p=0.033). In terms of other parameters examined, the three groups gave similar results.

The causes of early and late mortality of the recipients and the etiological factors causing liver failure are given in Table 3, Table 4, and Table 5, respectively.

Seventeen (7.7%) of 220 patients died in the first month after surgery. The most common cause of these deaths is sepsis (n=10).

After excluding the patients who died in the early period, 15 of the remaining 203 patients died in the late period, and the most common causes were sepsis (n=5), hepatocellular carcinoma recurrence (n=4), and COVID-19 (Coronavirus disease-2019) (n=3).

Etiological factors were cryptogenic liver cirrhosis in 50, Hepatitis B in 46, and NASH (non-alcoholic steatohepatitis) in 42 patients. These patients constituted more than half (62.7%) of all patients. Twenty-three (10.5%) patients died, and stricture developed in 18 (8.2%) patients (Table 6). Stricture was the most common complication.

Table 3. Reasons for early mortality

	Number	Percentage among deaths	Percentage in the entire cohort
Acute rejection	1	5.9	0.5
Aspiration pneumoıa	2	11.8	0.9
Mesenteric ischemia	1	5.9	0.5
Pneumonia	1	5.9	0.5
Portal vein thrombosis	1	5.9	0.5
Sepsis	10	58.8	4.5
Variceal bleeding	1	5.9	0.5
TOTAL	17	100.0	7.7

Table 4. Reasons for late mortality

	Number	Percentage among deaths	Percentage in the entire cohort
Aspiration pneumonia	1	6.7	0.5
Covid	3	20.0	1.5
HCC recurrence	4	26.7	1.8
Cardiac arrest	1	6.7	0.5
Portal vein thrombosis	1	6.7	0.5
Sepsis	5	33.3	2.5
TOTAL	15	100.0	7.4

COVID: Coronavirus disease, HCC: Hepatocellular carcinoma

Table 5. Reasons for liver failure in the recipients

	Number	Percentage
Alcoholic hepatitis	16	7.3
Budd-Chiari syndrome	7	3.2
Fulminant hepatitis	1	0.5
HBV	46	20.9
Fulminant HBV	2	0.9
HBV+HCC	1	0.5
HBV+HDV	8	3.6
HBV+Autoimmune	1	0.5
HCC	1	0.5
HCV	11	5.0
Congenital hepatic fibrosis	1	0.5
Cryptogenic cirrhosis	52	23.6
NASH	42	19.1
Autoimmune	11	5.0
PBC	6	2.7
Primary hyperoxaluria	1	0.5
PSC	4	1.8
PSC+Autoimmune hepatitis	1	0.5
PVT	1	0.5
Thalassemia	1	0.5
Wilson disease	6	2.7
TOTAL	220	100.0

HBV: Hepatitis B, HDV: Hepatitis D, HCC: Hepatocellular carcinoma, PSC: Primary sclerosing cholangitis
PVT: Portal vein thrombosis, PBC: Primary biliary cirrhosis, NASH: Non-alcoholic steatohepatitis

Table 6. Complications

	Number	Percentage among deaths	Percentage in the entire cohort
Splenic bleeding	1	1.5	0.5
Dementia	1	1.5	0.5
Exitus	23	35.4	10.5
Hepatic vein thrombosis	1	1.5	0.5
Cardiopulmonary arrest	1	1.5	0.5
Myocardial infarction	1	1.5	0.5
RE-operation	5	7.7	2.3
RE-Transplantation	1	1.5	0.5
Right hepatic artery dissection	2	3.0	0.9
Bile leak	4	6.2	1.8
Sepsis	1	1.5	0.5
Stricture	18	27.7	8.2
STRICTURE+Bile leak	3	4.6	1.4
Deep vein thrombosis	3	4.6	1.4
TOTAL	65	100.0	30.0

Discussion

In our study, living donor liver transplant recipients were divided into three groups according to their GRWR values, and recipients with GRWR values lower than 0.8, between 0.8-1, and higher than 1 were compared in terms of complications and clinical outcomes. The fact that the demographic data of the three groups did not differ statistically is a finding that increases the reliability of comparisons made in terms of postoperative complications and results.

In our study, bile leakage complication was observed less frequently in the group with the highest GRWR value than in the other groups. At the same time, the duration of hospitalization was calculated to be longer in the group with the lowest GRWR value. These findings support the preference for high GRWR values in living donor liver transplantation. However, it is a fact that there was no difference in the rates of many surgical complications, including hepatic artery thrombosis, rejection, and mortality, in our study between recipient groups with different GRWR values.

Wong et al. [11] compared patients with a GRWR value less than 0.6 and patients with a GRWR value between 0.6 and 0.8 and greater than 0.8 regarding complications and postoperative clinical outcomes after living donor liver transplantation. These researchers reported no significant difference between the groups regarding postoperative vascular and biliary complications. They also noted that SSS was observed at a very low rate, even in recipients with a GRWR value below 0.6. In our study, the lowest GRWR value was 0.67, and unlike the study of Wong et al. [11], the hospitalization period was longer. Also, the rate of bile leakage was higher in the group with a low GRWR value.

Sethi et al. [1] compared recipients with a GRWR value of less than 0.8 and recipients with a high GRWR value in terms of postoperative complication rates and outcomes in 200 living donor liver transplantations they performed over a 2-year period. This study found that the two groups were similar in terms of mortality in the first three months, length of stay in the intensive care unit, and hospital stay. In addition, the rates of complications such as SSS, hepatic artery thrombosis, portal vein thrombosis, sepsis, and liver dysfunction were similar in the two groups.

Levesque et al. [12] also found that respiratory failure was observed more frequently in the group with a high GRWR value in their comparative analysis of 162 living donor liver transplant recipients. On the other hand, the frequency of other complications was similar in the two groups [12]. These investigators also found that 1-year graft and patient survival rates were not different between the two groups.

Feng et al. [13] noted in their meta-analysis, which included 4001 patients and 18 studies,

that a GRWR value lower than 0.8 was associated with a lower rate of 1- and 3-year survival after living donor liver transplantation. In addition, these investigators demonstrated that SSS was more common in the low GRWR group. However, there was no difference between the two groups regarding perioperative mortality, biliary complications, postoperative bleeding, and acute rejection rates. In our study, bile leakage was observed at a lower rate in the recipient group with a high GRWR value compared to the other groups.

Yan et al. [14] compared living donor liver transplant recipients with a GRWR value less than or greater than 0.8 in a meta-analysis of 16 studies and 3272 patients concerning operative time, blood loss, cold ischemia time, biliary complications, acute rejection, postoperative bleeding, hospital stay, perioperative mortality. They reported no significant difference between the two groups concerning 1-, 3-, and 5-year survival [14]. Ma et al. [15] conducted a meta-analysis including 7 retrospective studies and 1821 patients who underwent live donor liver transplantation. They stated that although SSS was associated with low graft survival in the medium term, it did not affect graft survival in the long term. In our study, no difference was found in terms of early and late mortality between recipients with high and low GRWR values. However, it should be noted that the mean follow-up period in our study varied between 3-51 months.

Miyagi et al. [16] compared recipients with a GRWR value of less than 0.8 and greater than 3.5 in terms of catastrophic complications such as portal vein thrombosis, hepatic artery thrombosis, and hepatic vein thrombosis in 188 living donor liver transplantations they performed over 18 years. As a result of their analysis, these authors found that the 5-year survival in the group with a low GRWR value was significantly lower than in the other groups [16]. These authors also stated that concomitant splenectomy with liver transplantation would increase survival rates in the group with low GRWR values. Bell et al. [17] compared living donor liver transplant recipients with a GRWR value of less than 0.8 and greater than 0.8 in a meta-analysis including 1833 patients and 8 studies concerning short-term and long-term outcomes. These investigators concluded that although the rate of CBS in the first group was twice that of the second group (10% and 5%), the two groups were similar in terms of 5-year survival, biliary complications, vascular complications, perioperative bleeding, postoperative mortality, and rejection. These findings are similar to our results.

Although a GRWR value of lower than 0.8 seems as a factor causing prolonged hospital stay, and a GRWR value of higher than 1 seems to lower the risk of biliary complications after a live donor liver transplantation, these changes are not associated with the changes in total complication and acute rejection rates and patient survival.

Conflict of interest: No conflict of interest was declared by the authors

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Contributions of the authors to the article

E.E. conceived the idea, collected the data, performed the data analysis, interpreted the data and wrote the manuscript. A.D. provided critical feedback and revised the manuscript.

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Vascular and urological anomalies in children with horseshoe kidneys

Atnalı böbreği olan çocuklarda vasküler ve ürolojik anomaliler

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Abstract

Purpose: Horseshoe kidney is the most common fusion anomaly that congenital systemic and urological anomalies accompany most of the patients. In this study, we aimed to investigate its association with vascular anomalies and especially nutcracker syndrome along with accompanying urological and other systemic anomalies in children with horseshoe kidney.

Materials and methods: Twenty-six patients are diagnosed with horseshoe kidney in our clinic and 22 healthy children of the same age and sex were included in the study. All children were prospectively evaluated using Doppler ultrasonography in terms of renal artery and renal vein flow velocities, lumen diameters and vascular anomalies and presence of nutcracker syndrome.

Results: Urological anomaly was found in 50% of the children with horseshoe kidneys, and systemic anomaly in 44% of them. In Doppler ultrasonographic evaluations performed on patients to detect vascular pathologies and nutcracker syndrome; findings of nutcracker syndrome were present in 2 patients in the horseshoe kidney group, while they were detected incidentally in 1 patient in the control group. An accessory renal artery originating from the left common iliac artery was found in a case with horseshoe kidney, and a circumaortic left renal vein in one case.

Conclusions: In our study in which we investigated nutcracker syndrome based on the presence of vascular anomalies accompanying horseshoe kidneys in children, nutcracker syndrome findings were found in similar numbers in both groups.

We think that these children should be followed for a long time in terms of chronic kidney damage and vascular pathologies that may occur in adulthood.

Key words: Horseshoe kidney, child, nutcracker syndrome, vascular anomalies, urological anomalies.

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Öz

Amaç: Atnalı böbrek, konjenital sistemik ve ürolojik anomalilerin çoğu hastaya eşlik ettiği en yaygın füzyon anomalisidir. Bu çalışmada atnalı böbrek anomalisi bulunan çocuklarda eşlik eden ürolojik ve diğer sistemik anomaliler yanında vasküler anomaliler ve özellikle nutcracker sendromu ile birlikteliğinin araştırılması amaçlandı.

Gereç ve yöntem: Kliniğimizde atnalı böbrek tanısı alan 26 hasta ile aynı yaş ve cinsiyette 22 sağlıklı çocuk çalışmaya dahil edildi. Tüm çocuklar prospektif olarak renal arter ve renal ven akım hızları, lümen çapları ve vasküler anomaliler ve nutcracker sendromu varlığı açısından Doppler ultrasonografi ile değerlendirildi.

Bulgular: Atnalı böbrekli çocukların %50'sinde ürolojik anomali, %44'ünde sistemik anomali saptandı. Vasküler patolojileri ve nutcracker sendromunu saptamak için hastalarda yapılan Doppler ultrasonografik değerlendirmelerde; atnalı böbrek grubunda 2 hastada nutcracker sendromu bulguları mevcutken, kontrol grubunda 1 hastada saptandı. Atnalı böbrek anomalili bir olguda sol ana iliak arterden köken alan aksesuar renal arter ve bir olguda da sirkumaortik sol renal ven saptandı.

Sonuç: Atnalı böbrek anomalili çocuklara eşlik eden vasküler anomalilerin varlığından yola çıkarak nutcracker sendromunu araştırdığımız çalışmamızda, nutcracker sendromu bulguları her iki grupta da benzer sayıda bulundu. Bu çocukların erişkin dönemde ortaya çıkabilecek damar patolojileri ve gelişebilecek kronik böbrek hasarı açısından uzun süre takip edilmesi gerektiğini düşünmekteyiz.

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Anahtar kelimeler: Atnalı böbrek, çocuk, nutcracker sendromu, vasküler anomaliler, ürolojik anomaliler.

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Introduction

Horseshoe kidney is the most common fusion anomaly that occurs with the fusion of one pole of both kidneys, and its incidence has been reported at a rate of 1: 400 [1, 2]. In more than 90% of cases, fusion occurs between lower poles. Depending on the degree of fusion, the renal isthmus (the fused part of the kidney) may consist of a renal parenchyma or a fibrous band [3]. Most patients with horseshoe kidneys are asymptomatic and these patients are diagnosed incidentally with horseshoe kidneys. Some patients may present with flank pain and / or hematuria because anatomical abnormalities in patients with horseshoe kidneys cause urinary tract infection (UTI) and formation of stones by disrupting drainage in the collecting system. Congenital urological or systemic abnormalities are present in one third of the patients. Various arteries including aorta, iliac arteries, and rarely hypogastric and middle sacral arteries supply blood to the horseshoe kidney [4]. Although arterial and venous anomalies can be seen in fused kidneys, many studies have investigated especially arterial blood supply to the horseshoe kidneys. However, only few studies have investigated venous anomalies, and nutcracker syndrome or phenomenon in horseshoe kidneys, which is characterized by compression of the left renal vein between aorta and superior mesenteric artery (SMA) and pressure increase in the dilated left renal vein has not been investigated so far. Nutcracker syndrome may cause venous hypertension in the left kidney, leading to recurrent hematuria, orthostatic proteinuria, gonadal vein dilatation and pelvic varices due to pelvic venous congestion [5]. Awareness of this situation is of great importance in children and young adult patients, and patients may often receive delayed or erroneous diagnoses.

In this study, we aimed to investigate the accompanying urological and other systemic anomalies as well as vascular anomalies and especially their association with nutcracker syndrome in children with horseshoe kidney.

Materials and methods

Twenty-six patients diagnosed with horseshoe kidneys in our clinic between 2009-2020 and 22 healthy children of the same age and sex were included in the study. Demographic, clinical and laboratory data were recorded. This study was conducted in accordance with the Declaration of Helsinki, and it was approved by the ethics committee of Medical Faculty of Pamukkale University. At the time of diagnosis, the presence (if any) of additional urological, systemic abnormalities, UTI, hypertension, increased serum creatinine levels, decreased estimated glomerular filtration rate (eGFR), proteinuria and microalbuminuria were evaluated from their medical files. The eGFR of the cases were calculated using the Schwartz formula. An eGFR below 90ml / min / 1.73m^2 / was defined as chronic kidney injury (CKD) [6]. Protein / creatinine ratio >0.2 in the first morning urine sample was accepted as proteinuria. Calcium / creatinine and uric acid / creatinine values were estimated from spot urine samples and the results were compared with normal age-matched values [7]. UTI was determined in the presence of significant bacteriuria (>10^5 cfu / mL) in urine culture. Blood pressure was measured successively 3 times with a mercury sphygmomanometer after a 5-minute rest period and the values were averaged. Staging of blood pressures and definition of hypertension were made according to the latest consensus of the American Academy of Pediatrics [8]. Stages of vesicoureteral reflux (VUR) were determined by performing voiding cystourethrographies in patients with a history of UTI and / or hydronephrosis (HN) in patients with horseshoe kidneys [9]. The 99mTc-dimercaptosuccinic acid (DMSA) scintigraphy was performed in patients with recurrent urinary tract infection or if both kidneys of the patient differed in size as detected in urinary ultrasonography to determine renal functions and presence of scarring.

In DMSA scintigraphy, the presence of scar and a difference of more than 10% between renal functions of both kidneys was evaluated as loss

of function. The patients with hydronephrosis were investigated in terms of ureteropelvic obstruction (UPJO) by performing dynamic renal scintigraphy (MAG-3). These data were scanned from the system and recorded. Also, in patients requiring surgical operation, findings of computed tomographies performed for evaluation of vascular anatomy or renal stones were scanned from the patient files.

When the patients who were followed up with the diagnosis of a horseshoe kidney and the control group came to the clinic, they were evaluated with Doppler ultrasonography (USG) by the same two radiologists. On Doppler USG, renal artery and renal vein flow velocities were evaluated prospectively in terms of lumen diameters and variation anomalies and presence of nutcracker phenomenon. Doppler USG examination was performed after 6-8 hours of fasting. The patients were evaluated in supine position using a convex transducer operating in the 1-5 MHz frequency range and connected to an ultrasonography device (Logiq E9, GE Medical Systems, Wisconsin, USA). Left renal vein diameter was measured between the aorta and superior mesenteric artery (aortomesenteric part) and 3 cm medial from the renal hilus in the control and patient groups. In order to minimize variations in vascular diameters and flow velocity, each parameter was measured at least twice and the results averaged. During the flow velocity measurements, the Doppler angle was kept between 30°- 60°. Ultrasonographic evaluations were made by two observers in consensus. Detecting the left renal vein diameter / aorta-superior mesenteric diameter ratio above 2.25 was accepted as a nutcracker phenomenon [10]. The observers were unaware of the clinical and laboratory findings of the patients during the ultrasonographic evaluation.

Statistical methods

The data were analyzed with SPSS 25.0 package program. Continuous variables were expressed as mean ± standard deviation and categorical variables as numbers and percentages. The compatibility of the data to normal distribution was examined using the Shapiro-Wilk test. The t-test was used to examine the independent group differences, and the chi-square analysis to examine the differences between categorical variables. Spearman correlation analysis was used to examine the relationships between continuous variables. In all analyzes, $p<0.05$ was considered statistically significant.

Results

Twenty-six patients (13 girls, 13 boys) and 22 healthy children (10 girls, 12 boys) who were followed up with the diagnosis of horseshoe kidney were included in the study. The mean age of the patients during the study was 10.7±5.6 (0.8-18) years, and that of the control group it was 9.89±4.47 (2.84-17.78) years, without any statistically significant difference between the two groups in terms of gender and age. Kidney fusion anomaly with cross ectopia was detected in two patients (7.7%) with horseshoe kidneys, and lower poles of both kidneys were fused and localized in the abdomen of 24 cases (92.3%). Eleven patients (42.3%) were diagnosed incidentally, 3 patients were diagnosed during antenatal period, other patients received the diagnosis of horseshoe kidney while investigating for the presence of urinary incontinence (n=6) or recurrent urinary tract infection (UTI) (n=6). Urinary system anomaly was present in 50% of the patients. Hydronephrosis was detected in 8 patients, 3 of which were isolated, and VUR in 5 patients (the highest VUR grade was grade IV, 2 patients bilateral and 3 had unilateral VUR). Other urological anomalies are given in Table 1. A total of 3 patients underwent surgical intervention for urological anomalies. Nephropyelolithotomy operation was performed in a patient with UPJO + duplicated collecting system + kidney stones, subureteric deflux injection was performed in a patient with VUR due to proteinuria and recurrent UTI history, and one patient with UPJO underwent bilateral pyeloplasty.

Additional systemic anomalies were detected including a cardiac anomaly in 4, gastrointestinal system (GIS) anomaly in 3, genital anomaly in 1, skeletal anomaly in 2 patients, spinal dysraphism in 1 patient and Turner syndrome in 1 patient (Table 1).

Table 1. Demographic data and accompanying urinary system symptoms in patients with horseshoe kidneys

Characteristics	**n (%)**
Mean (± SD) age (years)	10.7±5.65 (0.8-18)
Sex	
Male	13 (50)
Female	13 (50)
Types of diagnosis	
Incidental	11 (42.3)
Bladder dysfunction	6 (23.1)
Recurrent UTI	6 (23.1)
Antenatal	3 (11.5)
Urinary system anomaly	
VUR	5 (19.2)
Isolated Hydronephrosis	3 (11.5)
UPJ obstruction	3 (11.5)
Extrarenal pelvis	1 (3.8)
Duplicated collecting system	2 (7.7)
Neurogenic bladder	2 (7.7)
Bladder diverticulum	1 (3.8)
Systemic anomaly	
Cardiac anomaly	4 (15.4)
Mitral insufficiency, mitral valve prolapsus	
Persistent anomalous pulmonary venous return	
Atrial septal defect	
Patent ductus arteriosus	
GIS anomaly	3 (11.5)
Anus imperforatus	
Ileal atresia	
Tracheoesophageal fistula	
Genital anomaly	1 (3.8)
Hypospadias	
Skeletal abnormalities	2 (7.7)
Scoliosis	
Spinal deformity	1 (3.8)
Meningomyelocele, hydrocephalus	
Turner Syndrome	1 (3.8)

UTI: Urinary tract infection, VUR: Vesicoureteral reflux, GIS: Gastrointestinal system

Eight patients (30.8%) had recurrent UTI, 6 patients who were diagnosed with horseshoe while being examined for UTI, and the other 2 patients suffered from urinary tract infection during follow-up. Kidney stones were detected in 5 patients (19.2%), hypercalciuria and hyperuricosuria were detected in one of these patients, and metabolic examinations of the other 4 patients were within normal limits.

Renal scar was detected in 2 patients (7.7%) in DMSA scintigraphy, the difference in renal functions of both kidneys in 7 patients (38.9%) was over 10% and ultrasonographic examinations of these patients revealed a significant difference between dimensions of both kidneys Proteinuria was present in 3 (11.5%), CKD in 1 (3.8%), and hypertension in 1 (3.8%) patient.

In renal Doppler USG examinations of both groups, any significant difference was not found between the patient and the control groups in terms of renal vein diameters at the aorta level and left para-aortic areas, and the highest and lowest flow velocities *(p*>0.05) (Table 2).

Table 2. Doppler Ultrasonographic data concerning diameters of hilar part the left renal vein, and aortomesenteric left renal vein with the patient examined in the supine position. Comparison between the patient, and the control groups

	Horseshoe kidney group (n=26)	**Control group (n=22)**	***P***
Diameter of the proximal renal vein (mm)	4.58±1.35 (2-6.3)	4.86±0.99 (3.5-7.40)	0.433
Diameter of left renal vein between aorta and superior mesenteric artery (SMA) (mm)	3.6±1.63 (1.8-8.2)	3.44±0.77 (2.5-6)	0.682
A/SMA	1.5±0.58 (1-3.15)	1.44±0.29 (1.12-2.5)	0.672
Number (%) of patients with A/SMA >2.25	2 (7.7)	1 (4.5)	0.607
VMAX/VMIN	1.99±0.39	1.79±0.22	0.051

A/SMA: The ratio between diameters of aorta and superior mesenteric artery, V MAX: Left renal vein peak blood flow velocity
V MIN: Left renal vein the lowest blood flow velocity

The ratio between the highest and the lowest flow rates in the left renal vein was higher in children with horseshoe kidneys compared to the healthy group without any statistically significant intergroup difference (*p*=0.052). In all children, renal vein diameters at the level of the abdominal aorta and the left para-aortic area were significantly correlated with age (*p*=0.001 for both, *r*=0.580, *r*=0.509, respectively). In the horseshoe kidney group, findings of nutcracker syndrome were present in 2 patients, while in the control group, they were detected incidentally in only 1 patient. Accessory renal artery originating from the left common iliac artery was detected in a case with horseshoe kidney and in another case the presence of a circumaortic left renal vein was revealed.

Discussion

In our study, at least one accompanying urological anomaly was found in 50% of the patients with horseshoe kidneys, and one concomitant systemic anomaly was detected in 35% of the patients. Nutcracker phenomenon was detected in 1 case in the control group, but in 2 of the cases evaluated for nutcracker anomaly in the disease group known to be accompanied with vascular anomalies. In addition, accessory renal artery originating from the left common iliac artery in a case with horseshoe kidney and in another patient circumaortic left renal vein were found. Nutcracker syndrome in horseshoe kidney has not been investigated to date. Since the horseshoe kidney is a fusion anomaly, a vascular anomaly such as nutcracker syndrome can theoretically be expected to be common. However, in our study, it was found that there was no significant increase in horseshoe kidney patients compared to control patients.

Horseshoe kidney is the most common fusion anomaly, and it is known to be twice as common in boys than in girls [11, 12]. In our study, the number of male and female patients were equal. Fusion between the lower poles

of both kidneys is known as the most common (>90%) fusion type in the horseshoe kidneys [11]. In accordance with the literature findings, in our study, fusion of the lower poles of both kidneys was seen in our 24 patients.

Most patients with horseshoe kidneys are asymptomatic. In these patients, horseshoe kidneys are diagnosed incidentally. Similarly, in our study, 11 patients (42.3%) were incidentally diagnosed as a result of ultrasonographic examinations performed for other indications, and 11.5% of the cases were diagnosed during antenatal period. Anatomical abnormalities in patients with horseshoe kidneys disrupt the drainage in the collecting system, causing infection and stones. Generally, symptomatic patients present with flank or abdominal pain due to stones or urinary tract infections [3, 12]. In some studies, while 9.8%-23.5% of the patients presented with urinary tract infection, 6.1%-17.1% of them with complaints of urinary incontinence [3, 13, 14]. In our study, the most common indications for presentation among symptomatic patients diagnosed with horseshoe kidneys were urinary incontinence and urinary tract infections (23.1% and 23.1% of the patients, respectively).

It is known that between one third and half of the patients with horseshoe kidneys have other congenital anomalies [3, 15]. In our study, 13 (50%) patients had additional urinary system anomalies. Hydronephrosis, VUR and UPJO are among the urinary system anomalies which are frequently seen in patients with horseshoe kidneys. In some studies, the incidence of concomitant hydronephrosis has been reported between 21-80% [1, 3, 16, 17]. In our study, a total of 8 patients had hydronephrosis, 3 of whom had only hydronephrosis without any comorbidities. Causes of hydronephrosis include VUR, UPJO, kidney stone, or external compression on ureters by an abnormal vessel. In some studies, incidence rates of VUR have been reported as 5.2-25%, respectively [1, 3, 15, 16]. Similarly, the incidence of VUR in our study was 19.2%. UPJO has been reported between 19.5% and 35% in patients with horseshoe kidneys in the literature [3, 15, 18]. UPJO in horseshoe kidneys is associated with high and lateral insertion of ureters into the renal pelvis, displacement of the fused isthmus, and the vascular support of the isthmus [19]. We recorded a lower incidence of UPJ obstruction in our study (11.5%).

Horseshoe kidney is an anomaly that specifically facilitates urinary tract infection. Infection is seen in one third of the patients [4]. According to the data obtained from 13 articles including 825 patients with horseshoe kidneys, Weizer et al. [16] found the incidence of UTI as 22.9%. In another study, the incidence of UTI was reported to be 42% [3]. Similar to the literature, 8 patients (30.8%) had UTI in our study, and 6 of them were diagnosed during the examination carried out with this indication. Ascending infection is the most common form of infection and VUR is a common underlying cause [15]. In our study, in half of the patients, UTI was accompanied by VUR.

The coexistence of horseshoe kidney with extrarenal diseases or syndromes has been reported in the literatüre [1, 3, 14]. Nine (34.6%) of our patients had 12 extrarenal diseases and syndromes. Patients with horseshoe kidneys had cardiac (n=4), genital (n=1), gastrointestinal (n=3,) skeletal (n=2), spinal pathologies (n=1), and Turner Syndrome (n=1). In our study, the most common extrarenal anomaly was also cardiac anomaly. Horseshoe kidney can coexist with many syndromes, including genetic disorders such as Turner syndrome and trisomy 13, 18, and 21 [20]. Our patient had mosaic Turner syndrome.

The prevalence of stones in the horseshoe kidney varies between 20 and 60% [16, 21, 22]. Although it is known that anatomical abnormality in horseshoe kidney causes stasis and stone formation, the results of studies investigating the contribution of metabolic abnormality to stone formation is contradictory. In one study, metabolic scanning was performed in patients with horseshoe kidneys and kidney stones, and at least one metabolic abnormality (most commonly hypercalciuria and hypocitraturia) was found in 30% of the patients [23]. In another study, 75% of metabolic abnormalities were found in patients with horseshoe kidneys and stones [24]. In contrast to these studies, in a study, the researchers could not find any difference in the frequency of metabolic abnormalities associated with kidney stones between patients with horseshoe kidneys and the general population [21]. In our study, 19.2% of the patients had stone disease without any significant difference

with the control group (9.1%) (p>0.05). In the study by Weizer et al. [16] 9 (39%) patients had nephrolithiasis, and 4 of them were operated. In our study, nephropyelolithotomy operation was performed on a patient with kidney stones. In our study, only one of the patients with stones had hypercalciuria and hyperuricosuria. When compared with the healthy control group, no significant difference was found in terms of the presence of hypercalciuria and hyperuricosuria (p:0.609, p:0.247).

Vascularization (in the arteries and veins) of the horseshoe kidney can be variable. There may be accessory and aberrant vessels and accompanying malformations [25]. While the kidneys are normally supplied by the renal arteries originating from the aorta, it has been shown that the isthmus can be supplied by the iliac, inferior mesenteric artery, sacral and lumbar arteries, especially in cases with rotation anomalies and ectopy accompanying the horseshoe kidney [18, 26]. This condition may cause problems especially regarding triage among patients with urological anomalies that require operation, and advanced examinations such as computed tomography and angiography are required to demonstrate vascularization to guide the surgical operation [25, 26]. In our study, CT imaging was performed for anatomical and vascular evaluation of the patients who would undergo bilateral pyeloplasty for UPJ obstruction, injection for VUR and nephropyelolithotomy for stone disease, and any intraoperative complication was not encountered. As could be seen in Doppler USG performed on our patients, accessory renal artery originating from common iliac artery was detected in only one patient. Coexistence of horseshoe kidney with abdominal aortic aneurysm has been reported in the literature with a rate of 0.12%. In a retrospective study of 25 patients with horseshoe kidneys operated for aortic aneurysm rupture; 16 patients were operated for aortic aneurysm rupture and 9 patients due to aortailiac stenosis [27]. Horseshoe kidneys in these patients were detected in preoperative imagings performed, and four of 16 patients with ruptured aneurysms were urgently operated. In the literature, arteriovenous fistula and related bleeding in adult patients, and in another case, obstruction in the vena cava inferior due to compression of the isthmus of the horseshoe kidney were reported [28, 29]. Although pathologies such as fistula and aneurysm were not detected in our patient group, we think that these patients should be followed up especially in terms of vascular complications that may develop in adulthood.

Nutcracker phenomenon is an anatomical disorder that does not show symptoms due to compression of the paraaortic part of the left renal vein between the aorta and the superior mesenteric artery. Nutcracker syndrome is due to this anatomical disorder; It is accompanied by symptoms such as flank pain, hematuria, pelvic congestion, and menstrual disorders [30]. In our study we searched for the possibility of nutcracker phenomenon in patients with horseshoe kidneys where concomitant vascular anomalies are frequently seen, we radiologically observed findings of nutcracker syndrome in 2 patients in the patient group and in 1 patient in the control group (aorta/superior mesenteric artery diameter ratio >2.25). However, in patients with nutcracker phenomenon in both groups, accompanying findings and symptoms such as hematuria, proteinuria, and left flank pain were not encountered. Any difference was not detected between the renal vein diameters and flow rates in the aorta and left paraaortic areas of both groups. The peak blood flow velocities in the left renal vein were –though mot statistically significant -higher in patients with horseshoe kidneys than in control patients. It is known that the incidence of malignancy increases in patients with horseshoe kidneys.

Although the cause is not known exactly, it has been suggested that the risk is higher especially in cases with fibrous isthmus during migration (ascent) of the kidney in the embryonic period. Wilms tumor is the most frequently seen tumor in children with horseshoe kidneys and is detected twice as much as the normal population [1, 31, 32]. Again in the literature, although rare, cases of extrarenal Willms tumor have been encountered in pediatric patients with horseshoe kidneys. It has been suggested that metanephric blastema cells remaining in the abdomen after metanephric blastema fusion in the intrauterine period cause development of extrarenal Wilms tumor [33]. The most common tumor seen in adult patients with horseshoe kidneys is renal cell carcinoma which is seen in an incidence similar to the normal population [34, 35]. In our cases horseshoe kidneys did not

accompany by tumors, and we think that patients with horseshoe kidneys not accompanied by tumors should be followed up by USG in terms of tumors that may develop in the future.

Small number of patients is one of the limitations of our study. Although renal Doppler USG is an adequate examination for the diagnosis of nutcracker syndrome, USG may be insufficient for detecting other vascular anomalies. However, computed tomography (CT), which is a successful method for detecting vascular anomalies could not be performed due to radiation risk.

In conclusion, studies on long-term follow-up results of patients with horseshoe kidneys are limited in number. In a study conducted in our country, after a 10-year follow-up of these patients, the rates of hypertension, proteinuria, and chronic kidney damage were found to be 10, 15, and 7%, respectively [3]. In our study, these rates were 3.8%, 11.5 and 3.8%, respectively. In our study, malignancy was not found in cases with horseshoe kidneys, but the frequency of vascular anomalies or nutcracker phenomenon was comparable to the control group. We think that annual lifelong controls of these patients for chronic kidney damage and vascular pathologies should be performed.

Conflict of interest: No conflict of interest was declared by the authors.

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Authors' contributions to the article

I.G. and S.Y. have constructed the main idea and hypothesis of the study. H.K.Z. and A.R.U. developed the theory and arranged/edited the material and method section. T.B. and F.U. have done the evaluation of the data in the Results section. Discussion section of the article written by I.G., H.K.Z. and S.Y. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

Research Article

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Ventriculoperitoneal shunt obstructions in the absence of radiological abnormalities: retrospective analysis of a pediatric cohort

Radyolojik anormalliklerin yokluğunda ventrikülоperitoneal şant obstrüksiyonları: pediatrik bir kohortun retrospektif analizi

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Abstract

Purpose: Ventriculoperitoneal shunts are still the mainstay treatment for pediatric hydrocephalus. They have a high complication and failure rate, requiring multiple revisions. In this study, we aim to investigate patients who required shunt replacement without any radiological findings.

Material and method: The files of patients under the age of 18, who underwent shunt revision between December 2015 and December 2020 in Bursa Uludag University Medical Faculty Neurosurgery Clinic were reviewed retrospectively. All the radiological studies, laboratory results and clinical conditions of the patients were examined.

Results: We identified 127 patients who required a revision of ventriculoperitoneal shunt for suspected mechanical obstruction. 6 patients (5%) had symptoms of raised intracranial pressure, but showed no radiographic evidence of progressive ventricular dilatation.

Conclusion: Dysfunction of a ventriculoperitoneal shunt does not always lead to associated radiological alterations. In a patient with signs of intracranial hypertension, revision of the system should be considered even in the absence of progressive ventricular dilatation in radiological studies.

Key words: Ventriculoperitoneal shunts, hydrocephalus, obstruction, computed tomography.

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Öz

Amaç: Ventrikülоperitoneal şant uygulanması pediatrik hidrosefali hastaları için halen temel tedavi yöntemidir. Yüksek komplikasyon ve başarısızlık oranına sahiptirler ve çoklu revizyon gerektirirler. Bu çalışmada radyolojik bulgu olmaksızın şant replasmanı gerektiren hastaların araştırılması amaçlanmıştır.

Gereç ve yöntem: Bursa Uludağ Üniversitesi Tıp Fakültesi Nöroşirürji Kliniği'nde Aralık 2015-Aralık 2020 tarihleri arasında şant revizyonu yapılan 18 yaş altı hastaların dosyaları retrospektif olarak incelendi. Hastaların tüm radyolojik çalışmaları, laboratuvar sonuçları ve klinik durumları incelendi.

Bulgular: Mekanik obstrüksiyon şüphesi nedeniyle ventrikülоperitoneal şant revizyonu gerektiren 127 hasta tespit edildi. 6 hastada (%5) artmış intrakraniyal basınç semptomlar vardı, ancak progresif ventrikül dilatasyonuna ait radyografik bulgu görülmedi.

