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Outpatient methotrexate treatment strategies for unruptured tubal ectopic pregnancy

Anrüptüre tubal ektopik gebeliklerde ayaktan metotreksat tedavi stratejileri

Alper Başbuğ [1], Aşkı Ellibeş Kaya [1], Mete Çağlar [2], Ali Yavuzcan [1]

Abstract

Aim: To evaluate the selection criteria for outpatient treatment of unruptured ectopic pregnancy.
Methods: A total of 124 unruptured ectopic pregnancies that had been treated with single-dose intramuscular methotrexate injections during the period from 2012 to 2017 at Duzce University Faculty of Medicine, Training and Research Hospital were evaluated.
Results: Success rate of the medical treatment with single dose methotraxate was 76.61% (n = 95) of 124 patient. The mean duration of hospital stay was shorter in successful medical treatment group (p=0.030). Combining β-hCG level at the first day of methotrexate treatment with size of ectopic focus and/or the presence of fluid in the abdomen significantly increased the sensitivity, specificity and positive predictivity for successfully treated with methotrexate (sensitivity = 70.3%, specificity =86.3%, positive predictive value =80%).
Conclusions: We can choose patients that will be good responder to methotrexate treatment of ectopic pregnancy without hospitalization by initial serum β-hCG values, size of ectopic focus and the presence of fluid in the abdomen.

Key Words: Ectopic pregnancy, methotrexate, outpatient treatment.

Öz

Amaç: Rüptüre olmamış ektopik gebeliğin ayaktan tedavisi için seçim kriterlerini değerlendirmek.
Yöntemler: Düzce Üniversitesi Tıp Fakültesi, Eğitim ve Araştırma Hastanesi'nde 2012-2017 yılları arasında tek doz intramusküler metotreksat enjeksiyonları ile tedavi edilen toplam 124 rüptüre olmamış ektopik gebelik retrospektif olarak değerlendirildi.
Bulgular: Tek doz metotreksat ile medikal tedavi 124 hastanın % 76,61'inde (n = 95) başarılı bulundu. Başarılı olarak tedavi edilen grupta ortalama hastanede kalış süreleri daha kısa idi (p=0,030). Metotreksat enjeksiyonunun 1.günü β-hCG düzeyinin ektopik odak büyüklüğü ve / veya batın içinde sıvı varlığı ile birleşmesi metotreksat ile başarılı bir şekilde tedavi edilmek üzere duyarlılık, özgüllük ve pozitif öngörüyü anlamlı olarak arttırmıştır (duyarlılık= %70,3, özgüllük= %86,3, pozitif kestirim değeri= %80).
Sonuç: Başlangıç serum β-hCG seviyeleri, ektopik odak büyüklüğü ve batında sıvı varlığı ile metotreksat tedavisine iyi yanıt verecek hastaları, hastane yatışı gerektirmeden seçebiliriz.

Anahtar Sözcükler: Ektopik gebelik, metotreksat, ayaktan tedavi.

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Introduction

Ectopic pregnancy (EP) occurs when developing blastocyst becomes implanted at a site other than the endometrium of the uterine cavity and EP is a significant cause of morbidity and mortality in the first trimester of pregnancy [1, 2]. It is managed expectantly, medically (with methotrexate (MTX) or surgically. While surgical approaches are the mainstay of treatment, advances in early diagnosis have facilitated the introduction of medical therapy with MTX [3].

As a single or multiple intramuscular injections, MTX is used in the treatment of EP [4-6]. A number of accepted protocols with injected MTX exist for the treatment of EP. Specifically, treatment with a systemic single dose of MTX has become a safe and effective management with promising results [7].

Further clinical experience with MTX and the increasing use of guideline-based protocols have increased the success of medical treatment of EP [8]. Medical management of ectopic pregnancy is generally considered to be less expensive than surgery [9, 10]. A major reason of low cost of medical treatment of EP is the reduced length of hospital stay. Outpatient medical treatment of unruptured EP results in low consumption of the resources [11]. In our country, no study has been done regarding to cost of the medical treatment of EP but some studies that have previously reported the mean length of hospital stay after medical treatment of EP and this time ranged between 4 and 10 days [12, 13].

The aim of this study was to determine factors associated with the success or failure of response to treatment with single dose MTX protocol in women with tubal EP and to determine the criteria for outpatient treatment of unruptured EP.

Material and methods

The study was approved by the local ethics committee (2017/12) and the study protocol adhered to the tenets of the Declaration at Helsinki. Written consent could not be taken due to the retrospective design of the study.

In our study, all consecutive cases of EP treated with an intramuscular single dose of 50 mg/m^2 MTX therapy from January 2012 to January 2017 in the Department of Obstetrics and Gynecology at Duzce University Faculty of Medicine were enrolled.

The EP diagnosis was based on atypical trends of β-hCG (human chorionic gonadotropin) levels and the absence of intrauterine pregnancy according to transvaginal ultrasound (TVUS).

Inclusion criteria were: female patients whose age are 18 years or older with diagnoses of unruptured tubal EP, absence of hepatic, hematologic, or renal diseases, hemodynamically stable patients, who were treated with a single dose 50 mg/m^2 intramuscular MTX.

Exclusion criteria were: female patients younger than 18 years, hemodynamically unstable patients, other locations of EP (abdominal, ovarian, cervical, cesarean scar), women who treated without a single dose 50 mg/m^2 intramuscular MTX, patients with renal and hepatic disease, immunodeficiency, active pulmonary disease and peptic ulcer. In addition, patients with MTX toxicity after treatment such as macular rush on the scalp, the neck, and the chest regions were excluded from the study.

After considering the inclusion and exclusion criteria, A total of 124 women with EP were included in the study and these patients were divided into 2 groups: those treated successfully with systemic MTX intramuscular administration (Group 1, n= 95) and those have failure after systemic MTX intramuscular administration (Group 2, n=29).

Demographic data such as age, body mass index (BMI), parity, last menstrual period date , current pregnancy history, previous history of infertility treatment, previous history of EP, use of intrauterine contraceptive device (IUCD) and clinical presentation such as abdominal pain, vaginal bleeding, and amenorrhea, serum β-hCG levels on days 1, 4, and 7, number of MTX doses; and the need for surgical therapy were recorded. BMI (kg/m^2) was calculated using the following formula: weight in kilograms divided by the square of height in meters.

Study Protocol

The patients received intramuscular MTX at a dose of 50 mg/m^2 of body-surface area, which was calculated with a calculator that uses height and actual body weight has been described in detail as MTX treatment protocol for tubal EP [14, 15]. If the decrease in β-hCG levels between the days 4 and 7 was more than 15 percent, the concentration of β-hCG was monitored weekly until β-hCG was undetectable. If the decrease in β-hCG between the days 4 and 7 was less than 15 percent, a second intramuscular dose of MTX 50 mg/m^2 was administered and if the decrease in β-hCG between the days 7 and 14 was more than 15 percent, the concentration of