Sonuç: Ventrikülоperitoneal şantın disfonksiyonu her zaman ilişkili radyolojik değişikliklere yol açmaz. İntrakraniyal hipertansiyon bulguları olan bir hastada, radyolojik çalışmalarda ilerleyici ventriküler dilatasyon olmasa bile sistemin revizyonu düşünülmelidir.

Anahtar kelimeler: Ventrikülоperitoneal şantlar, hidrosefali, obstrüksiyon, bilgisayarlı tomografi.

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Introduction

Hydrocephalus is a common condition in pediatric patients and characterized by ventricular enlargement caused by increased cerebrospinal fluid (CSF), thinning of the cerebral parenchyma, and increased intracranial pressure. Ventriculoperitoneal shunt is the preferred method of hydrocephalus treatment in the pediatric population. This method reduces morbidity and mortality of hydrocephalus patients, but this is not a curative solution, and does not fix the pathophysiology. The shunts treat hydrocephalus by shunting CSF from ventricle to another place that can be absorbed physiologically.

A ventriculoperitoneal shunt consists of 4 parts as proximal catheter, reservoir, valve, and distal catheter. The ventricular catheter is usually placed in the frontal horn of each lateral ventricle. Most modern shunt catheters drain into the peritoneal cavity. Mechanical obstruction, migration, over-drainage, infection, and fracture are the main reasons for failure.

After the shunt is applied, patients are routinely followed up at regular intervals. During follow-up, the patient's clinical condition, radiological examinations and, when necessary, blood tests are checked. The diagnosis of ventriculoperitoneal shunt failure may be obvious, but more often, the diagnosis can be confused with the symptoms of many childhood diseases like gastroenteritis, otitis, urinary tract infections, viral syndromes, and migraine. Therefore, diagnosing shunt dysfunction can be quite difficult and requires experience. If the correct and rapid diagnosis is not made, some serious results are seen in the patients, so patients with a V-P shunt should always be evaluated carefully and should be considered both radiologically and clinically.

The follow-up of all patients was performed at the outpatient clinic and craniography, posteroanterior chest radiography, and abdominal radiography were evaluated annually. The patients with clinically suspected shunt dysfunction but no disconnection could be detected on roentgenogram were evaluated with a computerized tomography (CT) to determine the presence of ventricular enlargement. Sometimes, when patients present with certain complaints (headache, altered consciousness, vomiting) no abnormality is detected in their examinations.

When history is taken from the family, there is a suspicion that the patient's condition may be serious. In our study, we aim to investigate patients who required shunt replacement without any radiological findings.

Materials and methods

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration.

All patients under the age of 18 who underwent shunt revision between December 2015 through December 2020 at Bursa Uludag University Medical Faculty Neurosurgery Clinic were reviewed, the patients who required shunt revision without radiological abnormality were included. The patient who had co-morbidity like congenital disease, tumor or infection were excluded. All the radiological studies, laboratory results and clinical condition of the patients were reviewed, perioperative findings were noted.

Results

We identified 127 patients who required a revision of ventriculoperitoneal shunt for suspected mechanical obstruction. The patients whose shunts were revised due to skin problems were excluded. The radiological examinations of 6 patients were reported as 'stable' or 'normal' with no evidence of malpositioned ventricular portion of the shunt or discontinued distal catheter. These six patients are the population of our study (Table 1). The initial age of shunting was 10 months. Male/Female ratio was 4/2. The most frequent etiology was hydrocephalus due to prematurity. 2 of the patients underwent shunt revision before. Headache and altered consciousness were the symptoms seen in our patients. In all patients the valve was filling with CSF after consecutive presses. No percutaneous tapping was executed in any of the patients because of infection risk. During the revision procedure all the patient's CSF pressure was found to be high. The cranial tip of the shunt was occluded in all the six patients. The CSF tests were obtained routinely and there was no evidence of infection.

Table 1. The general characteristic features of the study patients

Patient	Age	Prematurity	Gender	Etiology	Initial Shunt	Previous Revision
1	4	No	M	IVH	1 month	Yes
2	3	Yes	M	Hidro	birth	Yes
3	2	Yes	M	Mshi+hid	1day	yes
4	13	Yes	F	Hidro	8 month	Yes
5	10 m	Yes	M	Mshi+hid	1day	Yes
6	12	No	F	Hidro	7month	Yes

M: male, F: female, IVH: intraventricular haemorrhage, Hidro: primary hydrocephalus, Mshi: myelochisis

Discussion

The misdiagnosis of shunt malfunction can be serious condition which may lead to severe neurological deterioration or even death. To avoid it, every patient with ventriculoperitoneal shunt should be evaluated carefully. Shunt malfunction diagnosis is usually set on clinical and radiological findings stated by Sivaganesan et al. [1]. Malfunction without radiological abnormality is not reported frequently but is the most challenging condition that must be carried out by the neurosurgeons. We think that this condition is a result of a poor compliance of ventricles. Iskandar et al. [2] reported 11% of the patients with shunt revision who doesn't show enlarged ventricles. This ratio in our study has been found to be 5%. In our study routine percutaneous tap or invasive intracranial pressure monitoring was not performed due to risk of infection, despite McNatt et al. [3].

None of our patients had slit ventricle syndrome, despite of our suggestion of poor compliance. The patients with 'normal radiological findings' were more likely to suffer acute neurological deterioration, vomiting and nausea compared to rest of the study population, consistent with Engel et al. [4]. Our study showed that patients with hydrocephalus, particularly in the premature children, are more likely to present shunt malfunction without ventricular enlarging. Dahlerup et al. [5] found only headache as a symptom of shunt malfunction. Regarding to these findings we postulate that the prematurity predisposes to worsen ventricular compliance, so these patients should be evaluated very carefully at their follow ups.

Barnes et al. [6] signs, and radiographic findings accompanying presumed ventriculoperitoneal (VP mentioned that drowsiness is the best clinical predictor of VP shunt failure while headache and vomiting were less predictive. CT findings were very valuable especially if there is a possibility to compare with previous images, however, it should be kept in mind that not all cases of proven shunt failure presented an increase in ventricular size. Ventricular enlargement could be detected in 84% of the patients but 14% of the patients had unchanged ventricular size.

Small portion of pediatric shunt malfunction appears without radiological findings, so it's important to be aware of this entity when considering the need for surgical intervention in patient who had symptoms of raised intracranial pressure but doesn't demonstrate ventricular dilatation. According to this, the parents' opinions should be evaluated very carefully.

The physicians must not underestimate the observations of the parents and caretakers who have known the regular state of health that were generally complicated by various disabilities and especially that have had experienced shunt failure in the past. Watkins et al. [7] pointed out that families were at least as accurate as paediatricians in diagnosing shunt failure.

Conflict of interest: The authors declared no conflicts of interest concerning the authorship and publication of this article.

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Authorship and contribution

All authors have made substantive contributions to the study, and all authors endorse the data and conclusions. R.K., M.O.T. contributed to the preparation of the manuscript, research, literature review and analyses.

Research Article

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The effect of pre-treatment inflammatory response markers on survival in locally advanced unresectable and metastatic gastric cancer: a retrospective cross-sectional study

Lokal ileri rezeke edilemeyen ve metastatik mide kanserinde tedavi öncesi inflamasyon yanıtı belirteçlerinin sağkalım üzerine etkisi

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Abstract

Purpose: We evaluated the effect of pre-treatment inflammation response markers on overall survival (OS) and progression-free survival (PFS) in patients with locally advanced unresectable and metastatic gastric cancer.

Material and method: Patients with locally advanced unresectable and metastatic gastric cancer between January 2016 and December 2021 were included. Among these patients, 114 patients with ECOG (Eastern Cooperative Oncology Group) Performance status 0-2, who received at least one line of chemotherapy, had no comorbidities and brain metastases were included in the study. Pre-treatment platelet, lymphocyte, leukocyte, neutrophil, monocyte, albumin, C-reactive protein (CRP), lactatedehydrogenase (LDH) levels, histology types, age, surgical history, treatment history and ECOG Performance status were retrospectively analysed from their records. Threshold values were determined by ROC analysis. Kaplan-Meier survival analyses were used for survival analyses. Hazard ratio (HR) and confidence intervals (CI) of the factors affecting overall survival (OS) and progression-free survival (PFS) were calculated using Coxproportional-hazards model.

Results: The median age of the patients was 63.5±11.9 (28-80). Among the patients, 69 (60.5%) were in metastatic stage. 106 (93.0%) patients had poorly differentiated carcinoma histology. Progression developed in 88.6% (101) of patients and 98 patients (86%) were deceased. In the whole group, mPFS was 9.4±0.9 (95%CI 7.7-11.0) months and mOS was 14.1±1.6 (95%CI 10.8-17.2) months. When the Coxproportional-hazards model was used, the factors affecting OS were advanced age, metastatic stage, neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), derived neutrophil lymphocyte ratio (dNLR) and lactate dehydrogenase (LDH), while the factors affecting PFS were advanced age, metastatic stage, NLR, dNLR and LDH.

Conclusion: While NLR, PLR, dNLR, dNLR and LDH affect OS, LDH affects PFS. Systemic inflammatory markers of locally advanced unresectable and metastatic gastric cancers before chemotherapy can be used to predict prognosis.

Key words: Gastric cancer, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, prognosis.

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Öz

Amaç: Lokal ileri rezeke edilemeyen ve metastatik mide kanserli hastalarda tedavi öncesi inflamasyon yanıtı belirteçlerinin tüm sağkalım (TSK) ve progresyonsuz sağkalım (PSK) üzerine etkisini değerlendirildi.

Gereç ve yöntem: Ocak 2016-Aralık 2021 tarihleri arasında lokal ileri rezeke edilemeyen ve metastatik mide kanserli hastalar alındı. Bu hastalardan en az bir sıra kemoterapi almış ECOG (Eastern Cooperative Oncology Group) Performans durumu 0-2 olan, komorbiditesi ve beyin metastazı olmayan 114 hasta çalışmaya dahil edildi. Tedavi öncesi platelet, lenfosit, lökosit, nötrofil, monosit, albümin, C-reaktif protein (CRP), laktatdehidrogenaz (LDH) düzeyleri, histoloji tipleri, yaşı, cerrahi öyküsü, tedavi öyküsü ve ECOG Performans durumu dosyalarından retrospektif olarak incelendi. Tüm değerlerin eşik değeri ROC analizi ile belirlendi. Sağkalım analizleri için Kaplan-Meier Sağkalım analizleri kullanıldı. Coxproportional-hazards modeli kullanılarak tüm sağkalım (TSK) ve progresyonsuz sağkalım (PSK)'ı etkileyen faktörlerin hazardratio (HR) ve güven aralıkları (CI) hesaplandı.

Bulgular: Hastaların ortanca yaşı 63,5±11,9 (28-80) yıl. Hastaların 69 (%60,5)'u metastatik evredeydi. Yüzaltı (%93,0) hastanın histolojisi az differasiye karsinomdu. Hastaların %88,6'sında (101) progresyon gelişti ve 98 hasta (%86) vefat etti. Tüm grupta mPSK 9,4+0,9 (%95CI 7,7-11,0) ay ve mOS 14,1+1,6 (%95CI 10,8-17,2) ay saptandı. Coxproportional-hazards modeli kullanıldığında TSK'i etkileyen faktörler ileri yaş, metastatik evre, nötrofil lenfosit oranı (NLO), platelet lenfosit oranı (PLO), derive nötrofil lenfosit oranı (dNLO) ve laktak dehidrogenaz (LDH) iken; PSK'yi etkileyen faktörler ileri yaş, metastatik evre, NLO, dNLO ve LDH olarak bulundu.

Sonuç: Tedavi öncesi inflamasyon yanıtı belirteçlerinden NLO, PLO, dNLO ve LDH OS'yi etkilerken; LDH PSK'yi etkilemektedir. Lokal ileri rezeke edilemeyen ve metastatik evre mide kanserlerinin kemoterapi öncesi sistemik inflamatuvar belirteçleri prognozu öngörmede kullanılabilir.

Anahtar kelimeler: Mide kanseri, nötrofil-lenfosit oranı, platelet-lenfosit oranı, prognoz.

Doğan T, Yaren A, Demiray AG, Yapar Taşköylü B, Çakan Demirel B, Özdemir M, Güçlü Kantar T, Değirmencioğlu S, Gököz Doğu G. Lokal ileri rezeke edilemeyen ve metastatik mide kanserinde tedavi öncesi inflamasyon yanıtı belirteçlerinin sağkalım üzerine etkisi. Pam Tıp Derg 2023;16:434-445.

Introduction

Gastric cancer is the 5th most common cancer. It is the 4th most common cause of death [1]. Generally, being asymptomatic in the early stages of the disease, the diagnosis can be made in advanced stages. Fifty percent of gastric cancers are metastatic at the time of diagnosis [2]. In locally advanced stage, surgery, neoadjuvant/adjuvant chemotherapy and radiotherapy are the treatment options, while in metastatic stage, targeted therapy, palliative chemotherapy and immunotherapy are used to prolong survival and improve quality of life [3-5]. Despite many innovations in the treatment of gastric cancer in recent years, the median survival is still below 1 year [6]. Stage is the most important factor determining the treatment strategy and survival. However, the fact that patients at the same stage have different survival results when they receive the same treatment suggests different mechanisms such as systemic inflammation in the progression of gastric cancer [7]. In many cancers, systemic inflammation is known to lead to tumour initiation and progression by inhibiting apoptosis, stimulating angiogenesis and causing DNA damage [8, 9]. Lymphocytes, monocytes and neutrophils make an important contribution to the systemic inflammatory response, while platelet activation increases the inflammatory response by stimulating proinflammatory cytokines [10, 11]. In addition, the effect of lymphocytes on tumour suppressor activity [12], the contribution of neutrophils to the tumour development process with cytokine production [13], the effect of platelets on transendothelial migration and early steps of metastasis [14], and the behaviour of monocytes as pro-tumour cells that increase metastasis emphasize the importance of the role of peripheral blood cells in cancer prognosis [15].

The fact that some tumour markers used in the treatment response and prognosis of gastric cancer are not cost-effective and have low sensitivity and specificity limits their use in daily practice. Therefore, evaluation of peripheral blood cells and NLR, PLR, CRP, albumin and LDH levels may be guiding in daily practice. In the literature, these markers and ratios have been shown to be prognostic in many solid tumours such as colon cancer, lung cancer, breast cancer and gastric cancer [16-20].

Due to the limited number of studies that may enable the use of these markers in clinical practice in locally advanced and metastatic gastric cancer, we aimed to evaluate the effect of pre-treatment inflammation response markers on overall survival (OS) and progression-free survival (PFS) in patients with locally advanced unresectable and metastatic gastric cancer.

Material and method

Patients with locally advanced unresectable and metastatic gastric cancer who applied to Pamukkale University Medical Oncology Department Outpatient Clinic between January 2016 and December 2021 were retrospectively analysed. Among these patients, 114 patients who received at least one line of chemotherapy, ECOG performance score status 0-2, without comorbidities and brain metastasis were included in the study. Pre-treatment platelet, lymphocyte, leukocyte, neutrophil, monocyte, albumin, C-reactive protein (CRP), lactate dehydrogenase (LDH) levels of all patients were obtained from the hospital laboratory information system. NLR (neutrophil to lymphocyte ratio), PLR (platelet to lymphocyte ratio), dNLR (derived neutrophil to lymphocyte ratio) and LMR (lymphocyte to monocyte ratio) were calculated. The formula dNLR: neutrophil count / white blood cell count - neutrophil count was used. Haemogram parameters were analysed by electrical impedance and optical density method in Mindray CAL 8000 (Shanghai, China) auto analyser; LDH, CRP and albumin levels were analysed by electro chemiluminescent method in Cobas 702 (Roche Diagnostics, Manheim, Germany) analysers. In addition, histology types, age at diagnosis, surgical history, treatment and ECOG Performance status were analysed from patient files.

Overall survival (OS) was defined as the time from the date of metastasis diagnosis until the time of death, and progression-free survival (PFS) was defined as the time from the date of metastasis diagnosis until disease progression.

Statistical analysis

Mann-Whitney U and chi-square or Fisher's exact test were used for the values and percentages of clinicopathological variables of the patients. Receiver operating characteristic (ROC) analysis was used for the threshold values of calculated NLR, PLR, LMR, dNLR values, Kaplan-Meier method and logrank analysis were used for survival analyses. Univariate and multivariate analyses were performed using the Coxproportional hazards model. Hazard ratios (HR) and corresponding 95% confidenceinterval (CI) were recorded for each factor. SPSS (version 23.0) software package (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. A p value <0.05 was considered statistically significant.

Permission was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committee for the study.

Results

114 patients were included in this study. The median age of the patients was 63.5±11.9 (28-80) years and 79 (69.3%) were male. ECOG PS was 0 in 67 (58.8%), 1 in 27 (23.7%), and 2 in 20 (17.5%) patients. 61 (53.5%) patients had smoking history. Primary tumour localization was cardia 34 (29.8%), antrum 51 (44.7%), pylorus 2 (1.8%), corpus 27 (23.7%), respectively. Among the patients, 69 (60.5%) were in metastatic stage. The histology of 93.0% (106) patients was low differentiated carcinoma. 69 (60.5%) patients had a history of surgery, 38 (33.3%) patients had a history of adjuvant chemotherapy, and 32 (28.1%) patients had a history of RT. 14 (12.3%) patients received FLOT, 60 (52.6%) patients received DCF/mDCF, 28 (24.6%) patients received CF/CX+trastuzumab, 12 (10.5%) patients received XELOX/FOLFOX. Progression developed in 88.6% (101) of patients and 98 patients (86%) died (Table 1).

The threshold values of all values were determined by ROC analysis (Table 2). OS and PFS values were found according to the threshold values of biochemical values determined by ROC analysis (Table 3). In the whole group, mPFS was 9.4+0.9 (95%CI 7.7-11.0) months and mOS was 14.1+1.6 (95%CI 10.8-17.2) months.

When Coxproportional-hazards model was used, the factors affecting OS were found to be advanced age (p=0.021), metastatic stage (p=0.009), NLR (p=0.002), PLR (p=0.009), dNLR (p=0.002) and LDH (p=0.000) (Table 4).

Using the Coxproportional-hazards model, the factors affecting PFS were found to be advanced age (p=0.051), metastatic stage (p=0.003) and LDH (p=0.007) (Table 5).

History of adjuvant chemotherapy or radiotherapy, histological type and chemotherapy regimens had no effect on PFS and OS. All survival charts are shown in Figure 1.

Table 1. Clinico-pathological characteristics of the patients

	Number of patients (%)
Age (year) (median)	63.5+11.9
Gender Male	79 (69.3)
Female	35 (31.7)
Performance status	
0	67 (58.8)
1	27 (23.7)
2	20 (17.5)
Tumour localization	
Cardia	34 (29.8)
Antrum	51 (44.7)
Pylorus	2 (1.8)
Corpus	27 (23.7)
Stage	
Locally advanced	45 (39.5)
Metastatic	69 (60.5)
Histology	
Less differentiated	106 (93.3)
Moderately to well differentiated	8 (6.7)
Smoking history	
yes	61 (54)
no	53 (46)
Surgical history	
yes	69 (60.5)
no	45 (39.5)
Adjuvant KT history	
yes	38 (33.3)
no	76 (66.7)
RT history	
yes	32 (28.1)
no	82 (71.9)
Chemotherapy regimens	
FLOT	14 (12.3)
XELOX/FOLFOX	12 (10.5)
CF/CX + trastuzumab	28 (24.6)
DCF/mDCF	60 (52.6)
Progression	
yes	101 (88.6)
no	13 (11.4)
Survival	
yes	98 (86)
deceased	16 (14)

Table 2. Values found by ROC analysis

	Cut-off	AUC (95CI%)	*P* value	Sensitivity (%)	Specificity (%)
Age (years)	55.5	0.65 (0.52-0.79)	0.046	74.5	62.5
Albumin (gr/dl)	4.07	0.66 (0.53-0.80)	0.032	66.8	68.8
CRP (mg(L)	2.04	0.52 (0.37-0.67)	0.75	56.8	51.7
NLR	2.76	0.72 (0.61-0.82)	0.006	69.4	68.8
PLR	149 843	0.66 (0.54-0.77)	0.041	58.9	56.3
LMR	3.43	0.64 (0.53-0.75)	0.062	63.2	68.8
dLNR	1.95	0.71 (0.58-0.63)	0.007	65.3	62.5

Table 3. OS and PFS values according to the cut-off values determined by ROC analysis of biochemical values

Parameters	Overall survival (months) (95%CI)		Progression-free survival (months) (95%CI)	
Age ≤55.5 years	17.3±3.4 (10.5-24.1)	***p*=0.01**	12.2±3.8 (4.7-19.6)	***p*=0.003**
Age >55.5 years	11.8±1.6 (8.5-15.0)		8.4±0.7 (7.0-9.8)	
Male	14.6±1.7 (11.3-18.0)	***p*=0.134**	10.5±1.4 (7.8-13.1)	***p*=0.201**
Female	10.9±2.7 (5.4-16.3)		7.0±1.6 (3.8-10.2)	
Less differentiated	12.3±1.7 (8.7-15.8)	***p*=0.62**	8.7±0.6 (7.3-10.1)	***p*=0.79**
Moderately to well differentiated	15.7±4.9 (6.1-25.3)		11.5±1.1 (9.4-13.6)	
Locally advanced	22.3±2.8 (7.3-12.4)	***p*=0.000**	12.5±2.6 (7.4-17.6)	***p*=0.000**
Metastatic	9.3±1.3 (7.3-12.4)		7.3±0.6 (6.1-8.6)	
Albumin <4.07g/L	11.4±0.9 (9.5- 13.3)	***p*=0.01**	8.4±0.8 (6.9- 9.9)	***p*=0.043**
Albumin ≥4.07g/L	15.6±2.8 (10.1-21.3)		11.5±2.1 (7.3- 9.9**)**	
CRP <2.04 mg/L	15.5±1.5 (12.7-18.8)	***p*=0.038**	11.5±0.8 (9.9-13.2)	***p*=0.013**
CRP ≥2.04 mg/L	10.8±1.3 (8.2-13.4)		7.1±0.5 (6.1-8.1)	
NLR <2.76	19.0±4.2 (10.6-27.3)	***p*=0.003**	12.2±1.8 (8.5-15.8)	***p*=0.032**
NLR ≥2.76	11.8±1.6 (8.5-15.0)		8.4±1.1 (6.3-10.5)	
PLR ≥149 843	12.2±1.7 (8.7-15.5)	***p*=0.33**	8.7±0.8 (7.1-10.4)	***p*=0.42**
PLR <149 843	15.1±1.7 (11.5-18.5)		10.5±1.6 (7.3-13.7)	
LMR ≤3.43	10.8±1.1 (8.6-13.1)	***p*=0.022**	7.9±0.9 (6.3-9.7)	***p*=0.16**
LMR >3.43	16.3±2.4 (11.5-21.2)		12.0±0.9 (10.2-13.8)	
dNLR >1.95	12.2±1.8 (8.6-15.6)	***p*=0.037**	8.6±1.0 (6.6-10.6)	***p*=0.204**
dNLR ≤1.95	15.3±3.6 (8.1-22.5)		10.8±1.9 (7.1-14.6)	
LDH ≥180 (U/L)	11.1±1.1 (8.8-13.2)	***p*=0.043**	7.9±0.7 (6.6-9.3)	***p*=0.009**
LDH <180 (U/L)	16.3±3.7 (8.9-23.6)		12.1±1.1 (6.6-9.3)	

Table 4. Factors affecting overall survival

						95.0% CI forExp (B	
	B	**SE**	**Wald**	**Df**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Age	0.022	0.010	5.355	1	**0.021**	1.022	1.003	1.042
Type	-0.142	0.239	0.355	1	0.551	0.867	0.543	1.385
Histology	-0.201	0.408	0.243	1	0.622	0.818	0.368	1.820
Stage	0.643	0.244	6.917	1	**0.009**	1.902	1.178	3.071
Albumin	0.079	0.219	0.130	1	0.718	1.082	0.704	1.664
CRP	0.009	0.005	2.645	1	0.104	1.009	0.998	1.019
NLR	-0.166	0.053	9.814	1	**0.002**	0.847	0.764	0.940
PLR	0.000	0.000	6.916	1	**0.009**	1.000	1.000	1.000
LMR	-0.014	0.027	0.259	1	0.611	0.986	0.935	1.040
dNLR	0.428	0.136	9.877	1	**0.002**	1.534	1.175	2.004
LDH	0.003	0.001	14.109	1	**0.000**	1.003	1.001	1.004

Table 5. Factors affecting progression free survival

						95.0% CI forExp (B	
	B	**SE**	**Wald**	**Df**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Age	0.020	0.010	3.816	1	0.051	1.020	1.000	1.041
Type	-0.087	0.236	0.137	1	0.711	0.916	0.577	1.455
Histology	-0.256	0.397	0.415	1	0.519	0.774	0.356	1.686
Stage	0.721	0.242	8.833	1	0.003	2.056	1.278	3.306
Albumin	-0.104	0.215	0.234	1	0.629	0.901	0.591	1.373
CRP	0.004	0.005	0.533	1	0.466	1.004	0.994	1.014
NLR	-0.099	0.053	3.432	1	0.064	0.906	0.816	1.006
PLR	0.000	0.000	1.729	1	0.189	1.000	1.000	1.000
LMR	-0.023	0.026	0.787	1	0.375	0.977	0.928	1.028
dNLR	0.256	0.140	3.330	1	0.068	1.292	0.981	1.700
LDH	0.002	0.001	7.160	1	0.007	1.002	1.001	1.003

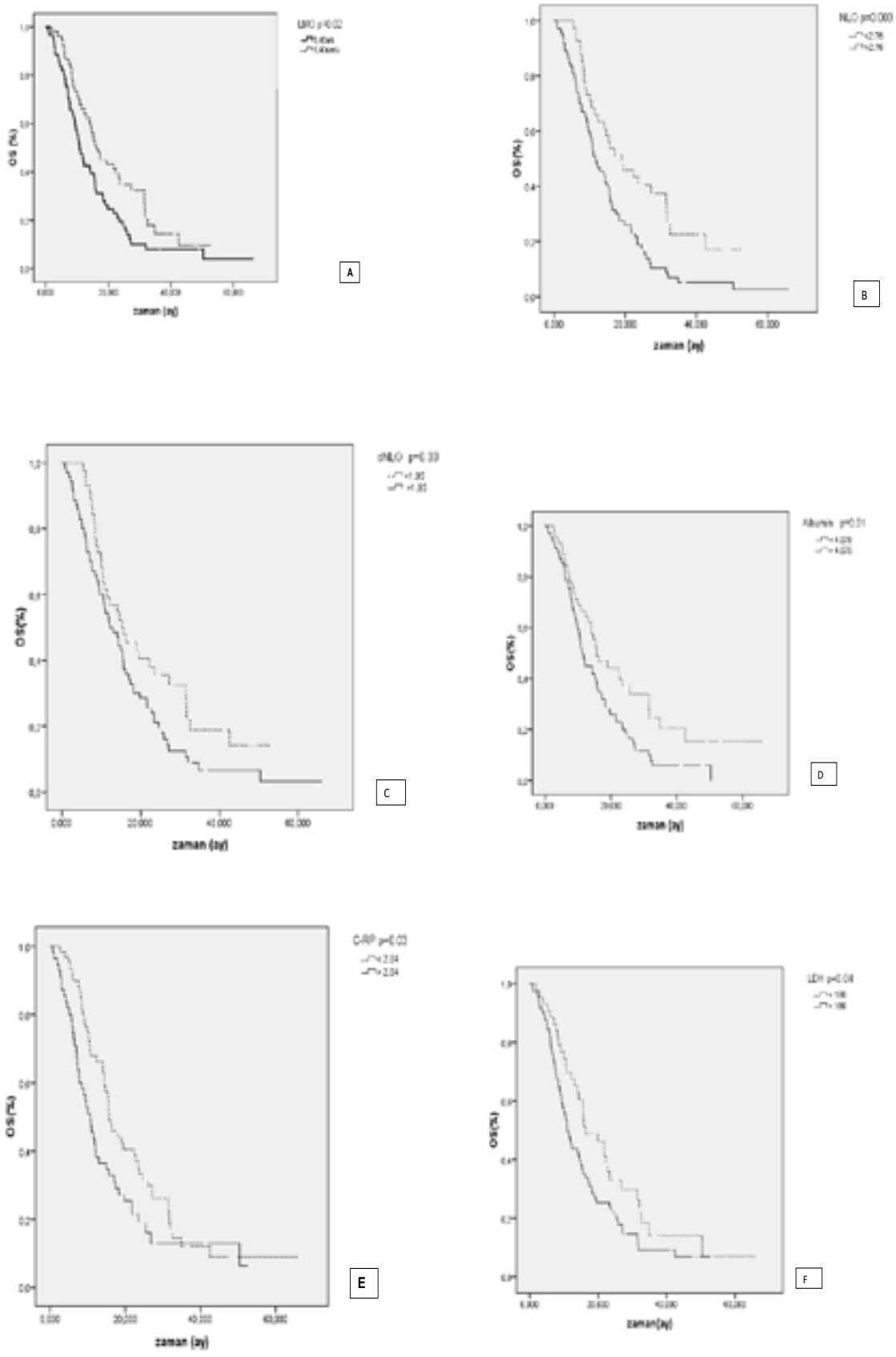

Figure 1. Kaplan-Meiers survival charts for factors affecting OS (A) LMR (B) NLR (C) dNLR (D) Albumin (E) CRP (F) LDH

Discussion

This study showed that NLR, LMR, dNLR, LDH, CRP and albumin, which are systemic inflammatory markers, have an effect on overall survival, and also NLR, LDH, CRP and albumin have an effect on progression-free survival in patients with metastatic and locally advanced unresectable gastric cancer. When prognostic factors were evaluated in multivariate analysis, NLR, dNLR and LDH were found to be the factors affecting both OS and PFS.

There is a synergy between systemic inflammation and tumour cells. While tumour cells contribute to the secretion of proinflammatory cytokines, systemic inflammation plays an important role in tumour invasion and progression. The most important peripheral blood cell involved in systemic inflammation is neutrophil. Neutrophils secrete inflammatory cytokines and provide adhesion and distant metastasis of circulating tumour cells. Lymphocytes contribute to the inhibition of proliferation and migration of tumour cells. Platelets, together with endothelial barriers, are involved in tumour cell escape from the immune system and epithelial mesenchymal transformation [9, 21]. Therefore, in recent years, it has been shown in many studies that the levels of these cells in peripheral blood and inflammation indices such as NLR, PLR, LMR) play a role as prognostic factors in many tumour types including gastric cancer [22-24].

Preoperative haematological parameters and ratios were evaluated in patients with early stage gastric cancer and they showed that low lymphocyte count, high PLR and NLR, low LMR were predictive for poor survival [25]. Furthermore, in a systemic review and meta-analysis, high NLR in early-stage patients who underwent curative resection was shown to correlate with older patients, male gender and short OS [26]. In another study, preoperative NLR in patients with stage II and III gastric cancer was shown to affect long-term and short-term outcomes, including postoperative complications [27]. Not only preoperatively but also postoperatively, low NLR in patients with early stage gastric cancer has been reported to favourably affect the prognosis in patients receiving adjuvant chemotherapy [28]. In patients with locally advanced unresectable gastric cancer, it has been shown that OS is shorter in the high NLR group [29]. In patients with locally advanced gastric cancer, neoadjuvant chemotherapy decreases all inflammatory markers such as NLR, PLR and LMR, and it has been emphasised that pre-treatment NLR and LMO are poor prognostic indicators. It has been reported that PLR and NLR before neoadjuvant chemotherapy decrease with chemotherapy and especially high PLR level is a poor survival indicator [30, 31]. In patients with locally advanced gastric cancer, high NLR and PLR negatively affected the degree of tumour regression after neoadjuvant chemotherapy [30], NLR was found to be predictive for PFS and OS, especially in female patients, and PLR was found to be predictive for PFS and OS in patients with stage III and dissected LN count <28 [32].

In metastatic gastric cancer, a scoring system using NLR and PLR before chemotherapy showed that patients with progression had a high score and a poor prognosis. In multivariate analysis, high NLR-PLR score was found to be an independent prognostic factor for OS [33]. In addition, in another study, it was found in patients with stage IV gastric cancer receiving cisplatin and S-1 treatment that the response rate was higher, progression was less common and OS was longer in patients with low NLR. In this study, it was also shown that CRP levels and NLR were correlated. It has been suggested that NLR is a useful marker for chemotherapy resistance, malnutrition, systemic inflammation and immunosuppression [34]. In PD-1 inhibitor recipients, low NLR was found to have a favourable effect on OS, but had no effect on response rate and disease control [35]. It has been suggested that the most important reasons for the effect of NLR on immunotherapy results may be due to the inhibition of the immune activity of lymphocytes by neutrophils by secreting various cytokines and chemokines and the reactions caused by the tumour inflammatory microenvironment. In addition, the predominance of lymphocytes at low NLR leads to a favourable inflammatory microenvironment. Therefore, patients with low NLR before immunotherapy have better treatment response and survival results [36]. In our study, NLR and dNLR were found to have an effect on OS in patients with locally advanced and metastatic gastric cancer in accordance with the literature.

Monocytes have an important role in cancer progression, angiogenesis, metastasis and suppression of immunity by releasing chemokines. High monocyte ratio leads to increased tissue-associated macrophage density, which is an indicator of poor survival outcomes in patients receiving immunotherapy [37]. LMR reflects the number of peripheral lymphocytes and monocytes infiltrating the tumour. Tumour-infiltrating lymphocytes are strong positive predictors in many tumour types, including gastric cancer [38]. Many studies have found an association between high preoperative LMR and PFS and OS in patients with gastric cancer [39, 40]. In gastric cancer, it has been suggested that low preoperative LMR affects survival and therefore more aggressive chemotherapy should be given in these patients [41]. However, there are no randomised clinical trials on this subject. Similarly, in a meta-analysis including patients with gastric cancer of different stages, low LMR was found to be prognostic for OS [42]. In our study, we found that LMR had no effect on OS and PFS. This may be due to the small number of patients and heterogeneity of the patient groups.

CRP, an important indicator of inflammation, is a classical acute phase reactant from the pentraxin family known to contribute to the progression of angiogenesis and metastases by increasing proinflammatory cytokines such as tumour necrosis factor α (TNF-α) and interleukin 6 (IL-6) [43]. Albumin is also frequently used in clinical practice as an important indicator of both inflammation and malnutrition. When CRP and albumin are evaluated together, they have been shown to be prognostic in many tumour types including gastric cancer [44-46]. In gastric cancers, reduced caloric intake due to stenosis in the gastric cardia or pylorus may lead to hypoalbuminemia. The demonstration of preoperative nutritional status by serum albumin is closely related to cancer prognosis. However, its clinical significance for gastric cancers is not fully understood. Ouyang et al. [47] found that preoperative low serum albumin levels, advanced stage and lymph node involvement were associated with an increased risk of death in 309 gastric cancer patients scheduled for surgery.

It has been reported that high CRP and low albumin levels affect OS duration in patients with locally advanced gastric cancer [48]. In a study conducted by Lu et al. [49] in 401 patients with gastric cancer, elevated CRP levels both preoperatively and postoperatively were found to be associated with poor prognosis. In our study, no correlation was found between CRP levels and OS and PFS. The reason for this may be that there are many factors affecting CRP levels. For example, the use of drugs, especially anti-inflammatory drugs, statins and metformin, may change CRP levels. The patient group included in Lu et al. [49] study was in stage 1-3 and the patient group in our study was in a more advanced stage. Advanced stage may also have affected crp levels.

Serum LDH levels are associated with tumour hypoxia, neo-angiogenesis and poor prognosis for many tumour types. In the metabolism of cancer cells, the oxidoreductase LDH acts by converting LDH to pyruvatyllactate in hypoxia and this has an important role in cancer metabolism. LDH is overexpressed in metastatic cancer cells and LDH levels have been correlated with tumour viability. Increased tumour LDH levels and increased mitotic index correlate with more aggressive cancer. Zhao et al. [50] evaluated serum LDH levels in 365 gastric cancer patients. High LDH levels were found to be an independent prognostic biomarker for poor prognosis. This study also showed the same result.

The main limitations of our study are its retrospective nature and the small number of patients. In the literature, most of the studies on systemic inflammation markers in patients with cancer are retrospective. Due to the retrospective nature of the studies, many different factors affecting inflammation could not be excluded. In these studies, inflammation markers have been shown to affect OS and PFS.

In conclusion, it has been shown that inflammation response markers can also be used in clinical practice to evaluate the prognosis of patients. Further studies are needed to determine the effects of inflammation markers on prognosis and to clarify the cut-off values.

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Authors' contributions to the article

T.D. and A.Y. constructed the main idea and hypothesis of the study. T.D. and A.Y. developed the theory and arranged/edited the material and method section. T.D., B.C.D., T.G.K., M.O. have done the evaluation of the data in the Results section. Discussion section of the article written by T.D., A.Y., A.G.D., and B.Y.T. S.D. and G.G.D reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

Research Article

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Evaluation of factors that affect remission and recurrence after endonasal endoscopic approach in Cushing disease

Cushing hastalığında endonazal endoskopik yaklaşım sonrası remisyon ve nükse etki eden faktörlerin değerlendirilmesi

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Abstract

Purpose: Clinical consequences of the endoscopic endonasal approach (EEA) for Cushing Diseases (CD) were investigated in a single-center series based on definitions and assessments of recurrence and remission.

Materials and methods: 825 patients were evaluated, including 64 patients with CD who underwent EEA at Ankara University Neurosurgery Department and were evaluated retrospectively between 2014 and 2021. Postoperative next-morning cortisol and adrenocorticotrophic hormone (ACTH) values were used to assess postoperative endocrinological remission.

Results: Twenty-two patients had macroadenoma, and 40 had microadenoma. In 2 patients, no lesions were detected in the sellar region, and a magnetic resonance imaging (-) CD diagnosis was done. Regardless of remission, the effect of the duration of glucocorticoid use after surgery on recurrence made examined. Glucocorticoid therapy was given in 46 patients (71%) after pituitary surgery. No recurrence was observed in 20 patients whose treatment was longer than one year. In 12 patients, the glucocorticoid therapy duration ranged from 6 months to 12 months, and four patients showed recurrence. The glucocorticoid therapy duration of >6 months predicted that recurrence would not occur (p<0.05).

Conclusion: The sustainability of hypocortisolemia is essential in the treatment of CD. The mainstay of CD treatment is appropriate postoperative follow-up and administration of the necessary medical and surgical interventions. Glucocorticoid therapy duration> six months after surgery predicts that recurrence will not occur. Long-term glucocorticoid therapy after surgery suggests surgical success.

Key words: Cushing disease, endonasal endoscopic approach, recurrence, remission.

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Öz

Amaç: Bu çalışmada, Cushing Hastalığı (CH) için endoskopik endonazal yaklaşımın (EEY) klinik sonuçları, remisyon ve nüks tanımları ve değerlendirmelerine dayalı olarak tek merkezli bir seride araştırıldı.

Gereç ve yöntem: Ankara Üniversitesi İbni Sina Hastanesi Nöroşirürji Anabilim Dalı'nda 2014-2021 yılları arasında EEY uygulanan 825 hasta arasında CH'lığı tanısı alan 64 hastanın verileri retrospektif olarak değerlendirildi. Postoperatif ertesi sabah kortizol ve adrenokortikotropik hormon (ACTH) değerleri postoperatif endokrinolojik remisyonu değerlendirmek için kullanıldı.

Bulgular: Yirmi iki hastada makroadenom ve 40 hastada mikroadenom saptandı. 2 hastada sellar bölgede lezyon saptanmadı, manyetik rezonans görüntüleme (-) CH tanısı kondu. Kırk hasta kadın, 12 hasta erkekti. Remisyondan bağımsız olarak ameliyat sonrası glukokortikoid kullanım süresinin nüks üzerine etkisi incelendi. Hipofiz cerrahisi sonrası 46 hastaya (%71) glukokortikoid tedavisi verildi. Tedavi süresi 1 yıldan uzun olan 20 hastada nüks gözlenmedi. 12 hastada glukokortikoid tedavi süresi 6 ay ile 1 yıl arasında değişmekteydi ve 4 hastada nüks görüldü. 6 aydan uzun glukokortikoid tedavi süresinin nüksün olmayacağını saptadığı öngörüldü (p<0,05).

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Sonuç: Hipokortizoleminin sürdürülebilirliği CH tedavisinde önemlidir. Ameliyattan sonra 6 aydan fazla glukokortikoid tedavi süresi, nüksün olmayacağını öngörmede yardımcıdır. CH tedavisinin temel dayanağı uygun postoperatif takip ve gerekli medikal ve cerrahi girişimlerin uygulanmasıdır.

Anahtar kelimeler: Cushing hastalığı, endoskopik endonazal yaklaşım, rekürrens, remisyon.

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Introduction

Cushing disease (CD) is the consequence of hypercortisolism that occurs in a pituitary corticotroph adenoma that releases adrenocorticotropic hormone (ACTH), and CH is a prevalent cause of endogenous Cushing syndrome (CS). As such, CD accounts for 75% of all cases of CS, with an incidence of 1.2-1.7 per million population and a prevalence of 39-940/ per million [1]. Furthermore, the CD is highly related to mortality, which is reported approximately twice that compared to the general population. However, the mortality rate of patients with CD who are in remission after treatment tends to be lower than that of patients not in remission [2].

CD treatment aims to achieve disease remission and long-term control without recurrence. Transsphenoidal surgery (TSS) is the first-line therapy for CD for tumor removal; microscopic or endoscopic TSS may be used. However, the remission and recurrence rates after the first TSS in patients with CD were reported to vary considerably, whereas high remission rates have been reported after endoscopic TSS [3].

A lifetime follow-up by endocrinologists is required after surgery for CD. Several factors may influence the outcomes after TSS, including the adenoma size, dural invasion, localization on preoperative imaging, intraoperative tumor visualization, preoperative ACTH level, urinary free cortisol (UFC)' levels, and histological confirmation of corticotroph adenomas. Hormone values should be measured after TSS, based on which the patient should be followed up. The main goal of the treatment of CD is to reduce cortisol production, which leads to clinical manifestations without causing a new hormone deficiency. Medical adrenalectomy, radiosurgery, and radiotherapy can be chosen in patients without remission after TSS.

This paper will discuss whether postoperative glucocorticoid therapy duration predicts recurrence and the effect of sex, Ki-67 index, and adenoma size on tumor gender.

Materials and methods

The study was designed in a reference center for pituitary surgery, of the 825 patients who received TSS between 2014 and 2021. Sixty-four patients diagnosed with CD were included in the study. Diurnal variation in ACTH and cortisol levels, 24-hour UFC measurement, and overnight or longer LDDST (2 mg/day for 48 hours) were used to diagnose CD. Inferior petrosal sinus sampling (IPSS) was performed on seven patients.

The patients were given 1 mg of oral dexamethasone at 11 pm, and the serum cortisol level was examined at 8 am in the LDDST. In addition, overnight 8-mg DST was used to distinguish CD from ectopic ACTH secretion. It involved the administration of '2 mg of dexamethasone' every 6 hours or a 'single dose of 8 mg DST' at 11 pm, followed by serum cortisol measurement on the next day, at 8 am.

One of the reliable tests to differentiate CH from the ectopic or pituitary origin is IPSS. IPSS is performed in cases of resistant CS after TSS, incompatibilities between biochemical and radiological imaging findings, and the absence of pituitary lesions on imaging [4, 5]. A 'petrosal sinus-to-peripheral ACTH gradient ratio' of ≥2.0 at baseline or ≥3.0 after CRH administration in the setting of sustained hypercortisolemia suggests a pituitary source of ACTH.

The most common reasons for patients to apply to the outpatient clinic are headaches and visual field loss, which was diagnosed with CD after an endocrinological evaluation. Preoperative MRI was performed for all the patients, and experienced radiologists evaluated the results. Adenomas <1 cm in size were considered microadenomas, and those >1 cm in size were considered macroadenomas [6-8] (Figure 1, 2).

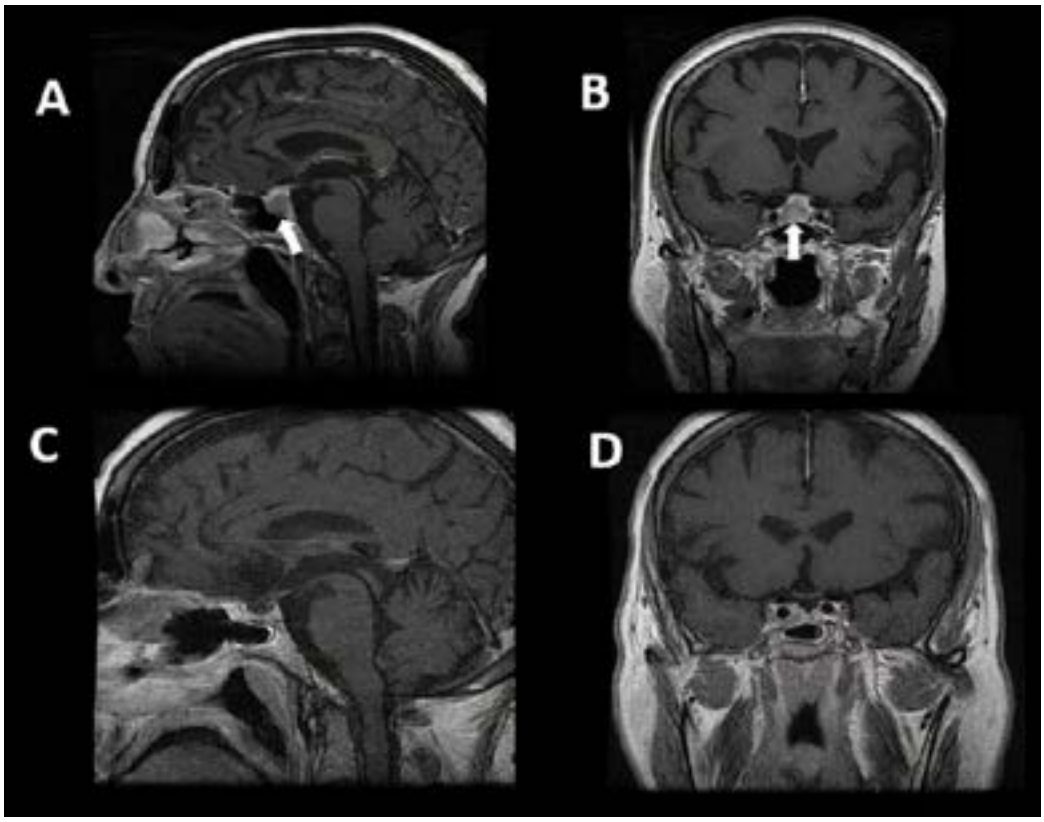

Figure 1. In contrast-enhanced pituitary MR images of a Cushing Disease with microadenoma

Pre-operative sagittal (A) and coronal (B) MRI sections showed the tumor (hypointense adenoma is indicated by a white arrow). Post-operative sagittal (C) and coronal (D) MRI sections no tumor is observed

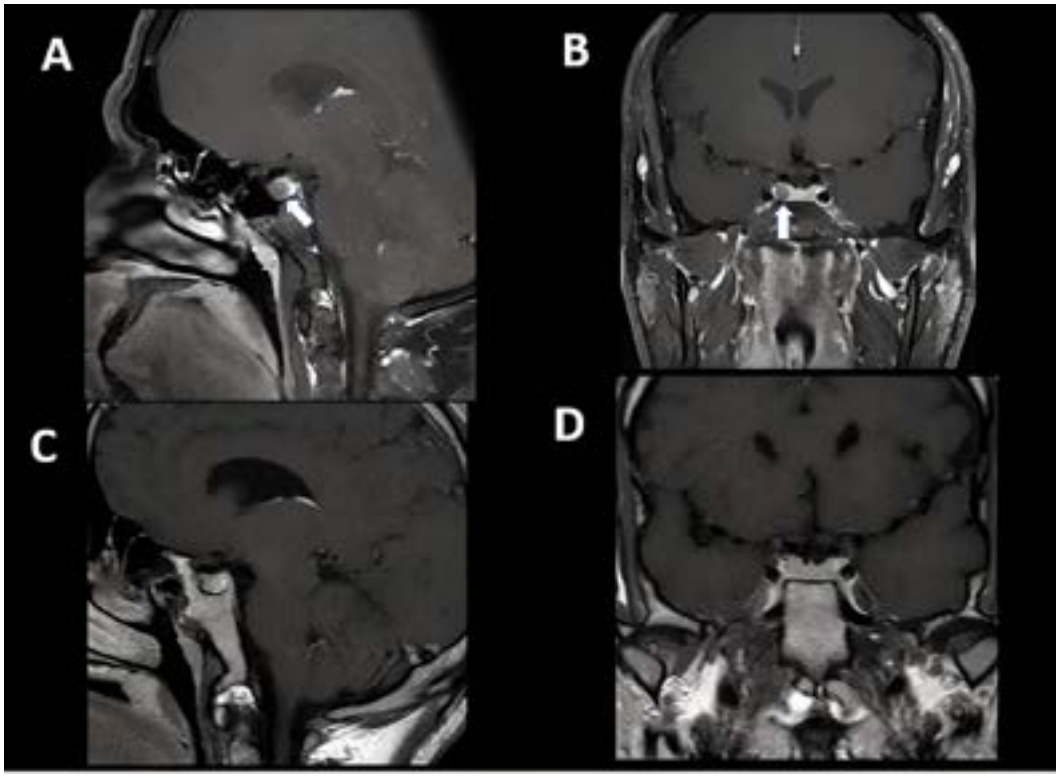

Figure 2. In contrast-enhanced pituitary MR images of a Cushing Disease with macro-adenoma

Pre-operative sagittal (A) and coronal (B) MRI sections showed the tumor (hypointense adenoma is indicated by a white arrow). Post-operative sagittal (C) and coronal (D) MRI sections no tumor is observed

The following day after the operation, all patients' cortisol and ACTH levels were measured. Our study evaluated remission based on the laboratory values obtained the following day after the surgery, with <2 µg/dl and <5 pg/ml as reference values, respectively. The postoperative duration of glucocorticoid use and the time to recurrence were investigated. Different morning cortisol cutoff values were used when remission was identified using biochemical tests, including 'morning cortisol levels.' Although these values ranged from 50 to 275.9 nmol/l, the cutoff of 50 nmol/l was most consistently used when morning serum cortisol level was measured without any other biochemical assay to define remission. In the pathological evaluation, the Ki-67 index values of the patients were also measured. Ki-67 index values <2% were evaluated as indicative of low mitotic activity [9-12]. Studies have evaluated whether the Ki-67 index affects tumor recurrence.

This study was approved by Ankara University Faculty of Medicine Human Arts Research Ethics Committee. No personal data or photographs were used against human and animal rights.

Statistical analysis

'IBM SPSS Statistics version 20 software (IBM Inc.)' was used for statistical analysis. The Pearson correlation analysis was used to test the relationship between age and recurrence. The Spearman correlation analysis was applied to test the relationship between glucocorticoid hormone therapy duration and recurrence. The chi-square test was applied to analyze the relationships of adenoma size, Ki-67 index, and next-morning ACTH value to recurrence.

Results

Sixty-four patients with CD who underwent EEA pituitary surgery at the referral clinic were included. Fifty patients (78%) were female, and 14 (22%) were male. The mean age was 41.6±12.68 (25-68) years, and the mean follow-up period of the patients was 25.5±8.24 (12-68) months. Twenty-two lesions were identified as macroadenomas, and 40, as microadenomas. Two patients had no lesions in the sellar region, so they were evaluated as having MRI (-) CD. (Table 1).

Of the patients, 34 (53%) were considered in remission biochemically for at least ≥1 year. Eleven patients (17%) developed panhypopituitarism. Nineteen patients (29%) did not achieve remission after TSS. Eight patients who had remission underwent reoperation because of tumor recurrence or relapse, of whom six again achieved remission after the reoperation. Twelve patients who did not achieve remission underwent reoperation, of

Table 1. Patients' distribution and laboratory values

	Microadenoma (n=40)	Macroadenoma (n=22)	MRI (-) CD (n=2)
Age, years	37 (19-61)	48 (23-70)	48 (43-54)
Female/male	37/3	14/8	1/1
Recurrent endoscopic TSS	16	3	1
Ki-67 index <2%	17 (5 with a tumor recurrence)	9 (3 with a tumor recurrence)	1
Serum cortisol value on the next day <2 µg/dl	14	1	1
Third-month control serum cortisol value <2 µg/dl	4 (Among 23 patients who underwent regular checkups)	1 (Among 18 patients who underwent regular checkups)	1
Serum ACTH value on the next day <5 pg/ml	11	3	1
Third-month control serum ACTH value <5 pg/ml	12 (Among 23 patients who underwent regular checkups)	4 (Among 18 patients who underwent regular checkups)	1
Panhypopituitarism after TSS	6	4	1
Persistent diabetes insipidus after TSS	3	2	
Cerebrospinal fluid rhinorrhea after TSS	2	2	1

TSS: transsphenoidal surgery, MRI: magnetic resonance imaging

whom 6 entered remission. During the repeated TSS (20 patients), 14 microadenomas, five macroadenomas, and 1 MRI (-) CD were found. Gamma knife surgery was performed in 1 patient with a microadenoma, and bilateral adrenalectomy was performed in 1 patient with a macroadenoma. After EEA, five patients (7.8%) had persistent central diabetes insipidus, and one patient (1.5%) had cerebral salt wasting. In 5 patients (7.8%), sellar floor repair was performed because of rhinorrhea.

The "Chi-Square Independence Test" was applied for a significant relationship between cortisol value on the first day after surgery and recurrence. The 24-h postoperative cortisol value was <2 μg/dl in 7 patients with microadenoma, <2 μg/dl in 1 patient with macroadenoma, and <2 μg/dl in 1 patient with MRI (-) CD. Of the patients with microadenoma who attended regular follow-up checkups, 9 and 5 were found to have 24-h postoperative cortisol values <2 and <5 μg/dl, respectively. Of those with macroadenomas who attended regular follow-up checkups, three had 24-h postoperative cortisol values <2 μg/dl <2 μg/dl in 2 patients with MRI (-) CD, which made regular control visits and in 1 patient with a recurrent microadenoma. There was no significant correlation between the cortisol value on the first day after surgery and recurrence (p=0.119).

The Ki-67 index was >10% in 5 patients, and four had a recurrence. In 17 patients, the Ki-67 index was <2%, and 2 had a recurrence. Of the patients with macroadenomas, 3 had Ki-67 index values >10%, and 2 had a recurrence. In 9 patients, the Ki-67 index was <2%, and one had a recurrence. One of the patients with MRI (-) CD had a Ki-67 index >2% and a recurrence. The "Chi-Square Independence Test" was applied for the Ki-67 index-affected recurrence. There was no significant correlation between the Ki-67 index and recurrence (p=0.640).

In 46 patients (71%), glucocorticoid administration was required after pituitary surgery. The postoperative glucocorticoid therapy duration was >1 year in 20 patients, of whom none had a recurrence. In 12 patients, the glucocorticoid therapy duration ranged from 6 to 12 months, and four patients showed recurrence. In 8 patients, the glucocorticoid therapy duration was <6 months, and four patients showed recurrence. In 6 patients, the glucocorticoid therapy duration was <1 month and four patients showed recurrence. "Spearman Correlation Analysis" was applied for the significant relationship between the duration of hormone use and recurrence. There was a significant correlation between the duration of hormone use and recurrence (p=0.003) (Table 2).

Table 2. Glucocorticoid therapy duration and time to recurrence

Relapse Patients		
Microadenoma (8)		
	GDT	**RT**
Patient 1	3 months	1st year
Patient 2	1 year	In the 3rd year
Patient 3	1 year	1st year
Patient 4	0	Within 18 months
Patient 5	6 months	In the 3rd year
Patient 6	0	Within 3 months
Patient 7	2 months	In the 6th year
Patient 8	3 weeks	In the 2nd year
Macroadenoma (3)		
	GDT	**RT**
Patient 1	3 months	In the 3rd year
Patient 2	6 months	Within 9 months
Patient 3	0	In the 5th year
MR - (1)		
	GDT	**RT**
Patient 1	0	Within 3 months

GDT: glucocorticoid therapy duration time, RT: recurrence time

Discussion

The glucocorticoid hormone therapy duration after surgery for CD has been reported to be a remission marker. Bochicchio et al. [22] reported that 5-year remission was achieved in 97% of the patients who received glucocorticoid replacement therapy for >1 year. Remission rates of 76% and 53% were reported in those who received glucocorticoid replacement therapy for <1 year and those without hormone replacement therapy. Bansal et al. [23] reported that continuing postoperative hypocortisolemia for >13 months predicted long-term remission at a mean follow-up of 74 months. Low postoperative cortisol level is an expected finding. Chronic hypocortisolemia after surgery can indicate remission [24]. Numerous studies are needed to predict short- or long-term remission. Alexandraki et al. [25] reported no improvement in the hypothalamic-pituitary-adrenal (HPA) axis over six months and one year and that predicts remission with specificity rates of 93% and 89%, respectively. Contrary to the findings of the other studies, Dimopoulou et al. [26] reported that long-term postoperative hypocortisolemia duration does not prevent CD recurrence. In our study, we discussed whether glucocorticoid therapy duration predicts recurrence, regardless of whether it affects hormonal remission. No recurrence was detected in the 28 patients who underwent glucocorticoid replacement therapy for >6 months during a mean follow-up of 5 years. Recurrence was observed in 12 patients who underwent replacement therapy for <1 year. In 4 patients, the need for hormone replacement was <2 weeks, which suggests surgical failure. However, postoperative glucocorticoid replacement therapy was not required in 8 patients, and recurrence was not detected in these patients. Our study's glucocorticoid therapy duration of >6 months predicted that recurrence would not occur (p<0.05). Postoperative hypocortisolemia can be affected by the amount of surgical resection, cortisol half-life, and reactive adrenal hyperplasia. These findings suggest the importance of repetitive hormone tests and correctly timing the need for replacement.

Cortisol and ACTH values measured on the next day after the operation can be used as early remission markers. Mayberg et al. [27] reported that in patients with cortisol levels <2.1 µg/dl in the first 72 hours after surgery, an 88% remission rate was achieved without a second surgery. This value could be used as a remission marker. In addition, low remission rates were found in patients with cortisol levels of 2.1-5.4 µg/dl (75%). Starke et al. [17] showed that low cortisol levels <5.4 µg/dl may be the best indicator of remission. However, Mayberg et al. [27] suggested that low cortisol levels the next day after the operation may be a short-term rather than a long-term remission marker. They attributed this to the continuation of cortisol production due to adrenal hyperplasia even if ACTH production was wholly stopped surgically. On the next day after surgery, they obtained a cortisol value of 74 nmol/l. In the literature, cortisol, and ACTH levels below a specific value have been evaluated as markers and predictors of hormonal remission. In our study, we examined whether cortisol and ACTH values predicted recurrence. The next day cortisol cutoff value was 2 µg/dl. Three of the 16 patients with cortisol levels <2 µg/dl on the following day had a recurrence one year later, and the cortisol value measured on the following day did not predict recurrence (p=0.119). Similarly, the cortisol values measured in the 42 patients who made a follow-up visit after 3 months did not predict recurrence (p=0.169). Ramm Pettersen et al. [28] reported that the probability of recurrence in patients with cortisol values >2 µg/dl in the first 72 hours after the operation is 2.5 times higher than in patients with cortisol values <2 µg/dl. However, the same study reported that 45% of the patients had cortisol values >2 µg/dl and did not include patients who were predicted to go into long-term remission.

The relationship between adenoma size and recurrence has been examined in many studies. In the study of Guaraldi et al. [13], patients with microadenoma benefited more from surgery. In addition, cavernous sinus invasion negatively affected the prognosis of macroadenomas. In the study of Clayton et al. [2], the remission rate was higher in patients with microadenomas. When only patients with macroadenomas were examined, the remission rate was higher in those who underwent endoscopic TSS. This can be explained by the surgeon's more expansive field of view in endoscopic surgery for invasive macroadenomas. Chandler et al. [14], Kaptain et al. [15], and Sarkar et al. [16] found that

the remission rate was higher in patients with microadenomas. In the study of Starke et al. [17], no significant difference was found between microadenomas and macroadenomas in terms of recurrence. The difference in recurrence rate according to adenoma size can be attributed to the experience of the surgical team and the choice of endoscopic or microscopic surgical approach. In our study, a proportionally higher recurrence rate was observed in the patients with macroadenomas than in those with microadenomas and macroadenomas, but the differences were not statistically significant (p=0.495).

Only a few studies have investigated the relationship between the Ki-67 index and CD recurrence. The cutoff Ki-67 index was 3% according to the 'World Health Organization classification,' and cases with Ki-67 index values above this cutoff were more aggressive and had poor prognoses [18]. A high Ki-67 index alone is not an indicator of poor prognosis. Liu et al. [19] reported that high Ki-67 index values did not significantly affect patients with recurrent CD. Kara et al. [20] reported a Ki-67 index >3%. They suggested its importance in CD cases with increasing tumor sizes, indicating invasion and aggressive prognosis. In the study of Keskin et al. [21], the Ki-67 index was 1.1%, and the high Ki-67 index was significant in CD recurrence. In our study, the cutoff Ki-67 index was 2%. In our series, Ki-67 index values >2 were not found to be significantly related to CD recurrence (p=0.640).

In conclusion, remission markers can change the frequency of patient follow-up or predict treatment response early. The most crucial aspect in treating CD is a proper follow-up after surgery and administration of the necessary medical and surgical interventions. In the treatment of CD, the sustainability of hypocortisolemia is essential. Glucocorticoid therapy duration> six months after surgery predicts no recurrence. Long-term glucocorticoid therapy after surgery also suggests surgical success. Postoperative cortisol and ACTH values did not predict recurrence in our study. This may be due to the amount of adenoma removed and variable compensatory mechanisms in the HPA axis.

Conflict of interest: No conflict of interest was declared by the authors.

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Authors' contributions to the article

M.C.K. and B.C.A. have constructed/constructed the main idea and hypothesis of the study. S.H. developed the theory and arranged/edited the material and method section. G.K. and C.M. have evaluated the data in the Results section. Discussion section of the article written by A.B.B., S.B. and M.A.U. M.C.K., B.C.A., S.H., G.K., A.B.B., C.M., and S.B. reviewed, corrected, and approved. In addition, all authors discussed the entire study and approved the final version.

Research Article

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Evaluation of the frequency of MEFV gene variants in patients with a pre-diagnosis of Familial Mediterranean Fever (FMF) in southeast Türkiye

Türkiye'nin güneydoğusunda Ailevi Akdeniz Ateşi (AAA) ön tanısı alan hastalardaki MEFV gen varyantlarının sıklığının değerlendirilmesi

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Abstract

Purpose: Familial Mediterranean Fever (FMF) is a hereditary auto inflammatory disease (MIM#249100). The most common symptoms are abdominal pain, high fever, and arthralgia. FMF is the result of variants in the MEditerraneanFeVer (MEFV) gene located on chromosome 16p13.3, which contains 10 exons and encodes the pyrin (marenostrin) protein. The frequency of MEFV gene variants that cause FMF varies according to ethnic groups, countries and even different regions in the same country. In our study, we aimed to determine the frequency and distribution of MEFV gene changes that cause Familial Mediterranean fever in southeast Türkiye.

Materials and methods: A total of 6.660 patients with a pre-diagnosis of FMF, including 3.495 women and 3.165 men, were included in the study. Fragment analysis was performed to investigate the MEFV gene variants of the patients and the 19 most common variants in the Turkish population were examined.

Results: We found at least one variant in 50.17% (3.341) of our 6.660 patients. In our patients, 108 different genotypes; in Exon 2, 3, 5 and 10 and we identified 16 different variants. We found 2.120 (63.21%) patients were heterozygous, 693 (20.74%) were compound heterozygotes, 275 (8.23%) were homozygous and 261 (7.81%) were complex genotypes. The five variants with the highest allele frequency are; R202Q (27.84%), M694V (22.83%), E148Q (21.98%), V726A (7.42%), and M680I (G>C) (6.39%).

Conclusion: We identified the most common prevalence of MEFV gene alteration in a large patient group in our region. High R202Q mutation rates were among the remarkable results of this study.

Key words: FMF, MEFV gene variants, fragment analysis.

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Öz

Amaç: Ailevi Akdeniz Ateşi (AAA) kalıtsal bir otoinflamatuar hastalıktır (MIM#249100). En sık görülen semptomlar yüksek ateş, karın ağrısı ve artraljidir. AAA, 16p13.3 kromozomu üzerinde yer alan, 10 ekzondan oluşan ve pirin (marenostrin) proteinini kodlayan MEditerraneanFeVer (MEFV) genindeki varyantların sonucudur. AAA'ya neden olan MEFV gen varyantlarının sıklığı etnik gruplara, ülkelere ve hatta aynı ülke içindeki farklı bölgelere göre değişmektedir. Bu çalışmada, Türkiye'nin güneydoğusunda Ailesel Akdeniz ateşine neden olan MEFV gen değişikliklerinin sıklığını ve dağılımını belirlemeyi amaçladık.

Gereç ve yöntem: Çalışmaya Ailevi Akdeniz Ateşi ön tanısı almış olan 3,495 kadın ve 3,165 erkek olmak üzere toplam 6.660 hasta dahil edildi. Hastaların MEFV gen varyantlarını araştırmak için fragman analizi yapıldı ve Türk popülasyonunda en sık görülen 19 varyant incelendi.

Bulgular: Çalışmaya dahil edilen 6,660 hastamızın %50,17'sinde (3,341) en az bir varyant tespit edildi. Hastalarımızda 108 farklı genotip; Exon 2, 3, 5 ve 10'da olmak üzere 16 farklı varyant belirledik. Hastaların 2,120'sinde (%63,21) heterozigot, 693'ünde (%20,74) bileşik heterozigot, 275'inde (%8,23) homozigot ve 261'inde (%7,81) kompleks genotip bulundu. Alel frekansı en yüksek olan 5 varyant sırasıyla; R202Q (%27,84), M694V (%22,83), E148Q (%21,98), V726A (%7,42) ve M680I (G>C) (%6,39) olarak belirlendi.

Sonuç: Bölgemizde geniş bir hasta grubunda yaptığımız bu çalışma ile FMF ön tanısı almış olan hastalarda en sık görülen MEFV gen değişikliklerinin sıklığını ve dağılımını belirledik. Yüksek R202Q mutasyon oranları bu çalışmanın dikkat çekici sonuçları arasında yer almaktadır.

Anahtar kelimeler: FMF, MEFV gen varyantları, fragman analizi.

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Introduction

Familial Mediterranean fever (FMF) is an autoinflammatory disorder (MIM# 249100) and is characterized by recurrent attacks of fever, inflammation of the serous membranes [1]. The most common symptoms are abdominal pain, joint pain and swelling, chest pain, self-limiting fever and erysipelas-like erythema. The frequency of attacks can vary from once a week to once a year. Between attacks, patients are completely normal and this feature is important for diagnosis [2]. Although FMF is an autosomal recessive disease, heterozygous individuals have also been reported to show symptoms associated with the disease [3]. This disease is common in the generation that includes our country. The incidence in Turks, Armenians, Arabs and Jews is much higher than in other societies. It can also be found less frequently in Greece, Italy and Spain, but with increasing immigrations, FMF is a disease seen all over the world today [4-6]. The carrier rate of FMF in Türkiye is 1/5 and its estimated prevalence is 1/1000 [7].

The *MEFV* gene responsible for FMF is located on chromosome 16p13.3, consists of 10 exons and encodes a 781 amino acid protein called marenostrin or pyrin (OMIM Protein Accession Number: NP_000234.1) [8, 9]. Mutations in the *MEFV* gene disrupt the role of the pyrin region, resulting in an uninterrupted inflammatory response. To date, 391 variants in the *MEFV* gene have been reported according to the Infevers database [10]. The most common variants in the *MEFV* gene have been identified in exon 10 and exon 2, but the spectrum of *MEFV* variants in FMF patients differs between populations and ethnic groups [11].

The diagnosis of the disease can be made by clinical signs according to TelHashomer criteria. However, identification of disease-causing *MEFV* gene mutations is useful for establishing or confirming the diagnosis of FMF [12, 13].

Here, we aim to contribute to Türkiye's *MEFV* variant spectrum data by presenting *MEFV* gene variant data in a large group of 6.660 patients referred to our laboratory due to FMF findings.

Materials and methods

The study was approved by Pamukkale University Non-Interventional Clinical Research Ethics Committee with the decision dated 08 February 2023 and numbered E-60116787-020-328733. A total of 6.660 patients (3.165 men, 3.495 women) referred from different clinics to our center (Gaziantep Dr. Ersin Arslan Training and Research Hospital Genetic Diagnosis Center) between 2016 and 2022 were included in the study. The *MEFV* gene variant analysis results of these patients who presented with a pre-diagnosis of FMF were evaluated.

Genomic DNA extraction

For variant analysis, genomic DNA isolation was performed from the peripheral venous blood sample collected in EDTA (ethylenediaminetetraacetic acid) tubes by using the "Maxwell RSC" DNA isolation kit (Promega/ USA) from the blood with an automated system (Maxwell RSC Promega/ USA). Spectrophotometric measurements were made for the obtained DNAs (Nano-drop/USA). 10-50 ng/µL DNA was used for the study.

Molecular analysis

In the fragment analysis method, PCR was performed with specific primers (GML SNP DEtective *MEFV* kit) for DNA material obtained from peripheral blood samples taken from patients. The obtained PCR product was evaluated by applying fragment analysis in ABI 3500 DNA Sequencer. Nineteen variants of *MEFV* gene were analyzed by fragment analysis method. These variants are; located in Exon 2: p.R202Q, p.S179I, p.E167D, p.E148Q; Exon 3: p.P369S, p.P350R; Exon 5: p.F479L, p.Y471X and Exon 10: p.R761H, p.A744S, p.V726A, p.K695R, p.K695N, p.M694I, p.M694V, p.I692del, p.M680I (G>A), p.M680I (G>C), p.G632A.

Results

Of the 6.660 patients with a pre-diagnosis of FMF, whose age range was between newborn and 80, 3.495 (52.48%) were female and 3.165 (47.52%) were male. No variant was detected in 3.319 patients (49.83%). At least one variant was found in 3.341 (50.17%) patients. Of the 3.341 patients with variants, 49% (n=1.638) were male and 51% (n=1.703) were female. 108 different genotypes and 16 different variants (4/16 with exon 2, 2/16 with exon 3, 1/16 with exon 5 and 9/16 with exon 10) were detected in these patients.

Heterozygous genotype was determined in two thousand one hundred twelve (63.21%) patients, compound heterozygous in six hundred ninety-three (20.74%) patients, homozygous in two hundred seventy-five (8.23%) patients, and complex genotype in two hundred and sixty-one (7.81%) patients (Table1). The most common variants as heterozygous were E148Q, R202Q and M694V, respectively and the most common homozygous variant we saw was M694V.

Table 1. Genotype distribution and frequencies of patients

Variant (n, %)	Genotype	Patients	
		n	%
Heterozygous	E148Q/wt	609	18.22
(n=2112, 63.21%)	R202Q/wt	580	17.36
	M694V/wt	322	9.63
	V726A/wt	175	5.24
	M680I (G>C)/wt	120	3.60
	P369S/wt	91	2.72
	R761H/wt	75	2.24
	A744S/wt	68	2.04
	K695R/wt	33	0.99
	M694I/wt	32	0.96
	I692del/wt	3	0.09
	M680I (G>A)/wt	2	0.06
	F479L/wt	1	0.03
	E167D/wt	1	0.03
	Subtotal	2.112	63.21
Compound heterozygous	R202Q/ M694V	178	5.33
(n=693, 20.74%)	E148Q/ R202Q	64	1.91
	E148Q/ M694V	58	1.74
	M680I (G>C)/ M694V	43	1.29
	E148Q/ P369S	38	1.13
	M694V/ V726A	38	1.13
	M680I (G>C)/ V726A	27	0.80
	M694V/ R761H	24	0.72
	E148Q/ M680I (G>C)	22	0.66
	E148Q/ V726A	21	0.63
	E148Q/ M694I	18	0.54
	R202Q/ V726A	18	0.54
	R202Q/ P369S	17	0.50
	R202Q/ M680I (G>C)	14	0.42
	R202Q/ R761H	13	0.39
	P369S/ R408Q	12	0.36
	M680I (G>C)/ R761H	9	0.27
	E148Q/ A744S	9	0.27
	R202Q/ A744S	8	0.24
	V726A/ A744S	7	0.20
	F479L/ E167D	7	0.20
	M694I/ M694V	6	0.18
	E148Q/ R761H	6	0.18
	M694I/ R761H	5	0.15
	M694V/ A744S	4	0.12
	V726A/ R761H	4	0.12
	M694I/ V726A	3	0.09
	E148Q/ K695R	2	0.06
	R202Q/ M694I	2	0.06

Table 1. Genotype distribution and frequencies of patients (continued-1)

Variant (n, %)	Complex genotype	Patients	
		n	%
Compound heterezygous (n=693, 20.74%) (continued)	P369S/ M694V	2	0.06
	M680I (G>C)/ K695R	2	0.06
	V726A/ K695R	2	0.06
	E148Q/ M680I (G>A)	1	0.03
	R202Q/ S179I	1	0.03
	R202Q/ K695R	1	0.03
	P369S/ V726A	1	0.03
	P369S/ A744S	1	0.03
	M680I (G>C)/ M680I (G>A)	1	0.03
	M680I (G>C)/ M694I	1	0.03
	M680I (G>A)/ R761H	1	0.03
	M694I/ A744S	1	0.03
	A744S/ R761H	1	0.03
	Subtotal	693	20.74
Homozygous (n=275, 8.23%)	M694V	81	2.40
	R202Q	70	2.09
	M680I (G>C)	37	1.11
	E148Q	34	1.02
	V726A	23	0.69
	R761H	15	0.45
	M694I	8	0.24
	A744S	5	0.15
	P369S	2	0.06
	Subtotal	275	8.23
Complex (total) (n=261, 7.81%)			
Homozygous/ Homozygous (n=81, 2.42%)	R202Q/ M694V	78	2.33
	E148Q/ P369S	1	0.03
	F479L/ E167D	1	0.03
	E148Q/ M694I	1	0.03
	Subtotal	81	2.42
Homozygous/ Homozygous/ Homozygous (n=1, 0.03%)	E148Q/ R408Q/ P369S	1	0.03
Homozygous/ Heterozygous (n=65, 1.94%)	R202Q/ M694V	45	1.35
	M694V/ R202Q	8	0.24
	E148Q/ P369S	3	0.09
	R202Q/ P369S	3	0.09
	E167D/ E148Q	1	0.03
	E148Q/ M694I	1	0.03
	R202Q/ K695R	1	0.03
	P350R/ R202Q	1	0.03
	M694I/ R761H	1	0.03
	M694I/ V726A	1	0.03
	Subtotal	65	
Homozygous/ Heterozygous/ Heterozygous (n=1, 0.03%)	M694I/ M694V/ V726A	1	0.03

Table 1. Genotype distribution and frequencies of patients (continued-2)

Variant (n, %)	Complex genotype	Patients	
		n	%
Heterozygous/ Heterozygous/ Heterozygous (n=107, 3.20%)	E148Q/ R202Q/ M694V	32	0.96
	R202Q/ M694V/ V726A	21	0.63
	R202Q/ M694V/ R761H	12	0.36
	R202Q/ M694V/ M680I (G>C)	6	0.18
	E148Q/ M694V/ R202Q	5	0.15
	E148Q/ P369S/ R202Q	5	0.15
	E148Q/ P369S/ R408Q	3	0.09
	E148Q/ P369S/ V726A	3	0.09
	E167D/ G/ V726A	2	0.06
	E167D/ F479L/ M694V	2	0.06
	E148Q/ P369S/ M694V	2	0.06
	R202Q/ M694V/ A744S	2	0.06
	A744S/ P369S/ R202Q	1	0.03
	E167D/ F479L/ R202Q	1	0.03
	E167D/ E148Q/ F479L	1	0.03
	E148Q/ R202Q/ M680I (G>C)	1	0.03
	E148Q/ P369S/ M680I (G>C)	1	0.03
	E148Q/ M694I/ M680I (G>C)	1	0.03
	P369S/ R408Q/ M694I	1	0.03
	R202Q/ M694V/ V726A	1	0.03
	R202Q/ P369S/ A744S	1	0.03
	E148Q/R202Q/ M694I	1	0.03
	R202Q/P369S/ V726A	1	0.03
	P369S/ R408Q/ V761H	1	0.03
	Subtotal	107	
Heterozygous/ Heterozygous/ Heterozygous/ Heterozygous (n=6, 0.18%)	E148Q/ R202Q/ M694V/ M694I	3	0.09
	E148Q/ R202Q/ P369S/ M694V	2	0.06
	E167D/ R202Q/ F479L/ M694V	1	0.03
	Subtotal	6	0.18
Patients with MEFV variants (total)		3.341	50.17
Patients without MEFV variants		3.319	49.83
Total number of patients		6660	

Of the 19 variants studied, R202Q had the highest allele frequency of 27.84%. The second variant with the highest allele frequency was M694V (22.83%) and the third variant was E148Q (21.98%). The other variants identified, in order of allele frequency, were as follows: V726A, M680I (G>C), P369S, R761H, A744S, M694I, K695R, E167D, F479L, I692del, M680I (G>A), P350R, S179I (Table 2).

Of the 19 variants examined by fragment analysis in the *MEFV* gene, 3 were not detected in any of our cases. These were the F471X, G632A and K695N.

The number of patients, distribution and frequency of *MEFV* variants detected in this study are given in Table 2.

Table 2. Allele frequencies of MEFV variants among 3341 patients

Exon number	Variant	Nucleotid change	Aminoacid change	rs number	Number of patients	Number of alleles	Variated allele frequency (%)
2	R202Q	c.605G>A	p.Arg202Gln	rs224222	1198	1395	27.84
10	M694V	c.2080A>G	p.Met694Val	rs61752717	977	1144	22.83
2	E148Q	c.442G>C	p.Glu148Gln	rs3743930	950	1101	21.98
10	V726A	c.2177T>C	p.Val726Ala	rs28940579	349	372	7.42
10	M680I (G>C)	c.2040G>C	p.Met680Ile	rs28940580	283	320	6.39
3	P369S	c.1105C>T	p.Pro369Ser	rs11466023	193	197	3.93
10	R761H	c.2282G>A	p.Arg761His	rs104895097	166	181	3.62
10	A744S	c.2230G>T	p.Ala744Ser	rs61732874	108	113	2.25
10	M694I	c.2082G>A	p.Met694Ile	rs28940578	87	99	1.98
10	K695R	c.2084A>G	p.Lys695Arg	rs104895094	41	41	0.82
2	E167D	c.501G>C	p.Glu167Asp	rs104895079	17	19	0.38
5	F479L	c.1437C>G	p.Phe479Leu	rs104895083	16	17	0.34
10	I692del	c.2076_2078del	p.Ile692del	rs104895093	4	4	0.08
10	M680I (G>A)	c.2040G>A	p.Met680Ile	rs28940580	4	4	0.08
3	P350R	c.1049C>G	p.Pro350Arg	-	1	2	0.04
2	S179I	c.536G>T	p.Ser179Ile	rs104895125	1	1	0.02
						Total:5010	

Discussion

FMF is an autoinflammatory disease [6, 14]. Defined as a Mediterranean Basin disease, FMF was first observed in Jewish and Armenian patients, then spread among Turks and Arabs through migration routes [15]. Türkiye is one of the countries with the highest prevalence of the disease (1:1000) and many studies have shown that the carrier rate is around 20-25% [16].

FMF disease is more common in males (male: female ratio of 1.2:1), the mean age of onset is 9.6, and the mean age at diagnosis is 16.4 [7]. When we look at the male-female ratio in our patients, the number of female patients is higher with a difference of 2%, and it differs from this situation.

The number and variety of variants in the *MEFV* gene involved in the etiology of FMF vary between populations [17]. In our study, 19 variants, which were reported to be frequently observed in cases sent to our laboratory with a pre-diagnosis of FMF, were screened. At least one change was detected in 50.17% of the cases. The changes in the first five that we found the highest frequency were R202Q, M694V, E148Q, V726A, M680I (G>C). It has been reported in the literature that these variants constitute approximately 85% of the variants in the Mediterranean region [5, 6]. We determined the frequency of these five variants in exon 10 (M694V, M680IG>C and V726A) and exon 2 (E148Q and R202Q) to be 86.5% in our study population. This rate is very similar to previously reported rates.

We found complex genotype in 7.81%, homozygous in 8.23%, compound heterozygous in 20.74% and heterozygous genotype in 63.21% of our patients. 25-33% of people diagnosed with FMF carry only one variant in the *MEFV* gene. These heterozygous carriers with a single variant may display the FMF phenotype [18]. We identified only one heterozygous variant in 2.112 (31%) of 6.660 patients who were clinically evaluated as FMF, but *MEFV* whole gene analysis is required in this group to make a clear interpretation of this issue for our patients.

The rate of complex genotype in our country varies between 0.7% and 1.3% [19, 20]. In a study conducted with Syrian patients, this rate was found to be 6.7% [21]. We determined 7.81% complex genotypes in our patients. This can be explained by the increase in the Syrian patient population and its effect on the genotype distribution, since our region is a region that receives heavy Syrian immigration.

R202Q is generally considered to be a benign variant, but there are also publications emphasizing its increased frequency in FMF patients compared to healthy individuals and contributing to the FMF phenotype, some studies highlighting that homozygous or compound heterozygous R202Q mutation types can cause FMF and amyloidosis. The incidence of R202Q in the Turkish population varies between 5 and 34% [22, 23]. R202Q was the most common variant that we identified first with a frequency of 27.84%. 580 patients were heterozygous and 81 patients were homozygous. R202Q and M694V compound heterozygosity was the most common compound heterozygosity.

M694V was reported as the most common first or second variant with a frequency ranging from 15.6% to 67.2% in studies conducted in different regions of Türkiye [24]. In our study, M694V was the second most common variant with a frequency of 22.83%. As in two studies, one with a cohort of more than 2.800 (frequency of M694V is 18.86%) patients and the other with more than 27.000 (frequency of M694V is 29.47%) patients, our study also shows that the M694V is the leading pathogenic variant in Turks [7, 25].

E148Q is a variant with conflicting pathogenicity, also seen in the healthy population. It is classified as a Variant of Indeterminate Significance (VUS) [26]. It has been reported that the frequency of E148Q mutations in Türkiye has changed from 3.5% to 30.8% [27]. In a comprehensive study conducted by the National Genetics Consortium, the frequency of E148Q was found to be 18.27% [25]. We found the E148Q frequency as 21.98% and this result was similar.

Oztuzcu et al. [28], in their study with 3.341 patients in the same region as us, between 2009 and 2013; they found the most common *MEFV* gene variant and allele frequencies as follows: M694I (1.62%), A744S (2.45%), R761H (4.96), V726A (8.31%), M680I (G>C) (8.98%), E148Q (26.88%), M694V (41.77%). They did not report R202Q. While the top five variants are similar, especially the allele frequency of the M694V variant (22.83% in our study) differs considerably. In another study conducted in Sanliurfa, which is very close to the region we study, the frequency of common MEFV gene variants is as follows; V726A (6.5%), R761H (8), M680I (10%), E148Q (16%), M694V (17%), R202Q (24%) [29]. Although the first five variants in the article are similar, especially the allele frequency of the M694V variant (22.83% in our study) is quite different from ours. While the most common variants in Gumus's [29] study were similar, the incidence of R761H variants was different from ours.

In our patients, among the variants we examined; We did not find three variants, the F471X, G632A and K695N.

No variant was detected in 49.83% (3.319) of the 6.660 patients in the study population. This high rate of unidentified variant in these patients may be due to many factors other than the regions we looked at, such as the presence of other rare variants, unknown mutations, or genetic heterogeneity.

Our study, with the number of 6.660 patients, is the study with the largest number of patients performed by a single center in the southeast region.

In FMF, the distribution of variants in the *MEFV* gene can vary greatly from one population to another, even within the same population. Various variants may have a characteristic distribution in certain regions. Molecular diagnosis of MEFV is a clinically useful tool and is valuable for molecular diagnosis in determining variant frequencies and distributions of regions. This study, which was conducted with 6.660 patients, is a study showing the distribution of *MEFV* gene variants in southeastern Türkiye.

Conflict of interest: No conflict of interest was declared by the authors.

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Author contribution

K.K. and A.I.G. responsible for medical examination and planning of the study. B.S. and D.K. performed data collection, analysis and calculations. D.K. wrote the draft with the contributions of all the authors. K.K. and D.K. discussed the results, reviewed and commented on the article.

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Effect of resin photopolymerization on primary teeth pulpal temperature change

Rezin fotopolimerizasyonunun süt dişleri pulpal sıcaklık değişimi üzerine etkisi

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Abstract

Purpose: The polymerization of restorative materials has the potential to increase pulpal temperature and may result in damage to the health of pulpal tissue. The aim of this study is to investigate the pulpal temperature change of primary teeth with two light-emitting diode (LED) light-curing units (LCUs) (Valo Cordless®, EliparTM DeepCure-S) and three restorative groups (Filtek™ Bulk Fill Flowable, Filtek™ Z250 Universal Restorative and empty cavity) by using a microcirculation model.

Material and methods: Ten sound human maxillary second primary molars were used. Standardized Class V cavity preparations were performed with a dentin thickness of 1 mm and restorative groups were cured with LED LCUs. The highest temperature point in the pulp chamber was recorded. A repeated measures ANOVA and paired samples t-test were used for analysis of the data (p<0.05).

Results: EliparTM DeepCure-S groups exceeded the accepted critical temperature point of 5.6°C for Z250, Bulk Fill, and empty cavity (7.6±0.36, 7.44±0.7, and 5.81±1.6, respectively). None of the groups cured with Valo Cordless® reached the critical point (5.35±0.54, 5.44±0.41, and 5.02±0.89, respectively). The values in the different groups cured with Valo Cordless® were not significantly different (p≥0.05), but empty cavity showed significantly lower temperature values than the composite resin groups when the EliparTM DeepCure-S device was used (p<0.05).

Conclusion: The study demonstrated a correlation between the increased power of LED LCUs and pulp damage in restorative procedures.

Key words: Dental pulp, deciduous tooth, microcirculation, temperature, composite resins.

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Öz

Amaç: Restoratif materyallerin polimerizasyonu pulpal sıcaklığı artırma potansiyeline sahiptir ve pulpa dokusuna zarar verebilir. Çalışmanın amacı, süt dişi pulpal sıcaklık değişimini bir mikrosirkülasyon modeli kullanarak iki LED ışık cihazı (Valo Cordless®, EliparTM DeepCure-S) ve üç restoratif grup (Filtek™ Bulk Fill Flowable, Filtek™ Z250 Universal Restorative ve boş kavite) ile karşılaştırmaktır.

Gereç ve yöntem: On adet sağlam insan üst ikinci süt azı dişi kullanıldı. 1 mm dentin kalınlığı kalacak şekilde standardize Sınıf V kavite preparasyonları yapıldı ve restoratif gruplarda LED ışık cihazları kullanıldı. Pulpa odasındaki en yüksek sıcaklık noktası kaydedildi. Verilerin analizi için tekrarlı ölçümler ANOVA ve eşleştirilmiş örneklemler t-testi kullanıldı (p<0,05).

Bulgular: EliparTM DeepCure-S grupları, Z250, Bulk Fill ve boş kavite için kabul edilen kritik sıcaklık noktası olan 5,6°C'yi aştı (sırasıyla 7,6±0,36, 7,44±0,7 ve 5,81±1,6). Valo Cordless® ile ışık uygulanan grupların hiçbiri kritik noktaya ulaşmadı (sırasıyla 5,35±0,54, 5,44±0,41 ve 5,02±0,89). Valo Cordless® ile ışık uygulanan farklı gruplardaki değerler arasında anlamlı fark yoktu (p≥0,05), ancak EliparTM DeepCure-S cihazı kullanıldığında boş kavite, kompozit rezin gruplarına göre anlamlı derecede daha düşük sıcaklık değerleri gösterdi (p<0,05).

Sonuç: Çalışma, LED ışık cihazlarının artan gücü ile restoratif işlemlerde pulpa hasarı arasında bir ilişki olduğunu göstermiştir.

Anahtar kelimeler: Diş pulpası, süt dişi, mikrosirkülasyon, sıcaklık, kompozit rezinler.

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Introduction

Dental pulp is a mesenchymal origin soft tissue of teeth that includes nerves, vascular structures, fibers, interstitial fluids, odontoblasts, fibroblasts, and other minor cellular components. Despite the low thermal conductivity of dentin, the pulp is highly sensitive of thermal stimuli [1]. Many dental procedures such as cavity preparation [2], polymerization of restorative materials [3], and finishing/polishing procedures [4] have the potential to increase pulpal temperature. An increase in intrapulpal temperature may result in significant damage to the health of this tissue. A classical study [5] achieved on rhesus monkeys demonstrated a temperature rise of 5.6°C, resulting in irreversible pulpitis in 15% of subjects. Many research studies on pulpal temperature rise refer to this study and it can be said that the widely accepted clinically significant dangerous pulpal temperature increase threshold is 5.6°C [6-9].

The development of bulk-fill Resin-Based Composite (bulk-fill RBC) restorative materials is the most striking innovation of recent times in resin technology [10]. Traditionally, RBCs have been placed in the cavity using a layering technique of 2 mm increments to ensure essential light penetration and reduce polymerization shrinkage [11]. This method prolongs the completion of the restoration process and increases the risk of air bubbles between increments and fluid contamination [12]. A bulk-fill RBC depth increment of 4 to 10 mm could be polymerized in a relatively short time with an adequate light source [13]. The manufacturer explains that this curing time is due to the more potent initiator system or/ and higher translucency [14]. The use of these materials could be an advantage when working with uncooperative patients, such as young children, due the shortened working time [15].

Dental visible light sources produce light belonging to the blue area of the electromagnetic spectrum to stimulate the photoinitiator and begin polymerization. An irradiation produced by those light sources is absorbed by the resin based restorations and results in high molecular vibration and heat generation [16]. This means that dental tissues are exposed to heat from two sources: the light energy of the light-curing units (LCUs) and the exothermic character of the polymerization reaction. Intrapulpal temperature changes are related to the characteristics of the LCUs, such as irradiance, wavelength, and curing time, as well as the characteristics of the composite, such as basic chemical base, shade, and filler content. Restoration size and tooth properties, including the quality and thickness of the remaining dentin, also affect intrapulpal temperatures [17].

About 40 years, halogen lamp technology that had been adapted from the airplane industry was the main light source used for curing dental resin composites [18, 19]. But in the last decade, LCUs using Light Emitting Diode (LED) technology have replaced Quartz-Tungsten-Halogen (QTH) devices [20]. LED has many distinct advantages: requires a low power, can be easily battery powered, no filament or optical filter, has a long lifetime source, and provides much greater photon-generating efficiency than any competitive light source [19]. Although the energy efficiency of these devices is high, they produce certain levels of heat.

The aim of this study is to investigate the temperature changes in the primary teeth pulp chamber of empty cavities and during the polymerization of a bulk-fill RBC and a microhybrid resin composite cured with two LED LCUs, aided by a microcirculation device originally designed and described in a study by Ertugrul et al. [21].

The specific objectives of this study are:

- To compare the maximum temperature rises between bulk-fill RBC and microhybrid resin composite.
- To compare the maximum temperature rises between two LED LCUs.
- To compare the maximum temperature rises between just radiant energy from LCUs and both radiant energy and exothermic reactions of composites.

Materials and methods

This study has been approved by the ethics committee of non-interventional clinical researchs of Pamukkale University. Ten intact caries-free human maxillary second primary molar teeth that had been extracted in the previous month were selected for the study. After the extraction of the teeth, the surface tissues and blood were removed under running

water and cleaned of soft tissues with pumice slurry for this in-vitro study. The teeth were stored at +4°C in 0.2% thymol solution until use. Roots were separated and removed about 2 mm below the cementoenamel junction, perpendicular to the long axis of the teeth, and the apical part of the pulp chambers were enlarged using a water-cooled diamond bur. Then, all organic tissue scraps in the pulp chamber were gently removed retrograde by an excavator and cleaned with 5.25% sodium hypochloride solution and cotton pellets for one minute. The teeth were then rinsed with distilled water and air dried. Non-retentive buccal Class V cavity preparation was done in the primary teeth with water-cooling diamond fissure bur. The cavity dimensions were approximately 3 mm width, 2 mm height, and 2.5 mm depth. Cavity edges were slightly rounded. 1 mm±0.05 mm dentin thickness was left between the axial cavity floor and pulp chamber, which was assessed with a dial caliper (Yates-Motloid Co., Chicago, IL, USA).

To achieve the temperature measurements, a Pulpal Blood Microcirculation Model (PBMM) (Figure 1), originally designed and described in study of Ertugrul et al. [21] was used. A small diameter access was drilled on the lingual surfaces of the teeth into the pulpal chamber with a diamond bur to insert a thermocouple wire. A thermocouple wire (TT-K-30-SLE; Omega Engineering, Inc, Stanford, CT, USA) was inserted in the pulp chamber and placed on the axial wall of the tooth using a silicone heat-transfer compound (ZM-STG2; Zalman Tech Co. Ltd, Dongan-gu, South Korea). To position the thermocouple wire and to seal the gap between the drilled access point and wire, a light curing flowable composite (Filtek Ultimate Flowable Restorative, 3M ESPE, St. Paul, MN, USA) with a sixth generation two step self-etch bonding system (Clearfil SE Bond, Kuraray®, Tokyo, Japan) was applied and cured with an LED LCU (VALO Cordless®, Ultradent Products Inc., South Jordan, UT, USA) at a light intensity of 1.000 mW/cm^2. The other end of the thermocouple wire was connected to a four-channel data logger (DT-3891G; CEM, Shenzhen, PRC), which connected to a computer for monitoring temperature changes in the pulp chamber.

The characteristics of the composite materials and LED LCUs are summarized in tables 1 and 2, respectively. The experimental groups were designed as follows: Group Z-EDC: Filtek TM Z250 Universal Restorative + Elipar™ DeepCure-S, Group BF-EDC: Filtek™ Bulk Fill Flowable + Elipar™ DeepCure-S, Group E-EDC: Empty cavity + Elipar™ DeepCure-S, Group Z-VC: Filtek TM Z250 Universal Restorative + Valo Cordless®, Group BF-VC: Filtek™ Bulk Fill Flowable + Valo Cordless®, Group E-VC: Empty cavity + Valo Cordless®.

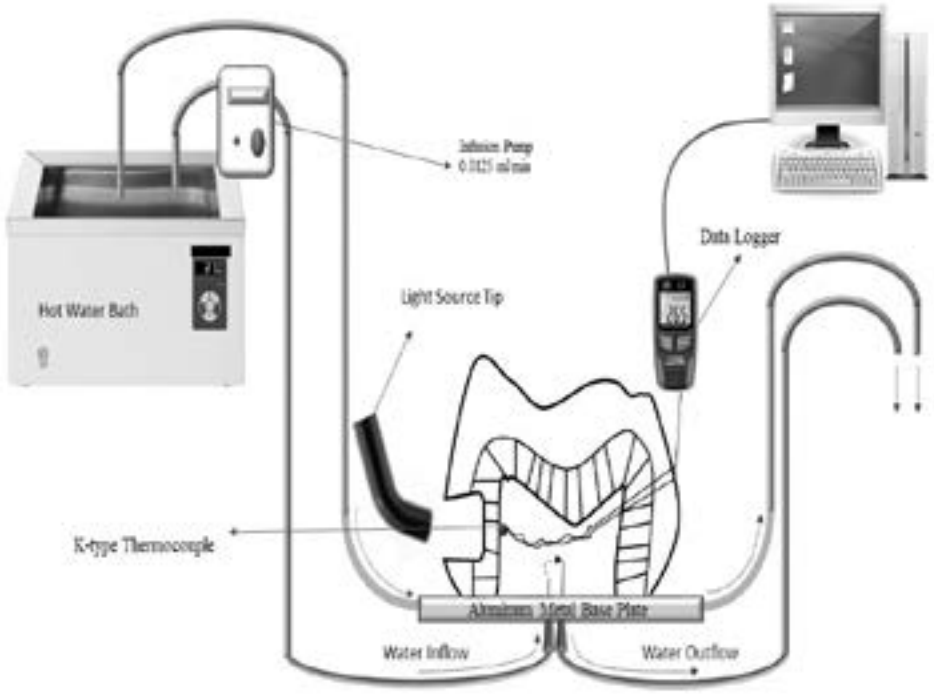

Figure 1. Schema of pulpal blood microcirculation model

Table 1. Characteristics of the composite materials used in this study

Composite materials	Composition	Manufacturer
Filtek™ Bulk Fill Flowable (A2 shade)	Bis-GMA, UDMA, Bis-EMA, procrylate resins, Ytterbium trifluoride, zirconia, silica (64.5 wt%, 42.5 vol%)	3M, ESPE, St. Paul, MN, USA
Filtek™ Z250 Universal Restorative (A2 shade)	Bis-GMA, Bis-EMA, TEGDMA, UDMA, zirconia, silica (82 wt%, 60 vol%)	3M, ESPE, St. Paul, MN, USA

Table 2. Characteristics of the light curing units used in this study

LCU	Light intensity in standard mode	Wavelength range	Lens diameter	Manufacturer
Valo Cordless®	1000 mW/cm^2	385-515 nm	9.75 mm	Ultradent, South Jordan, UT, USA
Elipar™ DeepCure-S	1470 mW/cm^2	430-480 nm	8.78 mm	3M Oral Care, St. Paul, MN, USA

The distilled water in the water bath was stabilized at 37°C and then circulation system commenced. Filtek™ Bulk Fill Flowable (A2) resin composite material was applied to the cavity on the buccal surface of the primary tooth on the aluminum base and polymerized for 20 seconds with the LED device Elipar™ Deep Cure-S with an irradiance of 1.470 mW/cm^2 (Figure 2). A measurement was then taken. With the assistance of a probe, the restoration was removed from the cavity and Filtek™ Z250 Universal Restorative was applied to the same cavity and cured with same LED device. A second measurement was then taken. Again, the restoration was removed with help of probe, and a third measurement taken on the empty cavity.

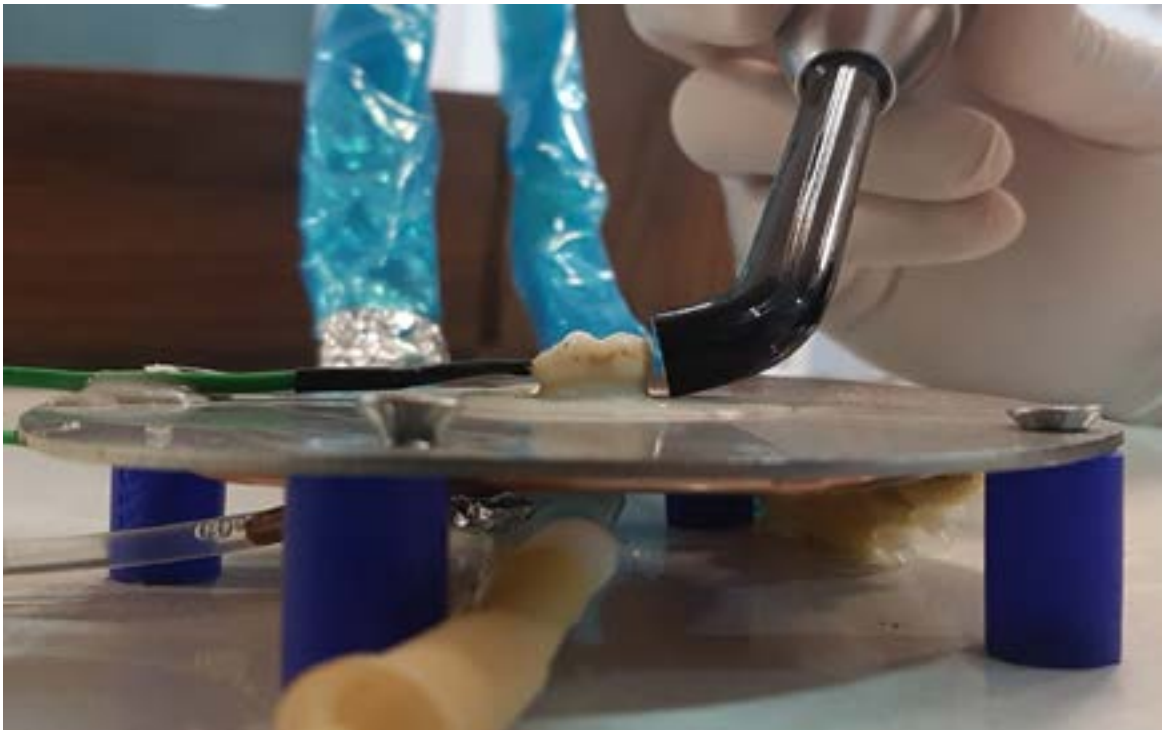

Figure 2. Light curing of restorative material on the aluminum base

On the same tooth, a Valo Cordless® was used with an irradiance of 1.000 mW/cm^2 and polymerization was performed for 20 seconds on the RBCs and empty cavity. After six temperature records, the tooth was removed. All ten teeth were adapted and tested using this same model and measurements were taken without etching and bonding. The distance between the light devices and the composites was set to 0 mm. The highest temperature point in the pulp chamber was recorded using software (Multiple Data Logger, AzeoTech, Inc, Ashland, Oregon, USA).

In the statistical analysis, the conformity of the data to the normal distribution was examined with the Shapiro-Wilk test. Parametric test conditions were satisfied, so repeated measures ANOVA and a paired samples t-test were used for comparing dependent groups with a SPSS program (SPSS version 23.0, IBM Corporation, Armonk, New York). The significance level was set to $p<0.05$ for all tests.

Results

Groups Z-EDC, BF-EDC, and E-EDC exceeded the accepted critical temperature point of 5.6°C (7.6±0.36, 7.44±0.7, and 5.81±1.6, respectively). None of the empty cavity and composite groups cured with the Valo Cordless® reached the critical point (5.35±0.54, 5.44±0.41, and 5.02±0.89). The highest temperature rise was the in Z-EDC group (8.2°C) and the lowest increment was in the E-EDC group (3°C). Both RBC groups (Z-EDC, and BF-EDC) cured with the Elipar™ DeepCure-S showed higher values than the groups cured with the Valo Cordless® (Z-VC, and BF-VC) ($p<0.05$). Within the Valo Cordless® ($p\geq0.05$) cured groups, the increase in temperature was not significant; however, the empty cavity group (E-EDC) showed significantly lower temperature values than the RBC groups (Z-EDC, and BF-EDC) using an Elipar™ DeepCure-S device ($p<0.05$) (Table 3).

Table 3. Average temperature rise values of the experimental groups and comparison (°C)

	Elipar™ DeepCure-S		Valo Cordless®		
	Mean±Std. Dev.	**Med (min - max)**	**Mean±Std. Dev.**	**Med (min - max)**	***p***
Filtek™ Z250 Universal (1)	7.6±0.36	7.6 (7-8.2)	5.35±0.54	5.45 (4.6-5.9)	0.0001* (t=11.741)
Filtek™ Bulk Fill Flowable (2)	7.44±0.7	7.6 (5.9-8.1)	5.44±0.41	5.5 (4.7-6)	0.0001* (t=7.081)
Empty cavity(3)	5.81±1.6	5.9 (3-7.8)	5.02±0.89	4.85 (3.9-6.6)	0.196 (t=1.397)
p	0.001* (F=10.241)(1-3, 2-3)		0.355 (F=1.096)		

Discussion

The thermal diffusivity of dentin is lower than that of enamel by 2.5 times [22]. Dentin acts as a barrier against heat, which is produced by the exothermic reaction of resin composites [23] and radiant exposure by LCUs [24]. However, in deep cavities where the amount of remaining dentin is low, these temperature increases can start coagulation and irreversibly damage the pulp. The amount of heat coming from the LCUs is determined by a number of factors including the light intensity, type of tip, and diameter of the tip [20].

In restorative dentistry, the utilization of LCUs using a high-energy output LED (LED-LCUs) has increased in recent years due to their shorter curing times and increased polymerization. Although the thickness of the composite and the remaining dental hard tissue provide some protection [25], the light source in polymerization processes is still considered the main risk to pulpal health [26].

Regardless of the expected output, different brands of LED-LCUs do not produce the same amount of heat. The light in the spectral distribution and the type and diameter of the LED-LCU tip used can affect heat generation [20]. The two contemporary LCUs used in this study are commercially available and widely used, but they emit light of different quantities and qualities. Valo Cordless® has three available power modes: standard, high, and extra power (1.000, 1.400, and 3.200 mW/cm^2, respectively).

These modes cure continuously for 20 seconds, 4 seconds, and 3 seconds, respectively. It has a 9.75 mm lens diameter and utilizable wavelength range of 385-515 nm. Elipar™ DeepCure-S has a single 1.470 mW/cm^2 power mode and pre-set cure times of 5, 10, 15, and 20 seconds, continuous mode (120 seconds), and tack cure mode. The lens diameter of this device is 8.78 mm, and it has a 430-480 nm wavelength range. Despite the differences in wavelength and tip diameters, the main reason for the measured average temperature difference seems to be that the devices emit different powers of light. Elipar™ Deepcure-S generates approximately 1.5 times more power than the Valo Cordless®, resulting in greater heat generation. One of the most important advantages of LED over QTH devices is that they are more energy efficient, producing more light and less heat [27]. With higher energy outputs (irradiance), there is a risk of increased temperature even with LED technology [28].

In this study, composite groups cured with the Elipar™ DeepCure-S had a significantly higher mean temperature rise compared to the empty cavity group, while no difference was observed in the Valo Cordless® groups. This may be related to the thermal insulation values of composite resins. Low thermal-conductive materials transfer less heat between materials compared to high thermal conductive materials.

Filtek™ Bulk Fill Posterior Restorative contains bisGMA, UDMA, bisEMA, and procrylat resins as its major composition. Filtek TM Z250 Universal Restorative contains bisGMA, TEGDMA, UDMA, and Bis-EMA [29]. In both Filtek™ Bulk Fill Flowable and Filtek TM Z250 Universal Restorative the major filler component is zirconia/silica filler with a particle size range of 0.01 to 3.5 μm [30]. Additionally, in Filtek™ Bulk Fill Flowable, zirconia/silica fillers are combined with ytterbium trifluoride (YbF3) filler with a range of particle sizes from 0.1 to 5.0 μm. The inorganic filler loading is about 42.5% by volume and 64.5% by weight in Filtek™ Bulk Fill Flowable and slightly lower for Filtek TM Z250 at 60% volume and 82% weight [29, 30]. Composite resins that contain quartz or silica exhibit more thermal diffusivity, whereas radiopaque fillers such as strontium and barium provide lower thermal diffusivity [31, 32]. The silicate particles or zirconia-silica clusters in the composition of the composites have the potential to transfer more heat during polymerization [31]. In this study, although the composite resin groups exhibit higher temperature values compared with empty cavity groups, the values were not significantly different to the groups cured with the Valo Cordless®. Conversely, with the Elipar™ DeepCure-S device, although bulk-fill composite has a lower zirconia-silica content than Z250 composite, which provides increased temperature diffusion and contains YbF3 to increase radiopacity, which provides low temperature diffusion, it gave similar temperature values to Z250. One of the potential reasons for this outcome may be the cavity dimensions and thickness of RBC used in this study.

A depth of 2.5 mm is suitable for Filtek™ Bulk Fill Flowable and its recommended maximum depth per increment is 4 mm. Regarding Filtek™ Z250 Universal Restorative, the recommended maximum depth is 2.5 mm in A2 shade. While the cavity design is optimal for bulk-fill composite, it is borderline for the Z250. As the thickness of the composite increases, the irradiation measured at the composite base decreases due to the decrease in light transmission [23, 33]. The conversion of carbon-carbon double bonds in monomers to carbon-carbon single bonds during the polymerization of the composite resin is an exothermic reaction. The degree of conversion is positively correlated with light intensity [34]. Thus, the decreased radiant heat and exothermic reaction, especially for the Z250 restorative due to the decreased light intensity, may have resulted in similar temperature increases for both composites at the bottom cavity surface. The deep cavity design and thick RBCs layer may have affected the polymerization reaction of Z250 and caused no significant difference in temperature because of the exothermic reaction, despite the lower zirconia-silica content of the bulk-fill composite. In a study by Shortall and Harrington [35], it was shown that the heat generated when light is applied to an empty cavity is greater than in the light curing of a 2 mm thick composite resin layer. This result is due to more heat being transferred during the polymerization of the adhesive layer compared to the composite resin. Guiraldo et al. [25] found that as the thickness of the light-cured composite resin increased, the temperature decreased significantly. This

is due to the fact that the composite both absorbs some of the light and generates heat during polymerization, and reflects some of the light back. The decrease in the intensity of the light limits the temperature increase due to irradiation. The power of the light devices used in our study is higher than those used in the studies mentioned, and it seems that as the light power increases, the extenuating capacity of the material loses its importance. This result is consistent with the study by Mouhat et al. [20] which showed that there is a risk of pulpal damage if the irradiance exceeds 1.200 mW/cm^2 in the thin dentin layer.

In this study, the curing of the empty cavity does not fully simulate the polymerization of the adhesive layer. However, the fact that the critical temperature is exceeded when Elipar™ DeepCure-S is used in the empty cavity and the critical temperature is formed approximately half a degree below the critical temperature when Valo Cordless® is used, reveals the importance of using cement as a barrier for adhesive restorative procedures using high-power LED-LCUs in deep primary tooth cavities.

In this study, after the resin is placed on the primary molar tooth for composite resin groups, a small indentation was created by inserting the probe tip into the corner of the composite, which was then light cured. After the temperature measurement was taken, the probe tip was placed in the preformed recess and removed from the cavity, and the next composite material was tested by placing it with the same method. After testing the empty cavity, the primary tooth was removed from the model, a new primary tooth was adapted, and all procedures were repeated. The anatomical and physiological structures of the teeth are different from each other; the thickness of the hard tissue and diameters and numbers of the dentinal tubules are variable. Some in vitro studies examining the effect of dental procedures on pulpal temperature increase aimed to provide standardization by performing the whole experiment on a single tooth [36-39]. Since applications performed on a single tooth may produce results affected by the specific anatomical and ultrastructural features of that tooth, we used ten primary molars by changing the tooth used in each test circulation. Thus, the validity and reliability of the experiment increased and standardization was achieved.

In this study, the mean temperature rises in the pulp chamber ranged between 5.81 and 7.6˚C for the Elipar™ DeepCure-S groups and 5.02 and 5.44˚C for the Valo Cordless® groups. While the Elipar™ DeepCure-S groups were above the critical temperature of 5.6˚C, Valo Cordless® groups were slightly below this temperature. The groups that used the Elipar™ DeepCure-S in high power mode were above the critical temperature of 5.6˚C, whereas the Valo Cordless® groups were close to but below this temperature. This indicates that there is a correlation between the increased power of LED-LCUs and pulpal damage in restorative procedures applied to primary teeth, and that 1.000 mW/cm^2 in the thin dentin layer may be a critical power threshold for pulpal tissue health. In addition, the absence of a significant difference in temperature increase between microhybrid and bulk-fill RBC polymerization used in the study shows that bulk-fill RBCs can be used within safety limits in primary teeth with the use of appropriate LCUs.

Within the limitations of the study, it was found that the high output power of LED-LCUs in deep primary tooth cavities may pose a threat to pulpal health. There was no difference in measured temperature between bulk-fill and microhybrid RBCs.

Conflicts of interest: No conflict of interest was declared by the authors.

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Authors' contributions to the article

Y.E. and I.F.E. have constructed the main idea and hypothesis of the study. Y.E. and I.F.E. developed the theory and arranged the material and method section. Y.E. and I.F.E. have done the evaluation of the data in the Results section. Discussion section of the article written by Y.E. and I.F.E. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

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Histopathologic features of inflammatory fibroid polyps and risk of cancer development: a case series

İnflamatuar fibroid poliplerin histopatolojik özellikleri ve kanser gelişme riski: bir vaka serisi

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Abstract

Purpose: Inflammatory fibroid polyp (IFP) is seen in the gastrointestinal tract. In most cases, somatic mutations in PDGFRA gene were observed and the true neoplastic origin of this entity was understood. It is a benign mesenchymal tumor and rarely recurs. The aim of the study was to reveal the histopathologic features of our IFP cases and to investigate the risk of cancer in one case.

Materials and methods: We performed a retrospective clinicopathological analysis of patients (n=12) who were reported as IFP between 2012 and 2022. Formalin-fixed, paraffin-embedded and hematoxylin-eosin (H&E)-stained slides of the cases were re-examined by two pathologists microscopically.

Results: All patients were adults and ranged in age from 30 to 85. Male to female ratio was 1:2. One polyp was localized in small intestine, one in colon, and the others in stomach. Histologically, there were hyperplastic epithelial changes (7/12), low-grade (3/12), and high-grade dysplasia (1/12) accompanying IFPs. One case was associated with early gastric adenocarcinoma.

Discussion: Although IFP appears as a benign mesenchymal tumor, it should be kept in mind that dysplasia and rarely carcinoma may accompany this lesion. Larger case series are needed to elucidate the mechanisms of dysplasia and carcinoma development associated with IFP.

Key words: Inflammatory fibroid polyp, gastrointestinal, dysplasia, carcinoma, histopathology.

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Öz

Amaç: İnflamatuar fibroid polip (IFP) gastrointestinal sistemde görülür. Çoğu vakada PDGFRA geninde somatik mutasyonlar gözlenmiş ve bu antitenin gerçek neoplastik kökeni anlaşılmıştır. Benign mezenkimal bir tümördür ve nadiren tekrarlar. Çalışmanın amacı, IFP olgularımızın histopatolojik özelliklerini ortaya koymak ve kanser riskini araştırmaktır.

Gereç ve yöntem: 2012-2022 yılları arasında IFP olarak bildirilen hastaların (n=12) retrospektif klinikopatolojik analizini gerçekleştirdik. Olguların formaline fikse, parafine gömülü ve hematoksilen-eozin (H&E) boyalı preparatları iki patolog tarafından mikroskobik olarak yeniden incelendi.

Bulgular: Tüm hastalar yetişkin olup yaşları 30 ile 85 arasında değişmekteydi. Erkek/kadın oranı 1:2 idi. Bir polip ince bağırsakta, biri kolonda ve diğerleri midede lokalizeydi. Histolojik olarak, IFP'lere eşlik eden hiperplastik epitelyal değişiklikler (7/12), düşük dereceli (3/12) ve yüksek dereceli displazi (1/12) görüldü. Bir vakada ise erken gastrik adenokarsinom gelişmişti.

Sonuç: IFP benign bir mezenkimal tümör gibi görünsede, bu lezyona displazi ve nadiren karsinomun eşlik edebileceği akılda tutulmalıdır. IFP ile ilişkili displazi ve karsinom gelişim mekanizmalarını aydınlatmak için daha geniş vaka serilerine ihtiyaç vardır.

Anahtar kelimeler: İnflamatuar fibroid polip, gastrointestinal, displazi, karsinom, histopatoloji.

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Introduction

Inflammatory fibroid polyp (IFP) is a benign mesenchymal tumor that is frequently seen in the gastrointestinal tract (especially in the stomach) and was first described by Vanek in 1949 [1, 2]. IFP was first named 'submucosal granuloma with eosinophilic infiltration' due to its histopathological features [2]. Although IFPs are most commonly observed in the stomach and small intestine, they can also be seen in the distal esophagus, appendix, colon and rarely in the gallbladder [3-5]. There is no clear gender predilection and patients are usually in the 6th and 7th decades [6, 7]. They are often detected as polypoid lesions during endoscopic examination or sometimes on computed tomography (CT) scans of the gastrointestinal tract. On gross examination, they are observed as sessile polyps up to 5 cm in size, sometimes with ulceration on the surface [8, 9]. Histopathology shows spindle and stellate cells (characteristic onion-skin appearance around vascular structures) located in the submucosa and sometimes in the lamina propria, and inflammatory cells rich in eosinophils [10]. Spindle cells do not show distinct pleomorphism or mitotic figures. Immunohistochemically, cells are positive with CD34 and PDGFRA, whereas CD117, DOG1 and S100 are negative [11].

Somatic mutations of the PDGFRA gene have been identified in 55-74% of gastric and intestinal IFPs and affect specifically exons 12, 14 and 18, as in some gastrointestinal stromal tumors (GIST), so IFP should be considered a true benign mesenchymal tumor of the gastrointestinal tract [12, 13]. It is not clear from which cell IFP originates, but in one study, it has been claimed that IFPs and GISTs with PDGFRA mutations originate from an interstitial cell called 'telocyte' [13].

IFPs rarely recur, and its treatment is often performed by endoscopic/surgical excision of the lesion. However, a family with multiple and recurrent IFPs has been described in the literature [14]. Although IFP is generally a benign submucosal neoplasm, some locally aggressive cases with invasion into the muscularis propria and subserosa have been described [15]. To our knowledge, IFP associated with carcinoma described in the literature are a total of 11 cases [7, 16-19].

We present our series of 12 IFP cases (1 localized to small intestine, 1 to colon and the remainder to stomach), including one case associated with early gastric carcinoma.

Materials and methods

We performed a retrospective clinicopathological analysis of patients (n=12) who were reported as IFP between 2012 and 2022 in our department. Clinical information of the patients (age, sex, endoscopy, surgical procedure, polyp localization, polyp size, etc.) were collected from computerized medical records of the hospital. Follow-up information was obtained by checking routine hospital visits of the patients or by contacting them by phone.

Formalin-fixed, paraffin-embedded and hematoxylin-eosin (H&E) or immunohistochemically - stained slides of 12 cases were re-examined by two pathologists microscopically. On microscopic examination, mucosal ulceration, lesion depth, presence of perivascular onion-skin appearance, lymphoid aggregates, eosinophils, vascular changes, gastric biopsy findings (Helicobacter pylori status, intestinal metaplasia, atrophy), architectural changes in the surface epithelium, the presence of dysplasia and intramucosal carcinoma were evaluated. Perivascular onion-skin appearance, submucosal lymphoid aggregates and eosinophils were classified as +, ++ or +++ according to their frequency in each case. Histopathologic classification of IFPs was made based on the study of Kim and Kim [10].

This study was performed in accordance with regulations issued by the Helsinki Declaration; the protocol was approved by the Local Ethical Committee at board meeting No. 06 on April 5, 2022.

Results

All patients were adults and ranged in age from 30 to 85 (median age 64.2 years). Male to female ratio was 1:2, with female predominance. Polyp size ranged from 4 to 62 mm (median size 21 mm). One polyp was localized in the small intestine, one in the colon, and the others in the stomach. Follow-up times of the cases ranged from 4 to 111 months (with median time 43.5 months). Two of the patients died for unknown reasons. Recurrence was observed in only one

of the cases after 4 years and the patient is still alive (This was our only case with intramucosal carcinoma and its recurrence was reported as 'IFP showing low-grade dysplasia in the surface epithelium').

Microscopic examination revealed a mesenchymal lesion consisting mostly of submucosal spindle/stellate cells and variable proportion of eosinophils in fibromyxoid stroma. The characteristic perivascular onion-skin appearance appeared more or less in the majority of cases. Considering the histopathologic classification of Kim and Kim [10], our cases were divided into fibrovascular and sclerotic groups (Figure 1A-D). Increased mitotic activity or necrosis was not observed. Immunohistochemically, the cells forming the lesion were positive for CD34 and negative for CD117, DOG-1, S100 and Desmin. Hyperplastic changes in the surface epithelium, low-grade dysplasia and increased Ki67 proliferation index in the dysplasia area are shown in Figure 2A-D; IFP-associated intramucosal carcinoma and increased p53 expression in the carcinoma focus are shown in Figure 3A-C.

Important clinical and histopathological features of the cases were summarized (Table 1).

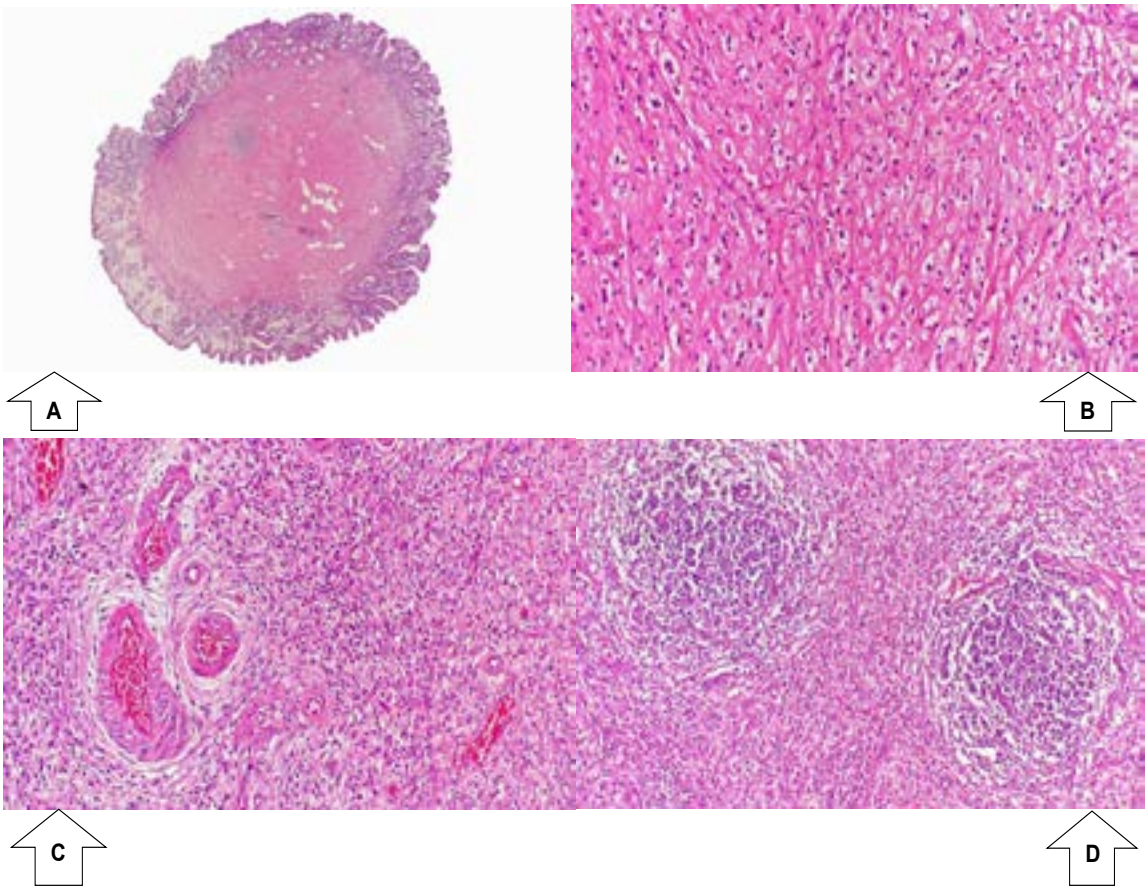

Figure 1A-D. In the sclerotic stage, thick collagen bundles and hyalinization are observed, while the number of inflammatory cells is slightly less, H&E, x20 magnification (1A) and x200 magnification (1B). In the fibrovascular stage, fibroblasts with onion-skin appearance around the vessels (1C), numerous inflammatory cells and numerous submucosal lymphoid aggregates (1D) are observed, H&E, x200 magnification

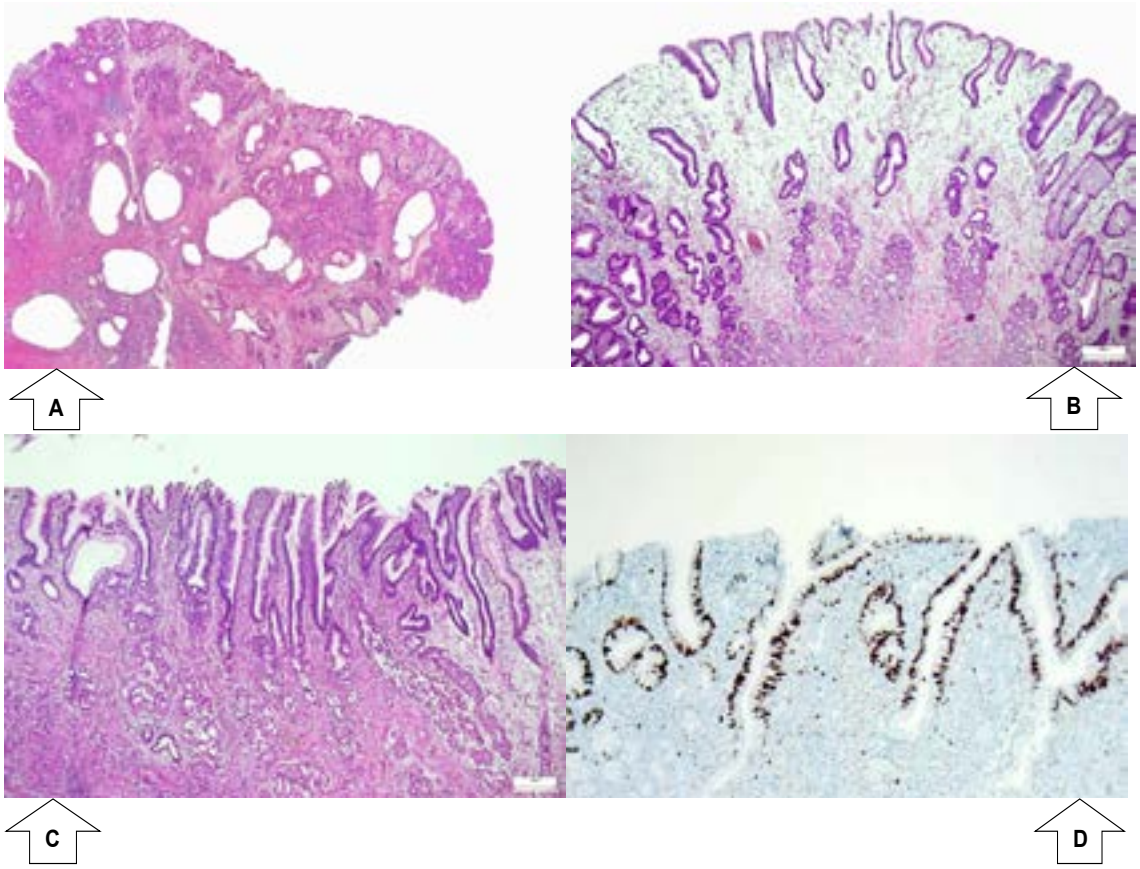

Figure 2A-D. Cystic dilatation of the foveolar epithelium and gastric cystic polyposa-like morphology covering inflammatory fibroid polyp, H&E, x20 magnification (2A). Corkscrew-like appearance of the foveolar epithelium covering the inflammatory fibroid polyp, H&E, x40 magnification (2B). Low grade dysplasia of the surface epithelium in a case of gastric inflammatory fibroid polyp, H&E, x100 magnification (2C). Increased Ki-67 proliferation index in low-grade dysplasia focus, immunohistochemistry, x100 magnification (2D)

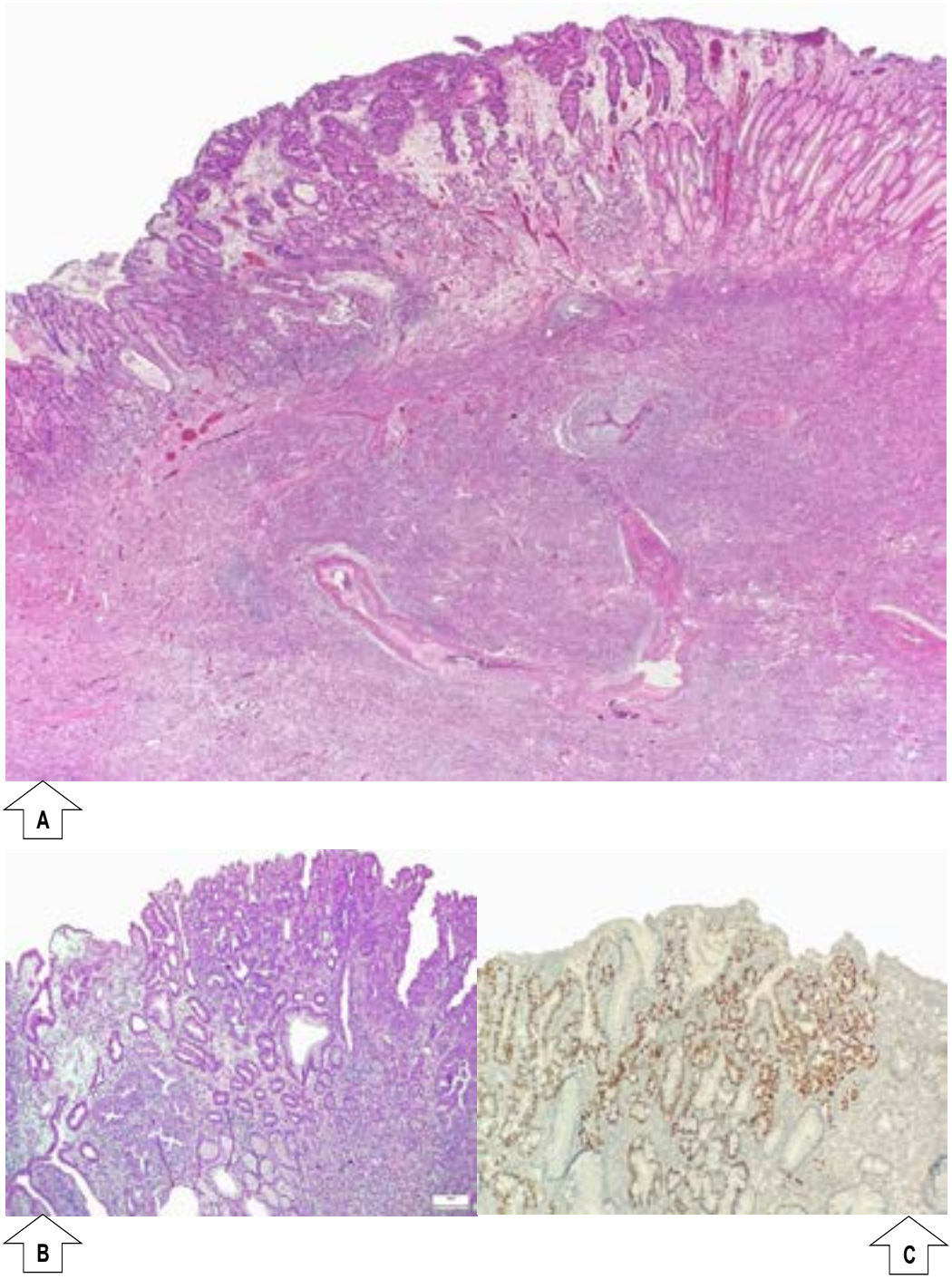

Figure 3A-C. Intramucosal adenocarcinoma on the background of inflammatory fibroid polyp (case no: 5), H&E, x20 magnification (3A). Atypical glands showing crowding, fusion, budding and invasion of the lamina propria (case no: 5), H&E, x100 magnification (3B). Intramucosal adenocarcinoma focus showing nuclear p53 (+) (case no: 5), immunohistochemistry, x100 magnification (3C)

Table 1. Clinical and histopathological findings of 12 gastrointestinal inflammatory fibroid polyps

	Clinical findings							
No.	**Age**	**Sex**	**Diameter (mm)**	**Localization**	**Surgical method**	**Colonoscopy**	**Follow-up (months)**	**Recurrens**
1	68	F	30	Stomach (Antrum)	Partial gastrectomy	N/A	55	-
2	58	M	62	Stomach (Antrum)	Partial gastrectomy	N/A	48	-
3	85	M	20	Stomach (Antrum)	Polypectomy	N/A	57	-
4	46	F	30	Stomach (N/A)	Polypectomy	N/A	111	-
5	67	F	35	Stomach (Antrum)	Polypectomy	N/A	39	+
6	62	M	9	Stomach (Antrum)	Polypectomy	Normal	28, Ex	-
7	72	M	12	Stomach (Antrum)	Polypectomy	Normal	27	-
8	68	F	18	Stomach (Corpus)	Polypectomy	Normal	8	-
9	64	F	22	Stomach (Antrum)	Polypectomy	N/A	4	-
10	69	F	10	Stomach (Corpus)	Polypectomy	N/A	3	-
11	30	F	4	Small intestine	Partial resection	Normal	97	-
12	81	F	30	Colon	Polypectomy	Polyp (IFP)	51, Ex	-

Table 1. Clinical and histopathological findings of 12 gastrointestinal inflammatory fibroid polyps (continued)

	Histopathological findings											
No.	**Depth**	**Mucosal ulceration**	**Changes in surface epithelium**	**Presence of hyperplastic polyp in the stomach**	**Gastric biopsy findings**	**Dysplasia**	**Intramucosal carcinoma**	**Perivascular onion-skin**	**Submucosal lymphoid aggregates**	**Histopathological pattern**	**Eosinophils**	**Vascular changes**
1	SM	-	-	-	Normal	-	-	++	+++	Fibrovascular	+++	Normal
2	SM + Mu	Focal	Cystic dilatation, corkscrew-like apperance	-	HP	Low grade	-	++	++	Fibrovascular	+++	Intimal thickening
3	SM + Mu	-	-	-	N/A	-	-	++	+	Fibrovascular	+++	Normal
4	SM + Mu	+	Cystic dilatation, corkscrew-like apperance	-	N/A	-	-	+	-	Sclerotic	++	Normal
5	SM + lower 1/2 Mu	-	Cystic dilatation, corkscrew-like apperance	+	CA, IM	Low and high grade	3 mm diameter focus	+	++	Mixed (fibrovascular and sclerotic)	+++	Intimal thickening
6	SM	-	-	+	Normal	-	-	+	++	Fibrovascular	+++	N/A
7	SM + lower 1/2 Mu	-	Mild hyperplastic changes	+	Normal	-	-	+	++	Fibrovascular	+++	Normal
8	SM + Mu	Focal	Mild hyperplastic changes	-	N/A	Low grade	-	+	+	Sclerotic	-	Normal
9	SM + lower 1/2 Mu	-	Cystic dilatation, corkscrew-like apperance	-	CA, IM	-	-	+++	++	Fibrovascular	+++	Intimal thickening
10	SM	-	-	-	N/A	-	-	+	+	Fibrovascular	++	Normal
11	SM, MP	-	-	-	N/A	-	-	-	-	Sclerotic	+	Intimal thickening
12	SM + Mu	Focal	Mild hyperplastic changes	-	N/A	-	-	+	-	Sclerotic	++	Normal

Discussion

In terms of patient age, our study was consistent with the literature (median age 64.2 years) [7]. Although some studies have reported that IFP is more commonly seen in males [7], our study showed female predominance (M:F=1:2). There are various hypotheses that IFP develops with an allergic or infectious etiology [20]. It was reported that IFP showed some morphological changes after eradication of Helicobacter pylori [21]. Helicobacter Pylori was present in only one of our ten gastric IFP cases. Considering that IFP can be seen throughout the entire gastrointestinal tract in addition to the stomach, the role of Helicobacter pylori in the etiology is controversial.

PDGFRA-mutant syndrome is by definition at least two IFPs and/or GISTs in an individual or a family [22]. Three families with multiple IFPs without mutation data were identified previously in the literature [14, 23]. Although we do not have molecular data, there were multiple IFPs with recurrence in one of our cases. We could not reach the family data of this case.

Two cases of IFP with local aggressive behavior and extension to the muscularis propria were reported [15, 24]. However, except for these two cases, gastric IFPs showing extension to muscularis propria and subserosa were previously described in the literature [10]. In our study, 11 out of 12 IFPs were located in mucosa and/or submucosa; only small intestinal IFP showed invasion of muscularis propria.

In 1988, Kim and Kim [10] classified gastrointestinal IFPs into 4 groups (nodular, fibrovascular, sclerotic and edematous) based on histology and size. According to this study investigating the evolutionary change of IFP, the mean lesion size of the sclerotic or edematous group was higher compared to the other groups. Our cases were histologically classified into two groups as fibrovascular and sclerotic, while 1 case showed mixed (fibrovascular and sclerotic) features. Our study differed from that of Kim and Kim [10] because we did not have any cases in the nodular or edematous stage and the mean lesion size of the fibrovascular group was higher than that of the sclerotic group (25.8 and 20.5 mm, respectively).

Hirasaki et al. [25] reported that gastric cystica polyposa morphology accompanying gastric IFP was observed in the superficial mucosa in one case. In a study by Mori et al. [16], gastric adenoma was reported to accompany 2 gastric IFP cases. We also focused on surface epithelial changes accompanying our IFPs. Histologically, there were hyperplastic epithelial changes (7/12), low-grade dysplasia (3/12), and high-grade dysplasia (1/12) accompanying IFPs. Although we do not have enough data at the moment, it may be possible to explain this association with different mechanisms: 1) Dysplasia may develop due to changes in the surface epithelium secondary to IFP. 2) Both entities may develop independently and coincidentally accompany each other. 3) A common trigger for both entities, such as Helicobacter pylori or chronic atrophic gastritis, can lead to their simultaneous occurrence.

Mori et al. [16] analyzed 50 gastric IFP cases and reported early gastric adenocarcinoma accompanying IFP in 4 cases, localized in the antrum and showing mucosal or both mucosal and submucosal involvement. In another study, Mori et al. [17] reported early gastric adenocarcinoma accompanying 2 non-polypoid IFP cases with down-growth pattern. We do not know the follow-up period of these patients, as we can only access the summary of both studies. Mucientes et al. [7] published a case of gastric IFP with early gastric adenocarcinoma in 2012. There was a 1 cm polypoid lesion located in the distal antrum and histomorphological examination revealed intestinal type carcinoma invading the mucosa and superficial submucosa. There was no recurrence or metastasis in the patient with a 108-month follow-up period. In our study, there was only 1 case of early gastric adenocarcinoma associated with IFP. Histopathologic examination of this 35 mm polyp in the antrum revealed a 3 mm diameter carcinoma focus confined to the mucosa. After a 39-month follow-up period, the patient showed recurrent IFP in the antrum. This recurrent polyp was 10 mm in diameter and accompanied by diffuse low-grade dysplasia of the surface epithelium, but no invasive carcinoma was observed. The patient had no distant metastasis.

There were a total of 11 cases of adenocarcinoma accompanying IFP in the literature to date. While 4 of these cases were reported as isolated case reports, the rate of adenocarcinoma accompanying IFP was found to be 8% (4/50) in the study by Mori et al. [16] and 7% (3/42) by Kolodziejczyk et al. [19]. In our study, cancer was associated with only one of our 12 IFP cases. Since our case with the second largest lesion size (35 mm) was associated with carcinoma, we hypothesize that the likelihood of cancer in IFP may increase with increasing lesion size. In addition, in our patient with the largest lesion size (62 mm), although no cancer was observed, low-grade dysplasia in the surface epithelium attracted our attention. However, we could not find information about the lesion sizes of cancerous cases in the largest case series in the literature including gastric cancer cases accompanying IFP [16, 19].

In conclusion, although gastrointestinal IFP appears as a benign mesenchymal tumor, it should be kept in mind that dysplasia and rarely carcinoma may accompany this lesion. Larger case series are needed to elucidate the mechanisms of dysplasia and carcinoma development associated with IFP.

Conflict of interest: No conflict of interest was declared by the authors.

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Authors' contributions to the article

E.C. and N.C.D. constructed the main idea and hypothesis of the study. Y.A.K. developed the theory and arranged/edited the material and method section. M.C. has done the evaluation of the data in the Results section. Discussion section of the article written by E.C. and N.C.D. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

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Investigation of the protective effect of rosmarinic acid in rats given high dose gentamicin

Yüksek doz gentamisin verilen sıçanlarda rosmarinik asidin koruyucu etkisinin araştırılması

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Abstract

Purpose: Gentamicin is an antibiotic, used to treat infections caused by microorganisms. Endogenous antioxidants are strengthened by using antioxidant protectors against the toxic effects caused by drugs. Rosmarinic acid has antioxidative, anti-inflammatory, antiapoptotic, and antitumoral effects. In our study, we aimed to investigate the protective effect, immunohistochemical changes, oxidative markers, histopathological changes and inflammation related Ifi44 expression of rosmarinic acid against gentamicin induced nephrotoxicity in rats.

Materials and methods: In our study, 32 rats randomly divided into four groups. These groups are consisted of control group, gentamicin group received gentamicin 100 mg/kg/day, gentamicin + rosmarinic group acid received gentamicin 100 mg/kg/day and rosmarinic acid 50 mg/kg/day, and rosmarinic acid group received rosmarinic acid 50 mg/kg/day. At the end of the study, histopathological, immunohistochemical, and biochemical changes in kidney tissues evaluated.

Results: Rosmarinic acid reduced creatine, urea, blood urea nitrogen, and total oxidative stress in blood serum. The toxic effect of gentamicin caused severe histopathological changes in the kidneys. A slight decrease in histopathological changes observed in the gentamicin + rosmarinic acid group. Antiproliferative Ifi44 expression was higher in the gentamicin group and gentamicin + rosmarinic acid group.

Conclusion: As a result of the application of rosmarinic acid, a decrease in oxygen radicals and an increase in antioxidant levels observed. When used in combination with gentamicin and rosmarinic acid, the protective effect of rosmarinic acid was partially observed, but it could not provide full protection.

Key words: Gentamicin, rosmarinic acid, Ifi44, rat.

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Öz

Amaç: Gentamisin, mikroorganizmaların neden olduğu enfeksiyonları tedavi etmek için kullanılan bir antibiyotiktir. İlaçların neden olduğu toksik etkilere karşı antioksidan koruyucular kullanılarak endojen antioksidanlar güçlendirilir. Rosmarinik asit antioksidan, antienflamatuar, antiapoptotik ve antitümör etkilere sahiptir. Çalışmamızda rosmarinik asidin sıçanlarda gentamisin ile indüklenen nefrotoksisiteye karşı koruyucu etkisini, immünohistokimyasal değişiklikleri, oksidatif belirteçleri, histopatolojik değişiklikleri ve enflamasyona bağlı Ifi44 ekspresyonunu araştırmayı amaçladık.

Gereç ve yöntem: Çalışmamızda 32 rat rastgele 4 gruba ayrıldı. Bu gruplar kontrol grubu, gentamisin grubu 100 mg/kg/gün gentamisin verildi, gentamisin + rosmarinik asit grubu gentamisin 100 mg/kg/gün ve rosmarinik asit 50 mg/kg/gün verildi, rosmarinik asit grubu rosmarinik asit 50 mg/kg/gün verildi. Çalışma sonunda böbrek dokularındaki histopatolojik, immünohistokimyasal ve biyokimyasal değişiklikler değerlendirildi.

Bulgular: Rosmarinik asit, kan serumunda kreatin, üre, kan üre nitrojeni ve toplam oksidatif stresi azaltmıştır. Gentamisinin toksik etkisi böbreklerde ciddi histopatolojik değişikliklere neden olmuştur. Gentamisin + rosmarinik asit grubunda histopatolojik değişikliklerde hafif bir azalma gözlendi. Antiproliferatif Ifi44 ekspresyonu gentamisin grubunda ve gentamisin + rosmarinik asit grubunda daha yüksekti.

Sonuç: Rosmarinik asit uygulaması sonucunda oksijen radikallerinde azalma ve antioksidan düzeylerinde artış gözlendi. Gentamisin ve rosmarinik asit birlikte kullanıldığında rosmarinik asidin koruyucu etkisi kısmen gözlenmiştir ancak tam koruma sağlayamamıştır.

Anahtar kelimeler: Gentamisin, rosmarinik asit, Ifi44, sıçan.

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Introduction

Gentamicin (GM) is widely used to treat infections caused by gram-negative and gram-positive microorganisms and is an aminoglycoside antibiotic. Clinicians stated that using this drug potentially causes nephrotoxicity and histopathological lesions are seen in 30% of patients. 90% of the GM used for therapeutic purposes retains its structure without being metabolized by the liver and is excreted by the renal tubules and especially the proximal convoluted tubules. [1, 2]. While extensive necrosis was observed with GM, significant apoptosis was observed in epithelial cells of rats in which a clinical dose was given, and proximal convoluted tubules were seen without necrosis [3].

Although the mechanism of GM-induced nephrotoxicity cannot be fully explained, it is suggested that it is caused by oxidative stress, inflammation, increased monocyte and macrophage infiltration, and apoptosis [4-7]. It is stated that reactive oxygen species can be balanced by strengthening endogenous antioxidants by using natural antioxidant preservatives against the toxic effects caused by drugs [8]. Rosmarinic acid (RA) is one of the most important and well-known polyphenolic antioxidants, abundant in various medicinal plants of the Lamiaceae family and historically used in traditional Chinese medicine. In various studies, it has been reported that rosmarinic acid has antioxidative, anti-inflammatory, antibacterial (both gram-positive and gram-negative bacteria), antiviral, antiapoptotic, antihyperglycemic, antitumoral (against various types of carcinoma, colorectal, pancreas, breast, lung, ovary, melanoma, etc.), analgesic, cardioprotective, neuroprotective and hepatoprotective effects [9-17].

Interferons (IFN) involved in inflammation are important cytokines. [18]. Microtubule-associated protein 44 (Ifi44) has been reported to be antiproliferative. Ifi44, also called interferon-α inducible protein 44 or p44 because it assembles to form microtubular structures, is a member of the Type I IFN-α inducible gene family. The functions of ifi44 include participation in microtubule formation, promotion of apoptosis, inhibition of proliferation, and participation in the autoimmune response. [19, 20]. It has therefore been suggested that Ifi44 may be associated with the inflammation involved in GM-induced nephrotoxicity [21]. In our study, we aimed to investigate the protective effect of RA against GM-induced nephrotoxicity in rats in terms of oxidative markers, histopathological changes, and immunohistochemically the expression of Ifi44, which is claimed to be associated with inflammation.

Materials and methods

In our study 32 wistar albino adult male rat weighing 230-250 gr was used. Rats were hosted in at room temperature (25°C) and in standard lighting (12 hours dark/luminous) cages. Tap water and pellet feed was provided as standard for feeding the animals. The procedures applied to the rats were carried out per the provisions of all national and international laws that are a party to Pamukkale University Animal Experiments Ethics Committee Directive.

Our study was approved by Pamukkale University Animal Experiments Ethics Committee (PAUHADYEK-2018/21) and was carried out with the support of Pamukkale University Scientific Research Projects Coordination Unit (project no: 2019SABE014).

After the rats were randomly divided into 4 groups (8 in each group) injections were made at the same times every day for 12 days. Rosmarinic acid (sigma-Aldrich Chemical Co.St. Louis, MO, USA) and gentamicin sulfate (GOLBIO, Gold Biotechnology; cat. G-400, CAS. 1405-41-0) were injected into rats prepared by mixing with physiological saline every day. Control group (C): Only 0.5 mL saline was injected intraperitoneally. GM group (G): It was dissolved in physiological saline corresponding to the dose of GM sulfate 100 mg/kg and injected intraperitoneally [22]. GM+RA group (GR): It was dissolved in physiological saline corresponding to the dose of GM sulfate 100 mg/kg and RA 50 mg/kg and injected intraperitoneally (RA was administered intraperitoneally one hour before GM sulfate administration) [23]. RA group (R): It was dissolved in physiological saline corresponding to the dose of RA 50 mg/kg and it was injected intraperitoneally [24].

On the 13th day, the body weights of the anesthetized rats were taken and recorded. The thorax was opened and the blood obtained by intracardiac puncture was collected in yellow biochemistry tubes and centrifuged. Urea,

Blood Urea Nitrogen (BUN), creatinine, Total Antioxidant Status (TAS), and Total Oxidant Status (TOS) (Rel Assay Kit Diagnostics, Gaziantep, Turkey) levels were determined from serum. Kidneys were removed, weighed, and fixed in 10% formaldehyde. 5-micron sections were taken from tissue that embedded paraffin. These sections were stained histochemically with hematoxylin and eosin (H+E) and periodic acid schiff (PAS) stains (Histomed BS-0046. Lot.092016.001). Staining was carried out according to the procedure specified in the PAS dye kit. The histopathological findings were evaluated in these sections.

Ifi44 (Invitrogen, PA5-96967, Lot: R93772) expression was evaluated immunohistochemically. Sections were incubated after deparaffinization. After washing in PBS, incubated in serum blocking solution (Thermo Fisher Scientific, TP 125UB, Fremont, USA) at room temperature. Primary antibody (Ifi44) diluted 1:100 was dropped on the sections and left overnight. Slides were treated with secondary antibodies (Thermo Fisher Scientific, TP 125UB, Fremont, USA). The slides were washed with PBS and incubated with HRP-streptavidin working buffer for 10 min. Sections were treated with DAP. Counterstaining was done with hematoxylin.

Sections which dyed both with histochemically and immunohistochemically methods were investigated under the light microscope (Olympus Microscope BX51).

Immunohistochemical evaluation

Photographs were obtained at X400 magnification from immunohistochemically stained sections of kidney tissue of each rat. Immune-reacting cells were counted in 10 different areas using the Image J program. The mean number of immune-reacting cells belonging to the groups was obtained.

Biochemical analysis

Urea, BUN, and creatinine levels were measured by spectrophotometric method immediately after obtaining the serum. The serum was kept at − 70°C until TAS and TOS levels were measured.

The principle of TOS measurement is based on the conversion of the ferrous ion chelator complex of the oxidants in the sample to ferric ion, which reacts with the chromogen in an acidic environment and causes an increase in absorbance. The increase in absorbance observed spectrophotometrically is directly proportional to the oxidant molecules in the sample. TOS was studied from the obtained sera by means of a commercial kit (Rel Assay Diagnostic, Lot.RL0024). The color intensity, which can be measured spectrophotometrically with an ELISA reader, is related to the total amount of oxidant molecules present in the sample. Results are expressed as μmol H_2O_2 Equiv/L. The principle of TAS measurement is based on the fact that all antioxidants in the sample convert the blue-green 2,2'-azino-bis ABTS (3-ethylbenzothiazoline-6-sulfonic acid) radical into colorless reduced ABTS. The change in absorbance of the sample is proportional to its antioxidant level. TAS measurement was made with a commercial kit (Rel Assay Diagnostic, Lot. RL0017) and evaluated spectrophotometrically with an ELISA reader. Results are expressed per μmol Trolox Equiv/L.

Histopathological evaluation

The sections of the groups were coded to avoid prejudices and were evaluated blindly by two researchers. Semi-quantitative assessment of kidney tissue and severity of damage were examined according to previously published criteria [25].

(i) Glomerular damage (% of renal parenchyma involvement): none=0, less than 25% of all renal parenchymal tubules=1, 25-50% of glomeruli exhibit nonspecific damage characteristics=2, that 50-75% of glomeruli exhibit nonspecific damage characteristics=3 and that more than 75% of glomeruli exhibit nonspecific damage characteristics=4; (ii) Acute tubular necrosis (% of renal parenchyma involvement): none=0, less than 25% of all renal parenchymal tubules=1, 25-50% of all renal parenchymal tubules=2, 50-75% of all renal parenchymal tubules=3 and more than 75% of all renal parenchymal tubules=4; (iii) Tubulointerstitial inflammatory infiltrates: none=0, limited leukocytes within the interstitium=1, and leukocyte infiltrating interstitium and tubules epithelial cell=2, the scoring system used was done according to the following measurement: (A) none nephrotoxicity:

0-1, (B) mild nephrotoxicity: 2-4, (C) moderate nephrotoxicity: 5-7, (D) severe nephrotoxicity: 8-10 [25].

Basal membrane thickness was evaluated semiquantitatively in the sections where PAS staining was performed by two researchers.

Statistical analysis

Data was analyzed with SPSS package program. Continuous variables average+/- standard deviation and categorical variables were given as numbers and percentages when parametric test assumptions were provided. One-way Analysis of Varyans (post-Hoc Turkey test) in comparison of independent group differences; when parametric test assumptions were not provided has been done. Kruskal Wallis Varyans Analysis (post Hoc Bonferroni should correct Mann Whitney U test) used the comparison to independent group differences. Chi-square always was used in comparison to categorical variables. *P*<0.05 was considered statistically significant.

Results

The mean body weights of the G and GR groups treated with GM were significantly reduced. A slight increase was observed in the mean kidney weights of the same groups (Table 1). When the mean body weights of the G and GR groups were compared with the C group, there was a statistically significant decrease. When the mean weights of the kidneys were evaluated, the weight of the left kidney was higher in the G group. The mean left kidney weight of the G group was statistically significantly increased when compared to the R group (Table 1).

Table 1. Mean body and kidney weights of rats in different study groups

Groups	Group C	Group R	Group GR	Group G
Body weight (gr)	228.08±22.04	225.02±42.70	177.17±9.69 ^{k}p	175.07±12.87 ^{k}p
Right kidney weight (gr)	0.88±0.12	0.93±0.20	1.02±0.11	1.08±0.06
Left kidney weight (gr)	0.88±0.15	0.88±0.17	1.05±0.18	1.09±0.05 ^{ʁ}p

^{k}p (p<0.05); statistically significant with group C, ^{ʁ}p (p<0.05); statistically significant with group R

Mild tubulointerstitial inflammation was observed in the renal cortex of two rats in the C group. Histological changes were not observed in the kidney tissue of the remaining six C group rats (Figure 1).

In all of the rats which administered GM; glomerular damage, tubular necrosis, and moderate nephrotoxicity as a result of tubulointerstitial inflammation scoring were determined. In five rats in the GR group that applied RA together with GM, the nephrotoxicity level was mild. Moderate nephrotoxicity was observed in the remaining three rats.

Two of the R-group rats had mild tubulointerstitial inflammation. No histological changes were noted in the kidneys of the remaining rats belonging to group R (Figure 1) (Table 2).

When the kidney damage of the G group was compared statistically with both C and R groups, it was highly significant (p<0.001). The kidney damage of the GR group was also statistically significant when compared with the C group and R group (p<0.001). There was no statistical difference between the G and GR groups in terms of kidney damage (p=0.070). When the kidney damage of group C and group R was compared, it was not statistically significant (p=0.928).

In the histological sections of the G and GR groups, there were loss, flattening, necrosis, and vacuolization in the epithelial cells of the tubules. Shrinkage of the glomerular structure of the Malpighi corpuscle, dilatation of the capsular cavity, and extensive tubulointerstitial inflammation areas were observed (Figure 1).

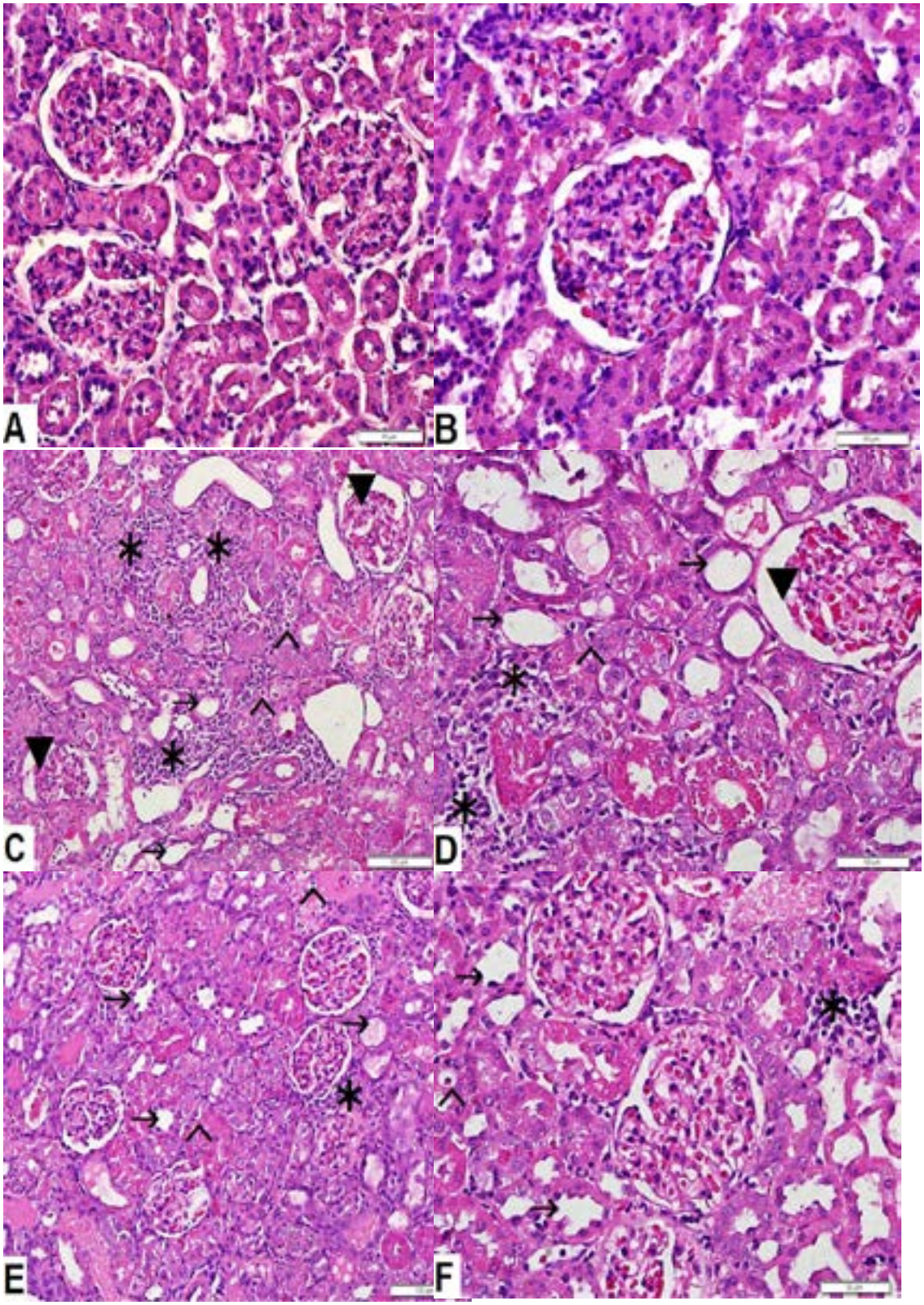

Figure 1. Microphotographs of the renal cortex of group C (A) and group R (B) (H&E X40). In rat kidney cortex treated with gentamicin (group G) (C X20, D X40) and gentamicin+rosmarinic acid (group GR) (E X20, F X40) intense areas of inflammation (*), vacuolized cells (^), dilated tubule and epithelial loss (→), glomerular damage and dilated Bowman's capsule (▲) (H&E)

Table 2. Histological changes in kidneys of rats in all groups

Rat no	Glomerular damage	Tubular necrosis	Tubulointerstitial inflammation	Total score	Scoring scale
C1	0	0	0	0	A
C2	0	0	0	0	A
C3	0	0	0	0	A
C4	0	0	0	0	A
C5	0	0	1	1	A
C6	0	0	0	0	A
C7	0	0	0	0	A
C8	0	0	1	0	A
G1	2	2	1	5	C
G2	2	2	1	5	C
G3	2	2	1	5	C
G4	2	2	1	5	C
G5	2	2	1	5	C
G6	2	2	1	5	C
G7	2	2	1	5	C
G8	2	2	1	5	C
GR1	1	1	1	3	B
GR2	1	2	1	4	B
GR3	1	2	1	4	B
GR4	2	2	1	5	C
GR5	1	1	1	3	B
GR6	2	2	1	5	C
GR7	2	2	1	5	C
GR8	1	1	1	3	B
R1	0	0	0	0	A
R2	0	0	1	1	A
R3	0	0	0	0	A
R4	0	0	0	0	A
R5	0	0	1	1	A
R6	0	0	0	0	A
R7	0	0	0	0	A
R8	0	0	0	0	A

No nephrotoxicity: (0-1)=A, mild nephrotoxicity: (2-4)=B, moderate nephrotoxicity: (5-7)=C, severe nephrotoxicity: (8-10)=D

When the sections of the C group and R group were examined, the brush border of the proximal tubules could be observed. However, the brush border structure of kidney tubules in the G and GR groups was lost. Especially in the G group, both glomerular and tubular basement membrane thickening was observed (Figure 2).

When we examined immunohistochemically, it was observed that the expression of Ifi44, which has an antiproliferative effect, was quite intense in the kidney tissues of the G and GR groups compared to the C and R groups (Figure 3). It was observed that the rate of Ifi-44 immunoreactivity in the G group was statistically higher than the other groups (C, GR, R) (p<0.001). The rate of Ifi-44 immunoreactivity in the GR group was statistically higher than in both the C and R groups (p<0.001). No statistically significant difference was found between group C and group R in terms of Ifi-44 immunoreactivity (p=0.954).

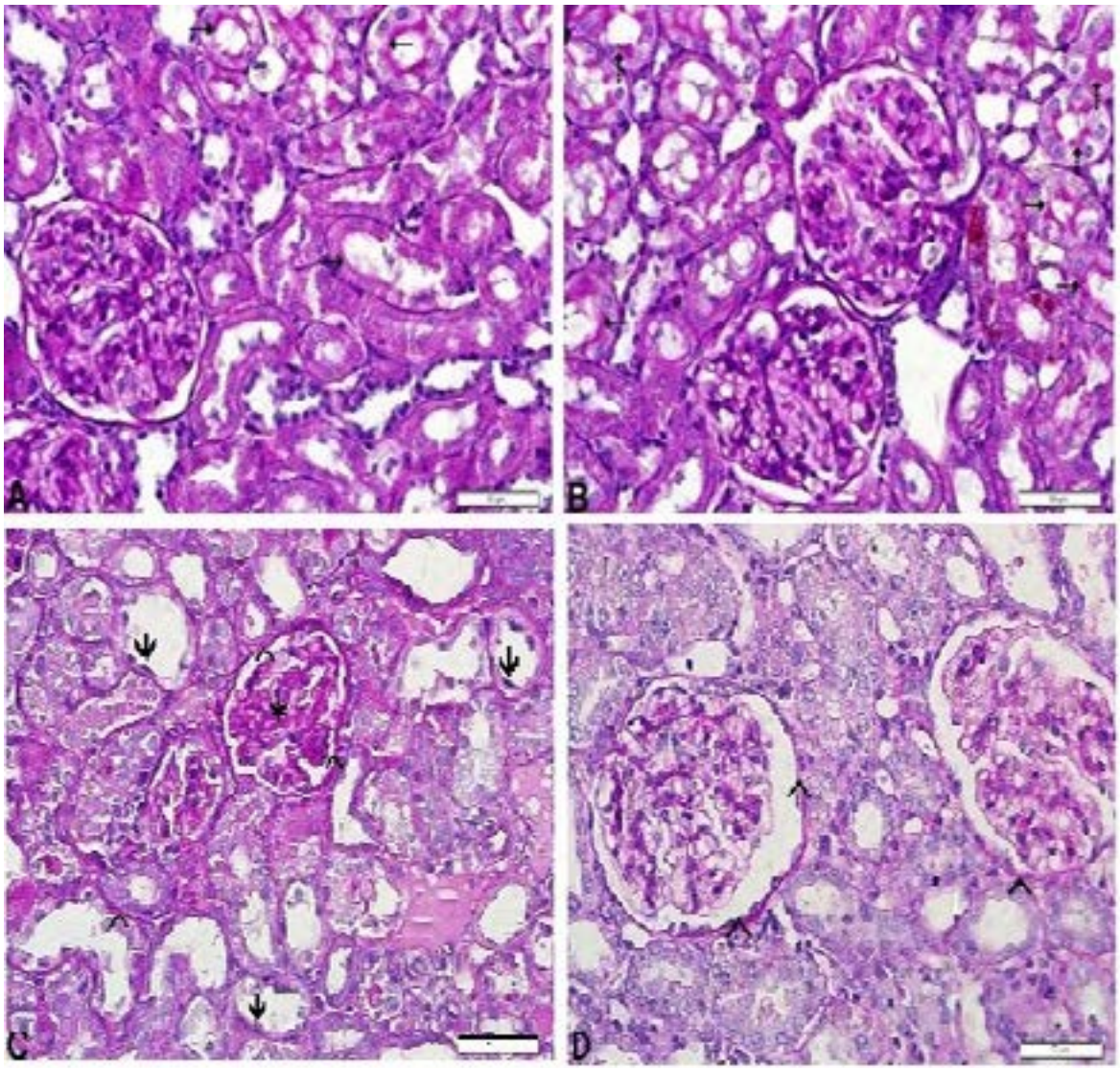

Figure 2. Normal tubule structures and brush border (→) in group C (A), and group R (B). Thickened basement membrane (^) and flattened tubule cells (↓), glomerular damage (*) in group G (C) and group GR (D) (PAS+ reaction) (X40)

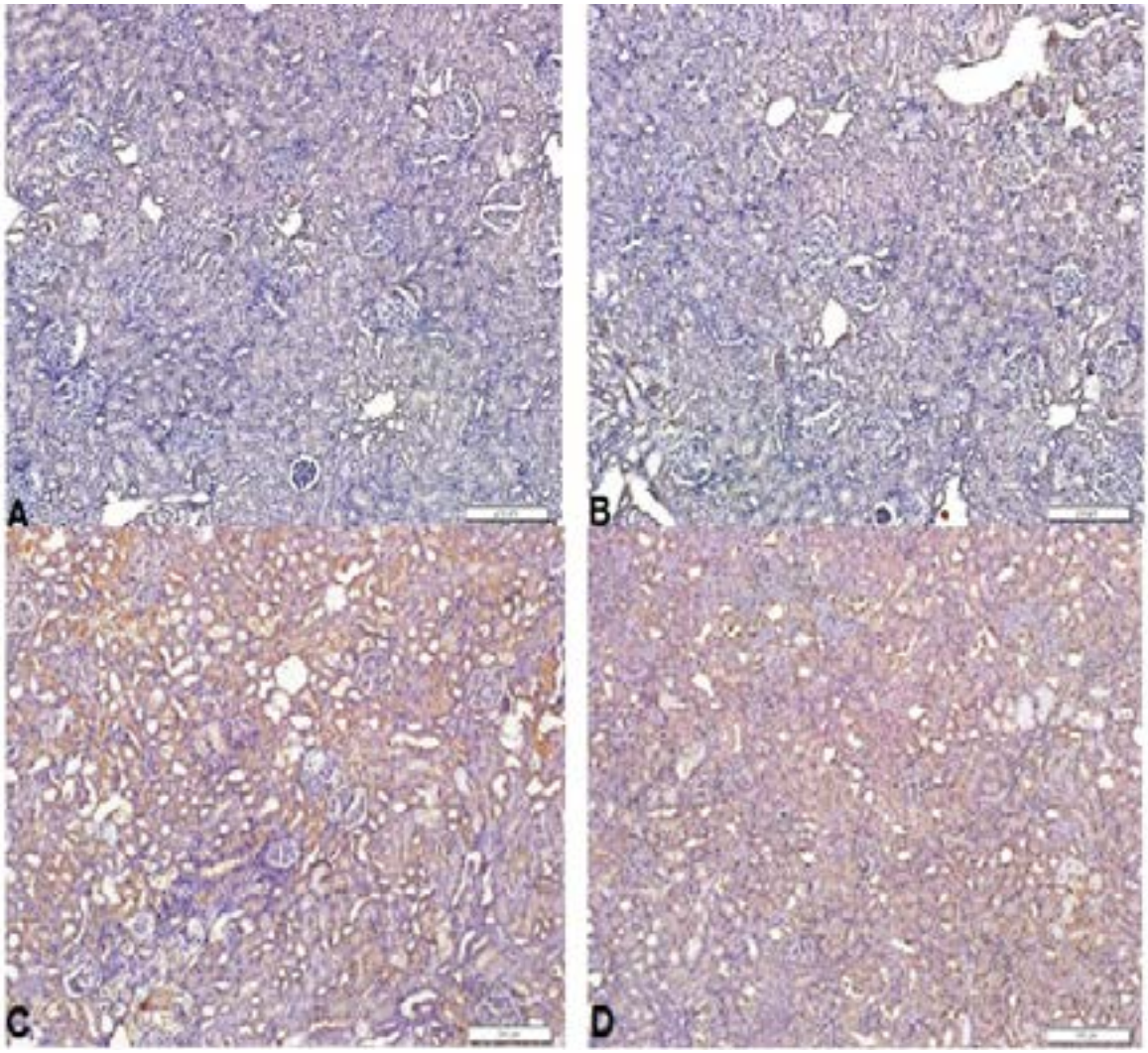

Figure 3. Immunohistochemical analysis of Ifi44 expression in kidney tissue. Low immunoreactivity is observed in A (C group) and B (R group), and high immunoreactivity in C (G group) and D (GR group) (X10)

Serum creatinine, urea, and BUN levels were higher in G and GR groups. Serum creatinine, urea, and BUN levels of the G and GR groups were statistically significantly higher when compared to C and R groups.

Serum TAS levels of G and GR groups were lower. However, the mean serum TAS level did not differ statistically between the groups.

It was observed that the mean serum TOS level was higher in the G and GR groups. Especially in the G group, the serum TOS level seemed to have increased significantly. Serum TOS level was significantly decreased in the GR group compared to the G group. However, the GR group was higher than the C and R groups. The serum TOS levels of the GM-treated (G and GR) groups were statistically significantly higher when compared with the C and R groups (Table 3).

Table 3. Biochemical values of the groups

Biochemical markers	Group C	Group R	Group G	Group GR
Creatinin (mg/dL)	0.35±0.05	0.31±0.09	1.36±0.50 ^{k}p, ^{ъ}p	1.16±0.32 ^{k}p, ^{ъ}p
Urea (mg/dL)	36.74±3.37	35.17±6.37	152.95±42.80 ^{k}p, ^{ъ}p	100.68±42.80 ^{k}p, ^{ъ}p
BUN (mg/dL)	17.17±1.57	16.44±2.98	71.48±20.00 ^{k}p, ^{ъ}p	47.05±20.04 ^{k}p, ^{ъ}p
TAS serum (µmol/L)	1.18±0.22	1.25±0.31	1.12±0.27	0.88±0.37
TOS serum (µmol/L)	44.39±13.67	34.28±7.99	146.63±80.47 ^{k}p, ^{ъ}p	68.78±9.96 ^{k}p, ^{ъ}p

^{k}p (p<0.05); statistically significant with group C, ^{ъ}p (p<0.05); statistically significant with group R

Discussion

Although its nephrotoxic effect is known, GM is still an antibiotic used against gram-negative bacterial infections. In order to examine the damage caused by GM, the results were evaluated experimentally by applying GM at different doses and times [21, 23, 26]. Studies have shown that both the body weight and kidney weight of rats given GM decreased compared to the C group [23]. It has been reported that the reason for this is acidosis and increased catabolism due to acute renal failure, loss of appetite, and decreased food intake [1]. In order to eliminate or partially reduce the damage of toxic substances that harm the body, natural agents with antioxidant effects are used. One of them is RA which is reported to have antioxidant, anti-inflammatory, antiapoptotic, and antitumoral effects [23].

In our study, mean body weight decreased in the G and GR groups and showed statistical significance when compared with the control group.

However, when the mean kidney weights were compared, an increase was observed in the G and GR groups, but statistical significance was observed only between the G group and the R group in the mean left kidney weight. When the mean kidney weights were compared, no statistical significance was observed between the C group and the other groups. In this respect, our study is compatible with the study stating that there may be an increase in kidney weight as a result of edema caused by acute tubular necrosis in rats given GM [27].

It has been suggested that increased serum creatinine, urea, and BUN values can be considered an indicator of nephrotoxicity in kidney damage due to GM exposure. In addition, there are different studies in which an increase in oxidative stress agents, monocyte-macrophage cell infiltration, inflammation, apoptosis, and brush border loss of tubular epithelial cells were observed as a result of experimental kidney damage caused by the application of GM at different doses and for different durations [23, 28-32]. In our study, it was observed that the

mean urea, creatinine, and BUN levels of the G and GR groups were high. It was observed that these values were lower in the GR group than in the G group. In this respect, our study supports the studies that apply RA treatment against the nephrotoxic effect of GM [23, 33, 34].

It was stated that oxidative stress is among the possible causes of renal damage in many studies [23, 35, 36]. GM causes increased superoxide anion production in renal cells. Accumulation of free oxygen radicals causes the initiation of protective mechanisms in renal cells. The reduction of one or more antioxidant systems leads to increase lipid peroxidation and more oxidative damage [23]. In our study, the serum TOS level of group G was considerably higher than the other groups.

Serum TOS level was lower in the R group than in the C group, and lower in the GR group than in the G group.

Serum TAS was found at the highest level in the R group. These values can be considered as an indicator of the antioxidative property of RA. As a matter of fact, our study was in agreement with studies reporting that it has an antioxidant effect by reducing RA oxidative stress [12, 37] and alleviates GM nephrotoxicity [33]. It was observed that the TAS level was lower in the GR group than in the other groups. This result has shown that the antioxidant properties of RA could not be seen in applied together with GM.

An increase in the biochemical values of the G group was observed, at the same time, it was observed that renal tubule and glomerular damage were quite high. Our findings were consistent with studies reporting proximal convoluted tubules, disruption of brush border and epithelial cell damage in their lumens, glomerulus damage, disruption of the Bowman capsule, and inflammation in animals given GM [23, 28-34]. In our study, kidney damage was statistically significantly higher in G and GR groups compared to C and R groups. Histological changes in the GR group were similar to the G group. Although it was not statistically significant in the GR group compared to the G group, the area of inflammation, glomeruli, and tubule damage was found to be less (p=0.070). According to these results in our study, we can say that the anti-inflammatory effect of RA was partially observed.

It was reported that GM causes damage through inflammation with excessive consumption of reactive oxygen species and causes an increase of the Ifi44 expression, which has an antiproliferative effect [19, 38]. RT-qPCR and western blot, and immunohistochemistry showed increased expression of Ifi44 in rat cochlear and kidney tissues following GM administration, suggesting that Ifi44 is associated with inflammations associated with GM-induced ototoxicity and nephrotoxicity [21]. In our study, Ifi44 expression was statistically significantly higher in our G and GR groups than in the C and R groups (p<0.001). The increase in the expression level of Ifi44 was also statistically significant in the G group compared to the GR group (p<0.001). These results at the expression level of Ifi44 showed that RA can`t fully demonstrate its antiapoptotic effect. It has showed that RA could not fully protect against the toxic effects of GM.

In our study also, it has been seen that RA which is used alone for protection purposes could not provide full protection against GM in parallel with the study stating that the combined treatment of RA and lycopene has a more beneficial preventive effect than RA treatment alone. The changes we recorded in the biochemical measurement were in agreement with the histological findings.

The biochemical results are parallel to the histological results and have revealed the importance of nephrotoxicity oxidative stress in the renal tissue caused by GM. The inability to detect TAS and TOS values in kidney tissue is one of the shortcomings of our study. The biochemical, histological, and immunohistochemical findings obtained as a result of our study showed the toxic effect of GM on renal tissue. As a result of RA application, a decrease in oxygen radicals and an increase in antioxidant levels were observed. However, when used together with GM, the protective effect of RA was observed partially, and its full protective effect could not be observed. We think it may be beneficial to apply it before encountering agents with toxic effects or at high doses in order to have protective effects. We are of the opinion that there is a need for comprehensive studies to investigate the effect of RA applied at different doses and times against toxic agents.

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Authors' contributions to the article

H.C. constructed the main idea and hypothesis of the study. H.C. developed the theory and arranged/edited the material and method section. H.A. contributed to the biochemical evaluation of the findings. D.G. contributed to the histological and immunohistochemical evaluation of the Results. The article written by H.C. In addition, all authors discussed the entire study and approved the final version.

Case Report

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J wave as a rare ECG finding of malignant cardiac arrhythmia

Malign kardiyak aritmilerin nadir bir EKG bulgusu olarak J dalgası

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Abstract
In this case report, we present a 76-year-old female patient diagnosed with ventricular fibrillation in the emergency department who died after cardiopulmonary resuscitation. The importance of observing J waves in a patient's electrocardiogram after spontaneous return to circulation is addressed in terms of the risk of arrhythmia.

Key words: J wave, malignant arrhythmia, death.

Altintas E, Erat M, Guzes EB. J wave as a rare ECG finding of malignant cardiac arrhythmia. Pam Med J 2023;16:500-507.

Öz
Acil serviste ventriküler fibrilasyon saptanan ve kardiyopulmoner resüsitasyon uygulanıp, yaşamını kaybeden 76 yaşında bir kadın hastayı sunduk. Bu olgumuzda spontan dolaşıma geri dönüş sağlandıktan sonra hastanın elektrokardiyogramında gördüğümüz J dalgasını aritmi riski nedeni ile önemini vurguladık.

Anahtar kelimeler: J dalgası, malign aritmi, ölüm.

Altıntaş E, Erat M, Güzeş EB. Malign kardiyak aritmilerin nadir bir EKG bulgusu olarak J dalgası. Pam Tıp Derg 2023;16:500-504.

Introduction

The American Heart Association (AHA) reported that in 2022, 347.000 adult patients with cardiac arrest received interventions outside hospital settings, whereas 9.7/1.000 adults with cardiac arrest were attended to the hospital [1]. The AHA guidelines recommend that reversible causes be considered during cardiac arrest interventions [2].

Sudden cardiac death has been defined as a natural, unexpected, or accidental incident that does not result from committing suicide or poisoning and occurs within one hour of cardiac arrest [3]. The causes of sudden cardiac arrest are classified as cardiac and non-cardiac. Cardiac causes, which constitute 70% of sudden cardiac arrest cases, are categorized into two main groups: structural heart diseases and rhythm disorders. Rhythm disorders include conditions such as Brugada syndrome (BrS) and long and short QT [4].

The J wave has been noted in life-threatening conditions, such as hypothermia, hypercalcemia, BrS, vasospastic angina, and myocardial infarction (MI) [5], and is used in the definitions of BrS and early repolarization syndromes [5]. A common characteristic of both phenomena, J wave syndrome is observed at the transition point from the terminal part of the QRS complex to the ST segment, that is, at the J point in the electrocardiogram (ECG) [6]. The J wave is characterized by a high risk of arrhythmia depending on the patient's underlying conditions [5]. In view of the foregoing, the objective of this report is to discuss a rare case of J wave syndrome with the risk of malignant arrhythmia.

Case presentation

A 76-year-old female hypertensive patient presented to the emergency department with a complaint of chest pain that had been ongoing for a week. However, she developed sudden cardiac arrest during admission to the emergency department. Cardiopulmonary resuscitation (CPR) was performed on the patient for two minutes, which resulted in the recovery of spontaneous circulation (ROSC).

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An ECG of the patient was taken following the ROSC. The ECG revealed an accelerated junctional rhythm, narrow QRS, and a ventricular rate of approximately 70 beats/min (Figure 1). Additionally, right axis deviation, >2 mm ST segment elevation in the D1, aVL, and V2 leads, 1 mm ST segment depression in the D2 lead, 3 mm ST segment depression in the D3 and aVF leads (inferior derivations) were detected. Notch-shaped J waves were present in the inferior-lateral derivations (D2, D3, aVF, D1, aVL, and V6).

It was learned that coronary angiography had been performed on the patient two days prior and that she had been discharged with 40% left anterior descending coronary artery stenosis. During the ROSC period after CPR, a notch-shaped J wave in the ECG in the inferolateral leads (Figure 2), a notched J-point elevation ≥0.1 mV, and a descending ST segment in the inferior derivations, especially in D2-aVF, were detected (Figure 3). The patient, who developed ventricular fibrillation (VF) and cardiac arrest shortly after CPR, was pronounced dead 30 minutes after CPR. During cardiac arrest, blood was drawn from the patient for laboratory tests, but the samples developed hemolysis in the laboratory, and the tests could not be performed. Because the patient was exitus, blood could not be drawn again. A signed consent form was obtained from the patient's daughter for the publication of this report.

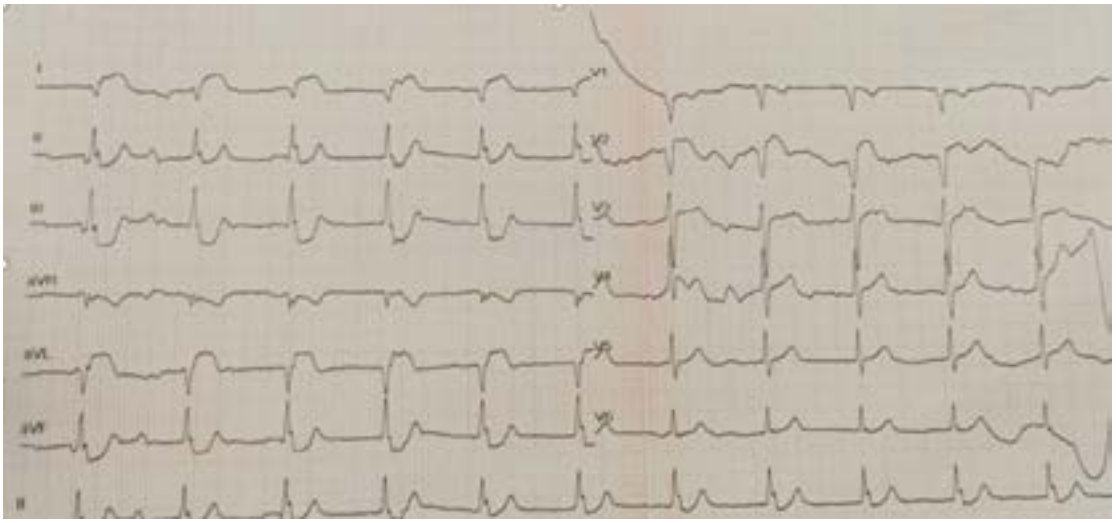

Figure 1. ECG of the patient after recovery of spontaneous circulation following cardiac arrest

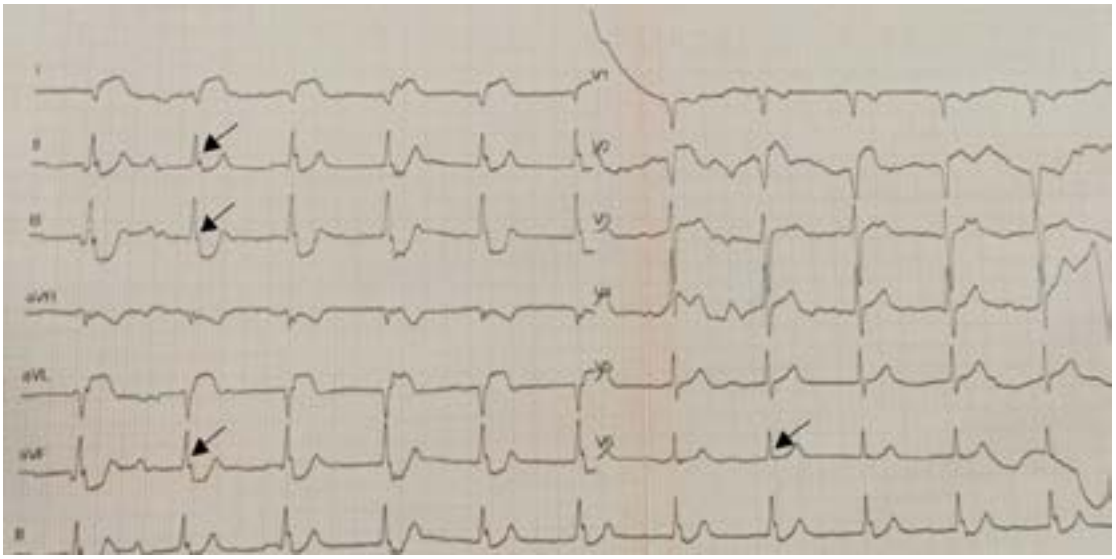

Figure 2. Notched-shaped J wave in the inferolateral derivations

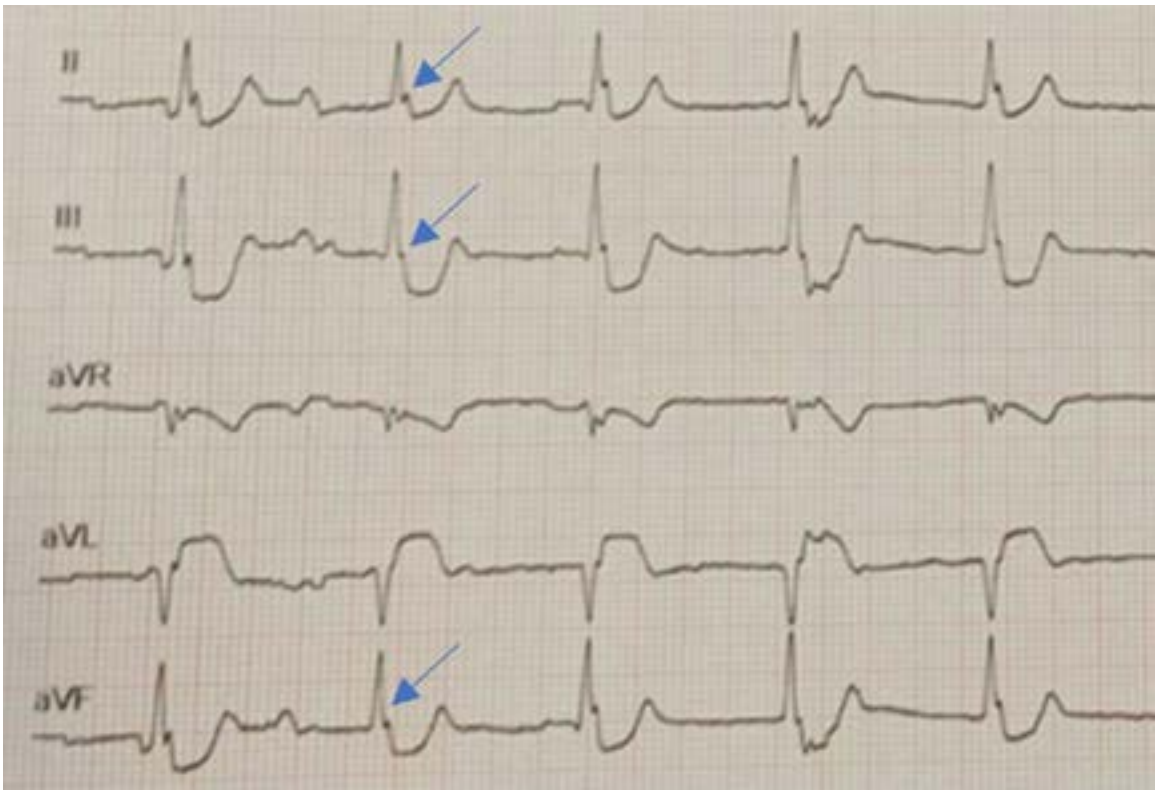

Figure 3. Notched J-point elevation ≥0.1 mV and descending ST segment in the inferior derivations

Discussion

The J wave, also known as the camel-hump sign or Osborn wave, is characterized in the literature by slurring or notching in the terminal part of the QRS in a standard 12-lead ECG. Additionally, it has been reported that J waves are associated with a high risk of arrhythmia depending on the underlying conditions. The most common causes include hypothermia, hypercalcemia, vasospastic angina, BrS, and MI [5-7]. In this report, we present a case with a malignant J wave characterized by inferolateral leads and a descending ST segment, in which the patient developed VF.

J point elevation, the height of the J wave, the ST segment slope (upward, horizontal, or downward slope), and the number of leads in the ECG are important features [8]. Early repolarization is defined as >1 mm elevation of the J point and ST segment in two or more consecutive derivations. The J wave is described as either benign or malignant based on its characteristics. Accordingly, a J point with a descending or horizontal ST segment is considered malignant, and a J point with a rapidly rising ST segment is considered benign [9]. Inferolateral leads in particular place a patient at risk of developing VF [10]. A slurred or notched J point or J-point elevation ≥0.2 mV is also associated with an increased risk [6].

J waves have been associated with cardiac arrhythmias in the acute and chronic phases of MI. Konishi et al. [11] reported that slow conduction and reentry related to scarring are prerequisites and may cause late activation of the myocardium, thus contributing to the J wave pattern. In a study in which the ECG findings of patients who developed MI and ventricular tachyarrhythmias (VT) were examined postoperatively, it was reported that the presence of the J wave was statistically significant in the ECGs of the patients who developed VTs. Based on this finding, it has been suggested that such patients should be further evaluated for additional treatment (e.g., radiofrequency catheter ablation) [12]. In another study, it was noted that this situation may resemble arrhythmias caused by the coexistence of living and fibrotic tissues in postoperatively infarcted myocardial tissue [13].

Three main pathogeneses have been described for cardiac arrhythmogenic diseases in patients with sudden cardiac arrest. These are a conduction abnormality, repolarization abnormality, and excitation abnormality. In a conduction abnormality, the cause of VF is a structural abnormality and the heterogeneity of depolarization caused by BrS, an inferolateral J wave, and an idiopathic structural abnormality. Ablation is the recommended treatment [14]. In a case report by Boukens et al. [15], electrophysiological mapping was performed in a patient with an early repolarization pattern. The clinicians reported that there are localized structural abnormalities and recurrent arrhythmias can be reduced by ablation treatment.

In comparison, in the case presented herein, we initially thought that the J wave was associated with lateral wall MI, given the ST elevation in the lateral leads and reciprocal ST depression in the inferior leads. On the other hand, the fact that the ECG was taken after CPR and that the patient's coronary angiography, which had been taken two days prior, revealed non-critical lesions suggested that the J wave may have been associated with vasospastic angina or idiopathic VF. Emergency room physicians therefore need to determine the presence of J waves in ECGs and should be mindful of possible VT and sudden death, especially in the presence of malignant J waves.

In conclusion, it is of critical importance to determine the presence of J waves in the ECGs of patients in the emergency department. If determined, the patient should be evaluated further for the underlying causes of the J wave. The physician should subsequently distinguish between the benign and malignant forms of the J wave and be mindful of life-threatening arrhythmia in the case of patients with malignant forms of the J wave.

Conflicts of interest: The authors declare no conflicts of interest.

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Consent to participate: The authors certify that they obtained all the appropriate patient consent forms. The patient's daughter provided her consent for the patient's images and other clinical information to be reported in this journal. The patient's daughter understands that the patient's name and initials will not be published, and that although due effort has been made to conceal the patient's identity, anonymity cannot be guaranteed.

Authors' contributions to the article

E.A.: Conceptualization, writing and editing of the review, supervision.

M.E.: Writing and editing of the review, supervision.

E.B.G.: Conceptualization, writing of the original draft.

Case Report

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Rheumatic carditis presented with only palpitation

Sadece palpitasyon ile kendini gösteren romatizmal kardit

Eyüp Aslan, Cem Karadeniz

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Abstract

Acute Rheumatic Fever (ARF) remains a serious public health problem and is common in the developing countries. Arrhythmias such as atrioventricular nodal blocks, premature beats, accelerated nodal rhythm, ventricular tachycardia and Torsades de pointes can be seen in the early stages of the disease.

We present a case of narrow QRS tachycardia in which palpitation was the only symptom of rheumatic carditis. After the disease became inactive with acetylsalicylic acid treatment, the tachycardia returned to normal sinus rhythm.

Key words: Child, rheumatic carditis, tachycardia.

Aslan E, Karadeniz C. Rheumatic carditis presented with only palpitation. Pam Med J 2023;16:506-509.

Öz

Akut Romatizmal Ateş (ARF) ciddi bir halk sağlığı sorunu olmaya devam etmektedir ve gelişmekte olan ülkelerde yaygındır. Atriyoventriküler düğüm blokları, erken atımlar, hızlanmış nodal ritim, ventriküler taşikardi ve Torsades de pointes gibi aritmiler hastalığın erken evrelerinde görülebilir.

Romatizmal karditin tek semptomunun çarpıntı olduğu bir dar QRS taşikardisi olgusunu sunuyoruz. Asetilsalisilik asit tedavisi ile hastalık inaktif hale geldikten sonra taşikardi normal sinüs ritmine döndü.

Anahtar kelimeler: Çocuk, romatizmal kardit, taşikardi.

Aslan E, Karadeniz C. Sadece palpitasyon ile kendini gösteren romatizmal kardit. Pam Tıp Derg 2023;16:506-509.

Introduction

Acute rheumatic fever (ARF) remains a serious problem for public health, and it is common in developing countries. It has a wide range of presentation and in some settings it can appear a dramatic event. Various rhythm problems such as first, second and third-degree atrioventricular blocks, premature contractions, accelerated junctional rhythm, ventricular tachycardia, and Torsades de pointes may occur during the acute stage of the disease [1-4]. The exact mechanism of conduction disturbances is unknown.

We present a case of narrow QRS tachycardia in which palpitation was the only symptom of rheumatic carditis. After the disease became inactive with acetylsalicylic acid treatment, the tachycardia returned to normal sinus rhythm.

Case report

A 10-year-old girl was referred to the paediatric cardiology department owing to palpitation for three hours. Her initial vital signs revealed a blood pressure of 122/72 mmHg, heart rate of 136 beats per minute (bpm), respiratory rate of 22 breaths per minute, and a temperature of 36.8°C. A grade 1/6 systolic murmur was at the left sternal border. She had no history of druge use, joint pain and/or arthritis; but it was reported of sore throat over the past three weeks prior to the presentation. An electrocardiogram (ECG) in the emergency room revealed narrow and regular QRS tachycardia (130 bpm). Accelerated nodal tachycardia or sinus tachycardia with first degree AV block with excessively long PR interval were suspected because the p wave was not clearly seen

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(Figure 1a). Transthoracic echocardiography revealed that, there was trace mitral valve regurgitation 8 mm in length, visible only at one view, no cardiac chamber enlargement (left ventricle end-diastolic diameter was 42 mm) and normal contractility (ejection fraction 68%, shortening fraction 38%). When AV nodal blocking via administered adenosine (100 µg/kg) to explain the rhythm, atrial sinus beats with 80 bpm were remained. Then the narrow QRS tachycardia repeated with 130 bpm short after again. (Figure 1b).

Laboratory investigations revealed neutrophilic leukocytosis (WBC 17.750/mm^3, N 82%), elevation of erythrocyte sedimantation rate (ESR) and C-reactive protein (CRP) (106 mm/hr, 27.8 mg/L (n<5), respectively), and elevated antistreptolysin O (ASO) titer 1230 IU/mL (n<200). Other biochemical laboratory findings, including level of troponin I, thyroid functions and serum electrolits were normal. It was conducted that laboratory examinations to the causes of elevations of the acute phase reactants. Peripheral smear, viral seralogy and urine examinations were normal. Chest radiography and abdominal ultrasound revealed also normal.

A first episode of ARF is diagnosed when a patient has evidence of recent streptococcal infection in addition to either two major or one major and two minor criteria according to the Modified Jones Criteria [5]. To be considered carditis, which is the major criterion, pathological mitral regurgitation must meet all four criteria: seen in at least two views, jet length ≥2 cm in at least one view, peak velocity >3 m/s, pansystolic jet in at least one envelope [5]. In addition to tachycardia, our patient had trace mitral valve regurgitation that did not meet the criteria for carditis, however she had elevated acute phase reactants. Although it did not meet the Modified Jones Criteria to diagnose ARF, we suspected rheumatic carditis because we could not found any other reason that lead to tachycardia and increased acute phase reactants. In addition, the ASO titer was also high. Finally, the diagnosis was considered as sinus tachycardia with first degree AV block with excessively long PR interval, secondary to rheumatic carditis. Acethylsalisilic aside (80 mg/kg/day) was administered for suspected inflammatory etiology. At the fourth hour of follow-up, the rhythm formed to sinus with 80 bpm with first degree atrioventricular (AV) block (PR:280 ms) (Figure 1c). Acethylsalisilic aside remained for two weeks, then progressively reduced followed two weeks and stopped. Electrocardiogram performed on fourth day after admission showed a sinus rhythm with a normal PR interval duration.

At the fourth month of follow-up just with penicillin prophylaxis, the patient had trace mitral regurgitation, and normal ECG with no complaints.

Signed informed consent forms were obtained from the parents of the patient.

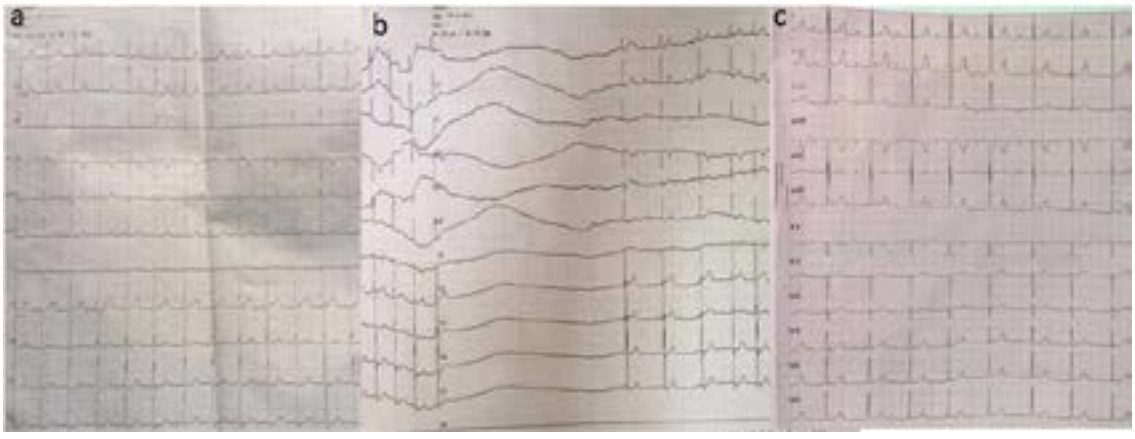

Figure 1. (a) The electrocardiogram of the patient showing narrow QRS tachycardia with a heart rate of 130 beats/min, (b) atrial beats remained 80 beats/min after adenosin administration, (c) first degree AV block with PR (280 msec) after acethylsalisilic aside treatement

Discussion

First degree AV block is a minor criterion in the Modified Jones Criteria [6]. Although not among the criteria, rhythm disorders such as second or third degree atrioventricular blocks, ventricular tachycardia, Torsades de pointes can also be seen [3, 4, 7]. In cases where no other cause of rhythm disturbance can be found, it may be considered to expand the definition of mitral regurgitation according to Doppler findings and to diagnose ARF.

Presence of arrhytmia was significantly related to the presence of carditis [8]. However, most rhythm problems are independent of valvular involvement, and they are thought to be due to inflammation of the myocardium and myocardial oedema. The tachycardia may occur in both rheumatic carditis and viral myocarditis. Unlike viral myocarditis affecting myocytes, rheumatic carditis seems to be less destructive on myocyte, which supported by the lack of myocardial necrosis observed in biopsy specimens from patients with active rheumatic carditis [9]. The authors preferred the term “myocyte degeneration” instead of “myocyte necrosis” on their histologic specimens [9]. This sparing affect on myocytes does not result in elevated troponin levels in acute rheumatic carditis [10]. In our patient there was only a trace mitral valve regurgitation, high levels of acute fase reactants, normal troponin level and narrow QRS tachycardia (130 bpm), considered in rheumatic carditis. Polat et al [11] found that QT dispersion increased in rheumatic fever and Kucuk et al. [12] showed that increased transmural dispersion of ventricular repolarisation parameters (Tp-e) which interval between the peak and the end of the T wave, can be used as an index of transmural dispersion of ventricular repolarisation which may lead to ventricular dysrhythmia. Inflamed myocardium is prone to dysrhythmia, and anti-inflammatory therapy may be beneficial in the treatment of dysrhythmias. After beginning the acethylsalisilic aside treatment, the rythym formed to sinus (80 bpm), with the first degree AV block (PR:280 ms). Most rhytm problems are temporary and self-limited to the acute stages of the disease and resolve completely with anti-inflammatory treatment by healing the myocardium [3]. With acetylsalicylic acid treatment, first degree AV block gradually resolved in four days.

In conclusion various types of rhythm disturbances may develop in the acute stages of rheumatic carditis. We present a rare case of AV nodal tachycardia following first degree AV block associated with rheumatic carditis. This diagnosis should be considered in patients, even though when there is not evidence with other features of ARF. Conduction disorders associated with rheumatic carditis often resolve following anti-inflammatory treatment.

Conflict of interest: No conflict of interest was declared by the authors.

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Informed consent: Written informed consent was obtained from the patient.

Authors' contributions to the article

E.A. constructed the main idea of the study. E.A. and C.K. developed the theory and arranged/edited the material and method section. E.A. and C.K. has done the evaluation of the data in the Results section. Discussion section of the article written by E.A. C.K. reviewed, corrected and approved the article. In addition, all authors discussed the entire study and approved the final version.

Case Report

Pamukkale Medical Journal
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A case report of tubal high grade serous carcinoma, which was diagnosed incidentally after appendectomy

Apendektomi sonrası tesadüfen teşhis edilen tubal yüksek dereceli seröz karsinom olgu sunumu

Pelin Höbek, Mehmet Anıl Onan

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Abstract

Primary tubal carcinoma is an uncommon tumor of female genitale system. The clinical approach of primary tubal cancers is similar to primary ovarian cancers. Fallopian tube carcinoma is hard to diagnosed preoperatively because of its indistinct symptoms. Optimal cytoreductive surgery is the most important treatment step in ovarian, tubal and peritoneal carcinomas.

We report a case of serous tubal intraepithelial carcinoma with appendix metastasis. A 65 years old post-menopausal woman (gravida 4, para 3) submitted to an external hospital with lower abdominal pain and acute abdominal symptoms. Appendectomy was performed on the patient with preliminary diagnosis of apendicitis. The pathology result was reported as high grade serous carcinoma infiltration. Staging surgery was performed with the diagnosis of carcinoma. Until the final pathology result, the diagnosis was considered as appendiceal metastasis of serous tubal cancer. Our clinical and surgical approach to the case, which was diagnosed incidentally with an appendectomy specimen and reported as high grade tubal serous carcinoma, is presented as a case study.

Key words: Adnexal diseases, appendiceal neoplasms, neoplasm metastasis.

Hobek P, Onan MA. A case report of tubal high grade serous carcinoma, which was diagnosed incidentally after appendectomy. Pam Med J 2023;16:510-514.

Öz

Tubanın primer karsinomları kadın genital sisteminde nadir görülen tümörlerdir ve klinik olarak primer over karsinomlarına benzerler. Belirsiz semptomları nedeniyle sıklıkla ileri evrede tanı alırlar ve preoperatif tanı koymak zordur. En önemli tedavi basamağı optimal sitoredüksiyonun sağlanmasıdır.

Bu olgu sunumunda apendektomi sonrası tesadüfen saptanan high grade seröz tubal karsinom olarak raporlanan olguya yönelik klinik ve cerrahi yaklaşımımızdan bahsedilmektedir. 65 yaşında postmenopozal hasta (gravida 4, parite 3) akut karın semptomları ile başka bir merkeze başvurdu. Apandisit ön tanısı ile hastaya apendektomi yapıldı ve apendektomi spesmeninin nihai patoloji sonucu seröz karsinom infiltrasyonu olarak raporladı. Hastaya seröz karsinom endikasyonu ile evreleme cerrahisi yapıldı. Appendektomi materyali ile tesadüfen saptanan ve high grade tubal seröz karsinom olarak bildirilen olguya klinik ve cerrahi yaklaşımımız vaka çalışması olarak sunulmaktadır.

Anahtar kelimeler: Ovaryum ve tubauterina hastalıkları, apendiks neoplazileri, tümör metastazı.

Höbek P, Onan MA. Apendektomi sonrası tesadüfen teşhis edilen tubal yüksek dereceli seröz karsinom olgu sunumu. Pam Tıp Derg 2023;16:510-514.

Introduction

Metastatic lesions to the appendix are exceptionally uncommon. Metastatic lesions may present acute appendicitis, remain asymptomatic or are diagnosed incidentally [1]. Appendix metastases often originate from gastointestinal tract [2].

Primary tubal carcinoma is an uncommon tumor of the female genital system that has a clinical behavior like ovarian cancer [3]. Tumors in the tubes are usually metastatic rather than primary. Metastatic tumors of the ovary, endometrium, gastrointestinal tract and breast should be excluded. Therefore, metastases from these regions should be excluded for a definitive diagnosis.

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The most common age of occurrence is between 50 and 65 years, and the mean age is 55 years. Fallopian tube carcinoma is hard to diagnose preoperatively because of its indistinct symptoms [4]. Clinical symptoms are lower abdominal or pelvic pain, abdominal swelling and pelvic mass. It is often diagnosed intraoperative or after histopathological examinations [5].

Histopathology is the gold standard method for diagnosing primary fallopian tubal carcinoma. High grade serous carcinoma is the most common histopathologic type. High grade ovarian serous carcinoma originate from the tubal epithelium and involves mutations in TP53 [6, 7].

PAX8 is a significant histological marker for most of the epithelial ovarian cancers, as it is expressed in about 90% of malignant ovarian carcinomas, specifically in high grade serous carcinoma. PAX8 is needed for the normal development of Müllerian duct that includes Fallopian tube, uterus, cervix, and upper part of vagina [8]. PAX8 positivity in appendectomy specimen suggested that primary carcinoma originated from ovary or tuba.

The treatment of primary tubal carcinoma is primary debulking or interval debulking surgery after neoadjuvant chemotherapy. Primary tumor and metastases should be removed by explorative laparotomy and staging surgery should be performed. Postoperative adjuvant chemotherapy should be given as the combination of carboplatin and paclitaxel [9].

Stage of the disease affects survival. The five-year survival rate is less than 50%. If the disease is caught in early stages, survival can be as high as 92%. Unfortunately, because of its nonspecific symptoms and lack of early sign, the 5-year survival rate is less than 30%. The stage of tumor at the time of diagnosis is the most important factor determining the prognosis. Other important prognostic factors include the residual volume of the tumor after cytoreduction and the histologic grade of the tumor [10]. Complete resection of all tumor cells has been shown to significantly improve outcome and overall survival [11].

Case presentation

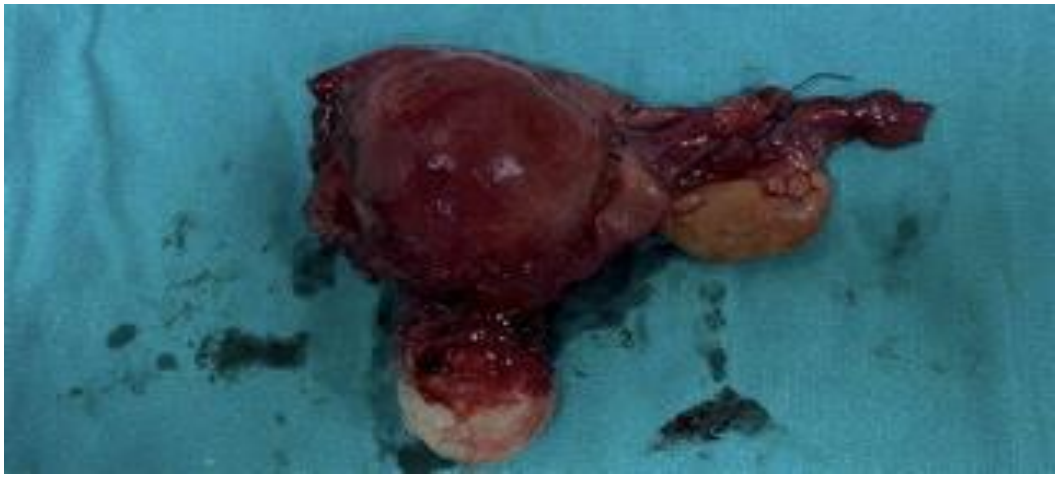
A 65 years old post-menopausal woman (gravida 4, para 3) submitted to an external hospital with lower abdominal pain and acute abdominal symptoms. She had three spontaneous vaginal deliveries and last menstrual date was 15 years ago. For her medical history, she has been using antihypertensive medication for ten years. Abdominal ultrasonography and pelvic tomography were performed and the patient was diagnosed as acute appendicitis. Appendectomy was performed with preliminary diagnosis of apendicitis. The pathology result was reported as high grade serous carcinoma infiltration. In the immunohistochemical study PAX8 and P53 were highly positive while WT-1 was detected negative. The patient was referred to us with the preliminary diagnosis of appendiceal metastasis of serous ovarian cancer.

Normal sized uterus and mobile cervix were observed on pelvic examination. No obvious adnexial mass was observed. Free ascites was not seen in the abdomen. İn laboratory examinations performed in our clinic, hemogram, complete urinalysis and routine biochemistry tests were unremarkable. The Ca 125 level was 197.8 U/ml (normal up to 35 U/ml), the Ca 19-9 levels was normal. There was no pleural effusion in the preoperative thorax tomography.

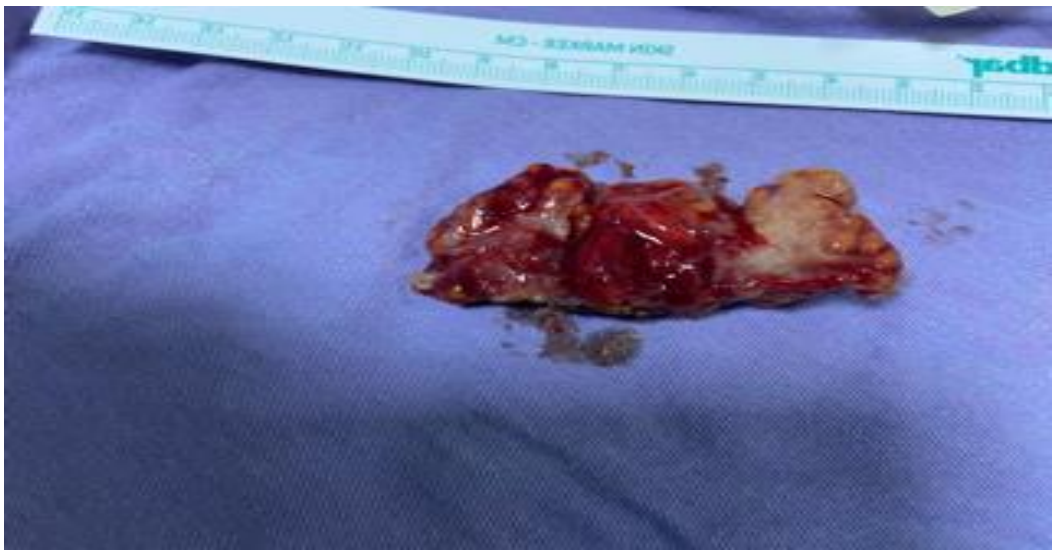
Staging surgery was performed with the diagnosis of ovarian carcinoma. In the expolaration, uterus, left ovary and tuba were observed as normal (Picture 1, 2). Milliary tumoral implants were observed on the right ovary, tuba and other intra-abdominal organs and peritoneum. Abdominal washing fluid was sent to intraoperative pathology and it was reported as malignant fluid cytology in papiller pattern. The patient underwent staging surgery including total abdominal hysterectomy, bilateral salpingo-oopherectomy, omentectomy with adhesiolysis and retroperitoneal lymph node dissection. The bilateral ovarian masses, fallopian tubes, uterus, omentum, lymph nodes and sample of peritoneal washing were sent for histopathological analysis. A tumoral lession of approximately 1 cm diameter was observed in the fimbrial section of the right tube. Until

the final pathology result, the diagnosis was considered as appendiceal metastasis of serous tubal cancer. It was determined that the cancer originated from right tube and no tumor focus was observed in the parenchyma of both ovaries. There was high grade serous carcinoma in the left paratubal soft issues and left tubal lumen. The absence of involvement in the ovarian parenchyma suggests tubal cancer. Lymphovascular invasion was present and high grade serous carcinoma invasion was observed in the uterin serosa. High grade serous carcinoma infiltration was reported in the omentectomy and lymph nodes materials. No tumoral implant was present in the liver and spleen capsule.

No complication developed in the postoperative period. Following discharge, the patient underwent medical oncology consultation for adjuvant chemotherapy. A regimen of carboplatin and paclitaxel was initiated, and six rounds of chemotherapy were administered. Control Ca125 value detected as 12.1. No pathological 18F-FDG uptake was observed in the control PET-CT examination taken 3 months after the operation.



Picture 1. Specimen, left ovary and tuba



Picture 2. Specimen, right ovary and tuba

Discussion

Preoperative diagnosis of primary fallopian tube cancer is rare. In many cases similar to our patient, the disease is asymptomatic and the diagnosis is made postoperatively in woman who had surgery for abdominal pathology [12]. In our patient tubal carcinoma was found to be incidental, consistent with the literature.

Tubal carcinomas are often metastatic rather than primary tumors. Most common metastases arise from primary ovarian carcinomas. It is often difficult to distinguish between tubal cancer and epithelial ovarian cancers because of their similar histologies. In this distinction, it is important that the tubal mucosa is involved and papillary is seen. If both the tuba and ovary are involved, the absence of tumor in the ovarian parenchyma is a finding in favor of tubal cancer. In our case report, ovarian cancer is excluded because there is no tumor in the parenchyma of the ovaries and tumoral infiltration is observed in the bilateral tubal mucosa.

Primary appendix tumors are exceptionally uncommon and carcinomas of the appendix often originate from metastases. Metastatic lesions may present with acute appendicitis, remain asymptomatic or are diagnosed incidentally [13]. In our case metastatic lesions presented as acute appendicitis. Because the patient exhibited acute appendicitis symptoms, an appendectomy was conducted, and serous carcinoma metastases was found.

Diagnosis is confirmed histopathologically, but intraoperative diagnosis is difficult due to rare tumors. Intraoperative diagnosis is thought to be misdiagnosed in approximately 27% of cases [14]. Since our patient had a preoperative diagnosis, full staging surgery was performed. In preoperatively or intraoperatively confirmed cases, cytoreductive surgery is the appropriate treatment opinion [15].

It is often diagnosed in advanced stage due to preoperative diagnostic difficulties, and detected incidentally in high stages. The patient with appendix involvement and carcinoma infiltration in the omentum and lymph nodes was diagnosed as FIGO stage 3C in the staging surgery.

Adjuvant chemotherapy plays an important role in the management of primer tubal carcinoma, usually with platinum-based combination chemotherapy [16]. A combination of carboplatin paclitaxel chemotherapy was started postoperatively and the patient received 6 cycles of chemotherapy regimen.

Conflict of interest: No conflict of interest was declared by the authors.

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Informed consent: Written informed consent was obtained from the patient.

Authors' contributions to the article

P.H. and M.A.O. have constructed the main idea and hypothesis of the study. They developed the theory and arranged/edited the material and method section, have done the evaluation of the data in the Results section. Discussion section of the article written by P.H. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

Case Report

Pamukkale Medical Journal
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A puzzling case presenting as a polypoid mass in the cecum in an adult patient: appendiceal intussusception

Erişkin bir hastada çekumda polipoid kitle olarak prezente olan şaşırtıcı bir olgu: apendiks intussusepsiyonu

Erdem Çomut, Hande Karabaş, Utku Özgen, Murat Özban, Neşe Çallı Demirkan

Posted date:23.03.2023 Acceptance date:24.04.2023

Abstract

Appendiceal intussusception is a rare condition in an adult patient and may not be initially considered in the differential diagnosis clinically or radiologically. It occurs due to an organic cause or idiopathically. We report a 74-year-old patient who had a polypoid lesion in the cecum on colonoscopy with no radiologic imaging and was ultimately diagnosed grossly and histopathologically as appendiceal intussusception. In conclusion, physicians are advised to consider appendiceal intussusception as an alternative diagnosis in all patients presenting with a suspected cecal mass.

Key words: Appendix vermiformis, intussusception, cecum, inverted appendix.

Comut E, Karabas H, Ozgen U, Ozban M, Calli Demirkan N. A puzzling case presenting as a polypoid mass in the cecum in an adult patient: appendiceal intussusception. Pam Med J 2023;16:516-521.

Öz

Apendiks intussusepsiyonu yetişkin bir hastada nadir görülen bir durumdur ve başlangıçta klinik veya radyolojik olarak ayırıcı tanıda düşünülmeyebilir. Organik bir nedene bağlı olarak veya idiyopatik olarak ortaya çıkar. Bu yazıda, kolonoskopide çekumda polipoid lezyon saptanan ve radyolojik görüntüleme yapılmayan, sonuçta gross ve histopatolojik olarak apendiks intussusepsiyonu tanısı konulan 74 yaşında bir hasta sunulmuştur. Sonuç olarak, hekimlere çekumda kitle şüphesi ile başvuran tüm hastalarda apendiks intussusepsiyonunu alternatif bir tanı olarak düşünmeleri önerilmektedir.

Anahtar kelimeler: Appendiks vermiformis, çekum, intussusepsiyon, apendiksin inversiyonu.

Çomut E, Karabaş H, Özgen U, Özban M, Çallı Demirkan N. Erişkin bir hastada çekumda polipoid kitle olarak prezente olan şaşırtıcı bir olgu: apendiks intussusepsiyonu. Pam Tıp Derg 2023;16:516-521.

Introduction

Appendiceal intussusception (AI) is a rare entity that can be difficult to diagnose preoperatively both clinically and radiologically. This entity is defined by the term 'intussusception' and is also referred to as 'appendiceal inversion' in the literature [1]. AI is more common in adults than in children. However, only 5% of all cases of intestinal intussusception occur in adults, the rest are diagnosed in children. Almost all pediatric cases are idiopathic, whereas adult cases usually present with an organic cause [2].

Here, we report a 74-year-old patient who was initially suspected to have a polypoid mass in the cecum on colonoscopic examination and subsequently diagnosed with AI with clinicopathologic correlation during gross and histopathologic evaluation after wedge resection.

Case

A 74-year-old male patient was admitted to an external hospital with abdominal pain and underwent colonoscopy. Colonoscopy revealed a 10 mm diamater polypoid lesion at the appendix orifice at the base of the cecum, which was evaluated in favor of submucosal lipoma. As the patient also complained of inability to urinate, transurethral resection of the prostate

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was performed and the pathology diagnosis was nodular adenomyomatous hyperplasia. The patient was referred to our institute for the lesion described in colonoscopy. Routine blood tests including complete blood count, liver enzymes, electrolytes and CRP were within normal limits. Re-colonoscopy was performed in our gastroenterology clinic and a 25-30 mm mass lesion with an orifice-like appearance at the base of the cecum, covered with normal mucosa was described (Figure 1, 2).

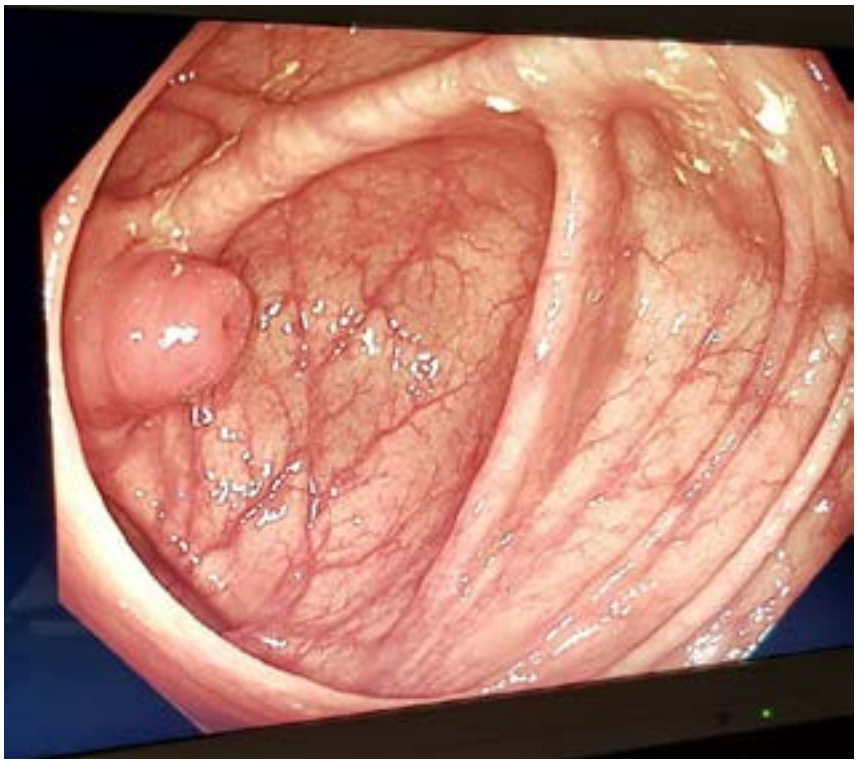

Figure 1. Colonoscopic view of the polypoid lesion located in the cecum with orifice-like appearance in the center

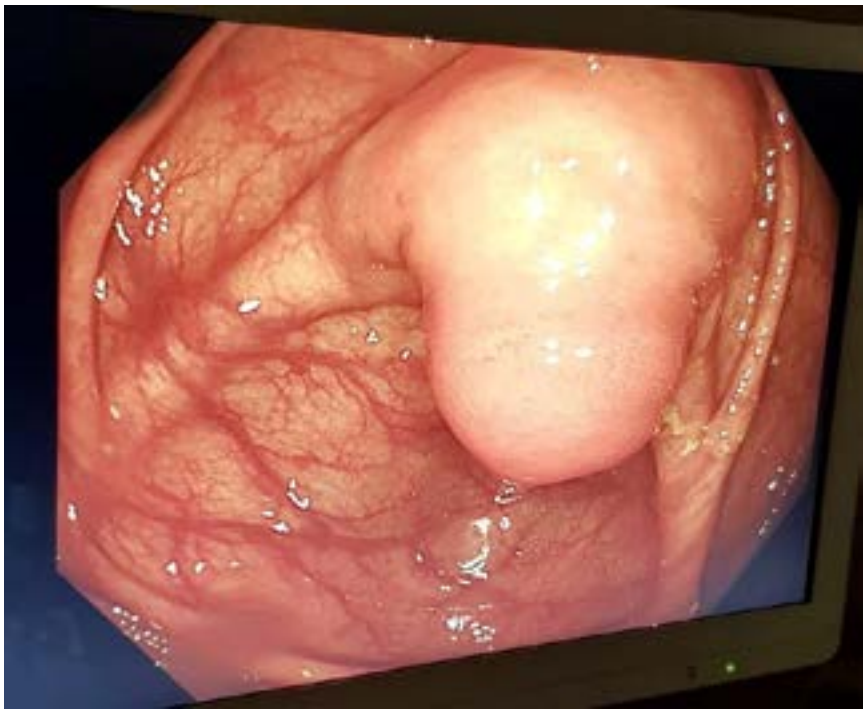

Figure 2. Colonoscopic view of the polypoid lesion from a different angle

A wedge resection including the appendix and partial cecum was performed and the specimen was photographed post-operatively (Figure 3). Gross examination gave the impression of intussusception of the appendix into the cecum, but the possibility of a tumoral mass could not be excluded. The entire specimen was sampled for histopathologic examination. Microscopically, a calcified nodule in the subserosal adipose tissue was noted (Figure 4) and a dome-like appearance covered with mucosa consistent with appendix protruding into the cecum was observed (Figure 5, 6). In the light of these findings and clinicopathologic correlation, the case was diagnosed as AI into the cecum. No post-operative complications were noted and the patient was recommended for annual colonoscopic follow-up.

Figure 3. Post-operative photograph of cecal resection shows a polypoid lesion with an orifice-like area in the center, covered with shiny mucosa

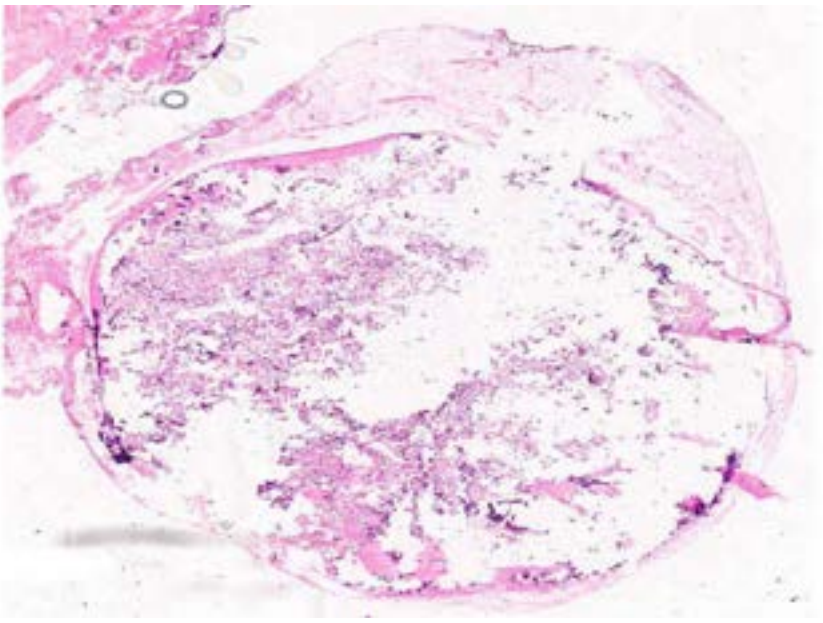

Figure 4. Histopathologic image of hyalinized nodule with foci of dystrophic calcification in subserozal adipose tissue, Hematoxylin&Eosin stain, x5 magnification

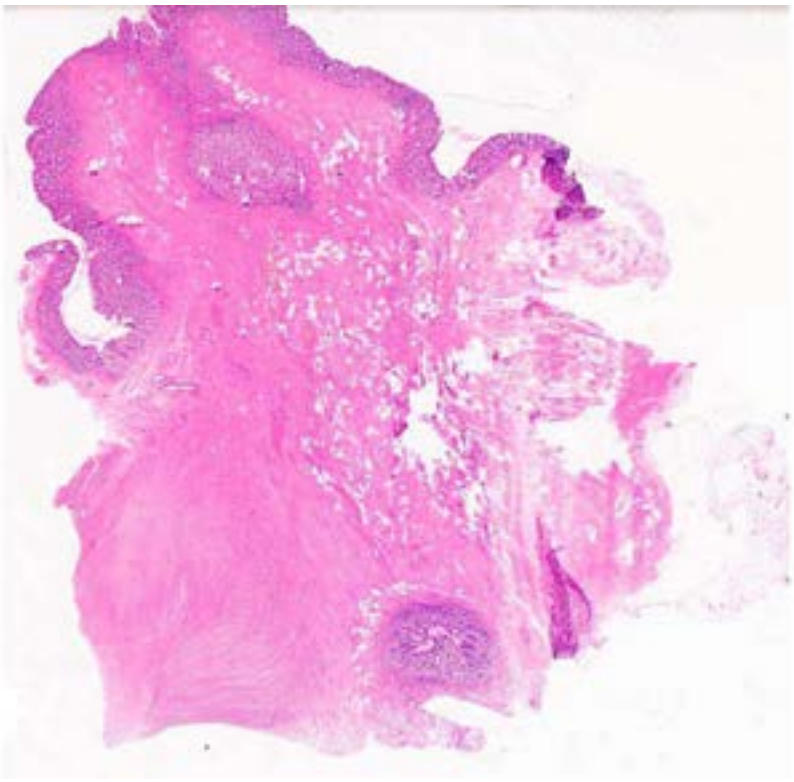

Figure 5. Dome-like appearance covered with mucosa, consistent with the diagnosis of appendiceal intussusception Hematoxylin&Eosin stain, x3 magnification

Figure 6. Closer observation of appendiceal mucosa with lymphoid aggregates Hematoxylin&Eosin stain, x8 magnification

Discussion

The pathogenesis of AI is not fully understood, but parasites, endometriosis, fecalitis, polyps, lymphoid follicular hyperplasia, neuroendocrine tumors, angiodysplasia, adenocarcinoma, mucinous neoplasia, abnormal mobility of the cecum or appendix, mobile mesoappendix and large appendiceal lumen seem to be the main causes of the disease [1, 3]. While endometriosis is the most common cause in adults, inflammation is the leading cause in children [4]. Cases of AI occurring without any of the above-mentioned causes have also been reported in the literature [3]. In our case, the calcified nodule in the subserosal adipose tissue may have caused motility disorder and thus intussusception.

AI may be categorized in 5 different anatomical groups according to where the intussusception starts, from the tip of the appendix to complete invagination of the appendix into the cecum, respectively (Type 1-5) [5]. Our case may be categorized as 'Type 3' because the intussusception starts at the junction of the appendix and the cecum.

Preoperative diagnosis of AI is difficult due to non-specific clinical features. Clinical symptoms of AI are classified in 4 different groups. In the first group, acute appendicitis-like features are seen. Patients in the second group have intermittent pain, vomiting, diarrhea and rectal bleeding. The third group has recurrent abdominal pain, vomiting and rectal bleeding (due to recurrent intussusception and self-reduction). In the fourth group, patients are asymptomatic [6]. Our patient was incidentally diagnosed with a cecal mass during colonoscopy for abdominal pain and belongs to the second group mentioned above in terms of clinical presentation.

Diagnosis of AI can be made by methods such as colonoscopy, barium radiography, ultrasonography and tomography. On computed tomography, target-like appearance or concentric ring sign on axial sections are findings that support the diagnosis. Failure to observe the appendix with a filling defect in the cecum on double contrast barium radiography may suggest the diagnosis of AI. Our patient did not have any radiologic imaging.

AI may appear as a polypoid lesion in the cecum on colonoscopy. A case of AI followed up for more than one decade with a diagnosis of cecal polyp has been reported [3]. In our case, colonoscopy was performed and the lesion gave the impression of a polypoid mass.

On microscopic examination, the dome-like appearance covered with mucosa, associated lymphoid aggregates and ganglion cells in the muscular layer may suggest the diagnosis of AI [1, 7]. In our case, dome-like pattern covered with mucosa, lymphoid aggregates and muscularis propria compatible with appendix were also noted in accordance with the literature.

Treatment of AI may be achieved by reduction of the appendix. However, considering the recurrence rates after reduction, appendectomy is recommended. According to Chaar et al. [5], partial cecal resection, which will be applied with appendectomy instead of simple appendectomy, may be a more ideal treatment. In the same study, Chaar et al. [5] reviewed the literature data on AI and found that appendectomy was performed in 42% of adults and 71% of children. They also noted that ileocecectomy was performed in 27%, right hemicolectomy in 21% and subtotal colectomy in 1% of adults [5]. With the early recognition of intussusception, a large resection of the colon can be prevented. In particular, patients with risk factors such as endometriosis, mucocele, and polyposis should be evaluated in terms of intussusception, and the treatment should be decided according to the patient, etiology and intraoperative findings [4]. Patient age may also influence the choice of treatment. For example, in pediatric patients, a minimally invasive method such as reduction is more favored as the likelihood of neoplasia is very low, whereas in adults, surgical options are more often preferred [8]. In our case, appendectomy and partial cecal resection were performed due to the possibility of a polypoid mass, and thus the incidentally diagnosed subserosal calcified nodule was also removed.

In conclusion, AI is a rare clinical condition that may be encountered especially by general surgeons, pediatric surgeons and gastroenterologists, but its preoperative diagnosis is difficult and its treatment is likely to be performed with colon resections with suspicion of malignancy. We think it is important to be aware of this entity and to consider it in the differential diagnosis.

Conflict of interest: No conflict of interest was declared by the authors.

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Informed consent: Information about the diagnosis and the procedure to be performed was provided to the patient or relatives of the patients, and a confirmation document was signed.

Authors' contributions to the article

N.C.D. and E.C., have constructed the main idea and hypothesis of the study. N.C.D., E.C., H.K., M.O. and U.O. developed the theory and arranged/edited the material and method section. E.C. and H.K., have done the evaluation of the data in the results section. Discussion section of the article written by N.C.D., E.C., H.K., M.O. and U.O. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

Case Report

Pamukkale Medical Journal
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A free floating left atrial ball thrombus treatment with oral anticoagulation

Oral antikoagülasyon ile tedavi edilen serbest yüzen sol atriyal top trombüsü

Harun Akarsu, Havane Asuman Kaftan Tellioğlu, Yiğit Davutoğlu, Gürsel Şen

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Abstract

Transesophageal echocardiography (TEE) revealed a free-floating left atrial ball thrombus in a 56-year-old male patient who was taking warfarin for mechanical prosthetic mitral valve and had recently short-term warfarin interruption for noncardiac surgery and bridging with enoxaparin was admitted to an external center for left abdominal pain and after the detection of spleen and renal infarct, the patient was referred to us for further examination. The patient, who was considered to be at high risk for surgical intervention by the cardiac surgeons, was treated with a warfarin regimen and on the 14th day of the treatment, computed tomography (CT) scan showed that the thrombus disappeared. According to this case report, if patients who have a free-floating left atrial ball thrombus are at high risk for surgical intervention, warfarin therapy can be considered as an alternative to surgery.

Key words: Anticoagulation, echocardiography, thrombus.

Akarsu H, Kaftan Tellioglu HA, Davutoglu Y, Sen G. A free floating left atrial ball thrombus treatment with oral anticoagulation. Pam Med J 2023;16:522-527.

Öz

Dış merkeze karın ağrısı nedeniyle başvurup böbrek ve dalakta enfarktüs saptanması nedeniyle ileri inceleme için hastanemize yönlendirilen, mekanik protez mitral kapak nedeniyle varfarin almakta olan ancak yakın zamanda kalp dışı cerrahi nedeniyle varfarin kesilip enoksaparin ile tedavi öyküsü olan 56 yaşındaki bir erkek hastaya tarafımızca yapılan transözofageal ekokardiyografide (TEE) serbest yüzen sol atriyal top trombüsü saptandı. Kalp cerrahları tarafından cerrahi müdahale açısından yüksek riskli olarak değerlendirilen hasta, varfarin rejimi ile tedavi edildi ve tedavinin 14. gününde bilgisayarlı tomografi (BT) taramasında trombüsün kaybolduğu görüldü. Bu olgu sunumuna göre, serbest yüzen sol atriyal top trombüsü olan hastalar cerrahi girişim açısından yüksek risk altındaysa, cerrahiye alternatif olarak varfarin tedavisi düşünülebilir.

Anahtar kelimeler: Trombüs, antikoagülasyon, ekokardiyografi.

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Introduction

Thrombus that moves freely in the left atrium and is not attached to any wall is called left atrial ball thrombus (LABT), [1]. As previously described by Hisatomi et al. [2], a free-floating thrombi in the left atrium that do not attach to the atrial wall or mitral valve are extremely rare, however as a source of embolism, it can lead to potentially catastrophic consequences.

A free-floating ball thrombus is most commonly detected in mitral stenosis, left atrial dilatation, atrial fibrillation and congestive heart failure. Mitral stenosis and a dilated left atrium induce blood stasis, resulting in thrombus formation, [3]. As it is known, treatment options in LABT are anticoagulant therapy, thrombolytic infusion and surgical treatment.

In this case report, we present a patient with LABT that we treated with oral anticoagulant. Our aim is to present our observations about the approach to be followed in patients with LABT.

To the best of our knowledge, all but one of the patients with left atrial thrombus causing peripheral embolization, reported so far, were treated surgically [4]. Therefore, the case we present is the second case successfully treated with oral anticoagulation.

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Case report

A 56-year-old male patient was admitted to another health center due to left sided and abdominal pain lasting for 2-3 days and abdominal CT was performed in there. On contrast-enhanced abdominal CT, there is an appearance of acute infarction in the cortical area of left kidney, especially in the upper pole and middle part. Also hypodense areas were observed in the anterior and middle parts of the spleen, making us to think infarct areas due to arterial embolism. Therefore, the patient was referred to us as a more advanced center for diagnosis and treatment.

The patient had mechanical mitral valve replacement and atrial septal defect repair performed in 2007. The ECG revealed atrial fibrillation with an avarage ventricular rate of 105 beats/min. He had received an anticoagulation regimen with warfarin since mechanical mitral valve replacement but warfarin therapy was interrupted and bridging was done with enoxaparin due to the bronchoscopy and endobronchial ultrasound processes 15 days ago. Factor Xa was not evaluated during short-term enoxaparin therapy. It was seen from the hospital records of the patient that the preoperative PT-INR value was 1 and when the patient applied to us, it was 1.6. The warfarin therapy was discontinued a week before the operation. After the operation, the patient used warfarin irregularly.

Initially, we performed Transthoracic Echocardiography (TTE) for the investigation of infective endocarditis and thrombus, showed a dilated left atrium (LA) (60 mm), mitral valve area was found as 2.65 cm^2 with a mean gradient of 7 mm Hg. Usual characteristics of a ball thrombus in the LA was not examined in 2 and M-mode echocardiographic examinations. TTE confirmed normal prosthetic valve.

We decided to perform TEE when no evidence of infective endocarditis or thrombus was detected by TTE. TEE suspected the existence of a free floating thrombus sizing 16*13 mm (Figure 1, Video 1). No connection could be demonstrated between the mass and the atrial wall, and the mass was seen to moving freely (Figure 1, Video 2).

We performed cardiac CT for a more detailed analysis of the findings we obtained with TEE. Giant thrombus was observed in the left atrium (Figure 2), and there are diffuse infarcts in both kidneys on CT performed in our center. Moreover, a decrease in density was observed in the spleen parenchyma and infarctions were seen in the middle and lower pole posterior sections. Emergency surgical intervention was not planned for the patient by the general surgeons.

He had productive cough. WBC was 15.98 k/ul and CRP was 294 mg/L in his blood analysis. Therefore, samples for blood cultures and procalcitonin were taken from the patient. Procalcitonin value was 0.395 ng/ml and there was no bacterial growth in blood culture. Additionally, for the investigation of infective endocarditis, Spect-CT performed and no pathological involvement was observed in the cardiac area and around the prosthetic valve material.

Due to very high risk of new embolic events and surgical treatment did not adviced by the cardiac surgeons, intensive anticoagulation therapy was considered as a treatment. In addition, thrombolytic therapy was not preferred primarily because the patient had a recent history of surgical intervention and peptic ulcer. Thus, we adjusted the warfarin therapy by trying to keep the PT-INR:3-4

CT angiography was performed after 14 days of treatment. Free floating or fixed thrombus was seen neither in the LA (Figure 3) nor inside the left atrial appandage.

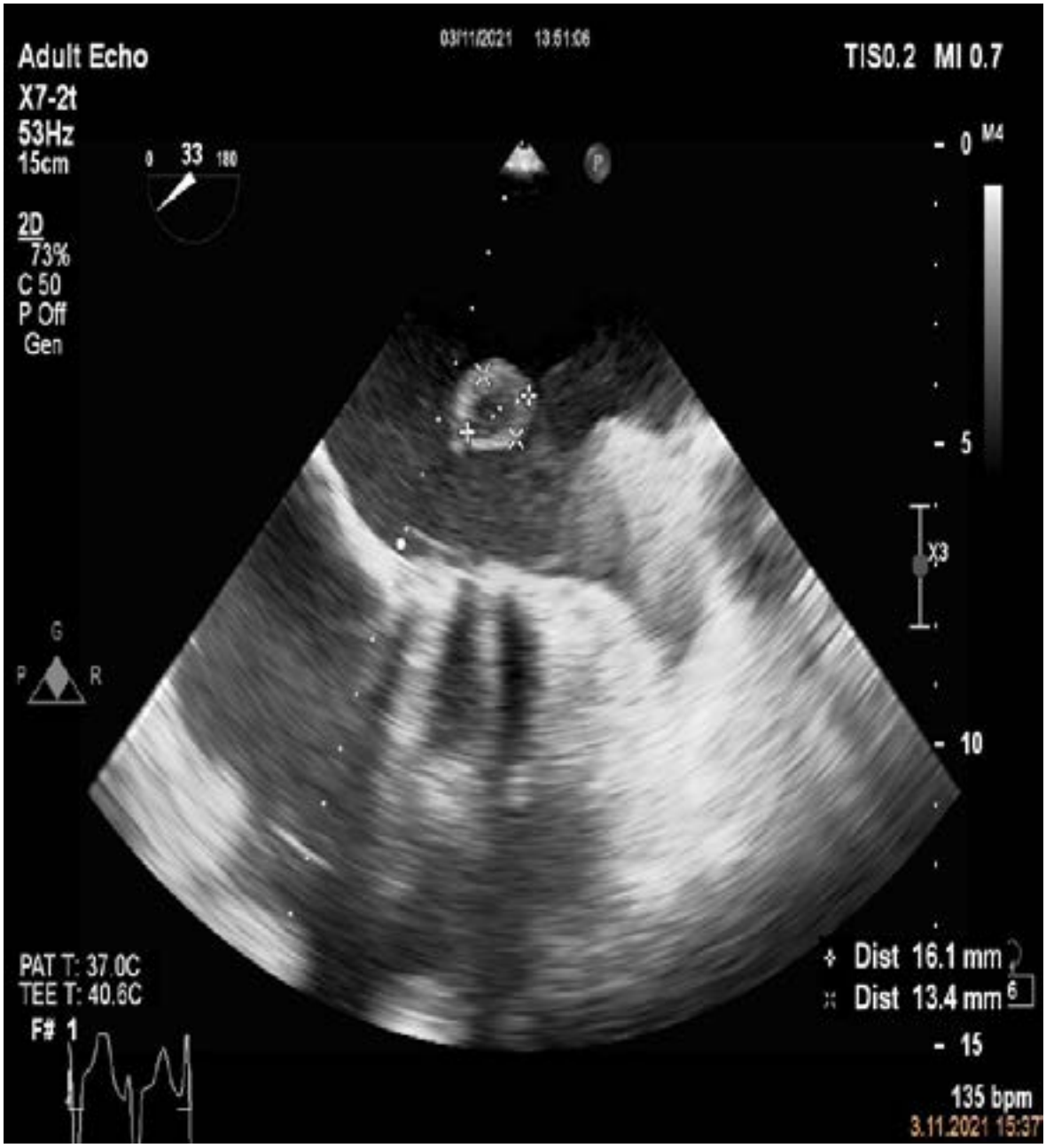

Figure 1. Transesophageal echocardiographic visualization of the thrombus

Video 1. A free-floating ball thrombus in left atrium with TEE
https://www.youtube.com/watch?v=7NVJE7sPXNI

Video 2. Spontaneous echo contrast and thrombus appearance in the left atrial appendage with TEE
https://www.youtube.com/watch?v=macjXFoOglg

Figure 2. The thoracic and abdominal aorta CT angiography showing thrombus in the left atrium

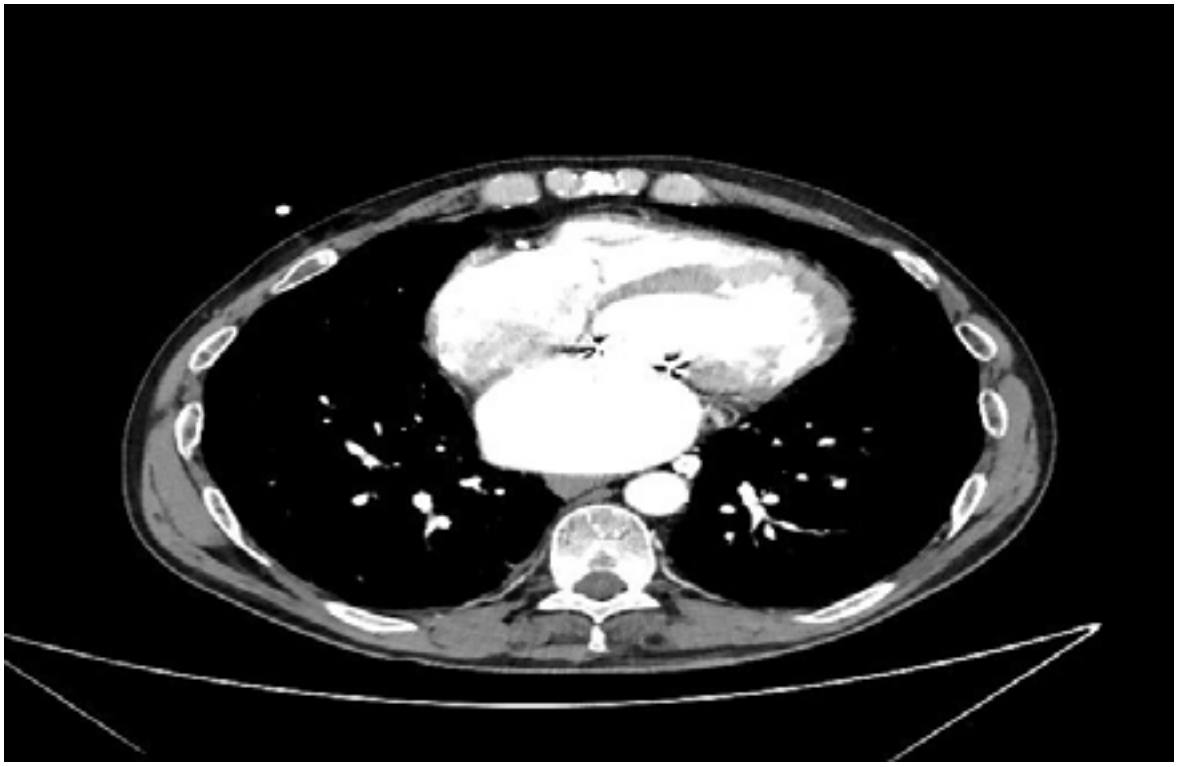

Figure 3. After 14 days control: Thoracic aorta CT angiography revealing complete disappearance of the large atrial thrombus in the left atrium

Discussion

LABT is extremely rare in patients with a mechanical prosthetic mitral valve with INR in the effective range but without valve dysfunction. On the other hand, it has been suggested that left atrial thrombus may occur even after a relatively short interruption of anticoagulant therapy in patients with prosthetic valves [3]. In this case, we considered that the cause of thrombus formation was due to the patient's recent interruption of warfarin therapy.

After diagnosis of free-floating ball thrombus, the recommended treatment method is surgical removal of the thrombus, but thrombolitic and anticoagulation therapy are recommended as alternative treatment methods in high-risk cases with various complications and in patients who refuse surgery.Thrombolytic therapy may represent a viable option for the treatment of LA thrombus to prevent embolization and stroke [5]. However, thrombolytic therapy was not preferred in our case due to the high bleeding tendency and relative contraindications. Our case, which was considered as high risk by surgeons and not suitable for thrombolytic therapy, was treated with anticoagulants. We targeted a similar INR level to the case previously published by Nurra et al. [4], and no hemorrhagic or embolic complications developed.

Another important issue is that if any operation is planned, especially in patients with mechanical prosthetic valves, keeping the warfarin interruption as short as possible and effective bridging treatment without causing bleeding and ischemic complications should be carefully evaluated. A perioperative bridging therapy with a low molecular weight heparin is recommended in patients with mitral valve replacement. During UFH treatment, follow-up with factor 10a level may be required. Anti-Xa activity is a reflection of UFH concentration, but routine application of Anti-Xa testing is currently not evidence-based [6].

In conclusion, we presented a case with left atrial ball thrombus caused infarct formation in the spleen and kidney, whose findings regressed after effective anticoagulation.

Conflict of interest: No conflict of interest was declared by the authors.

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Informed consent: An informed consent form was obtained from the patient. The case was written after obtaining the patient's consent.

Authors' contributions to the article

H.A., H.A.K.T. and Y.D. constructed the main idea and hypothesis of the study. H.A., H.A.K.T. and G.S. developed the theory and edited the material and method section. H.A. and H.A.K.T. have done the evaluation of the data in the Results section. Discussion section of the article written by H.A., H.A.K.T., Y.D. and G.S.

H.A., H.A.K.T., Y.D. and G.S. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.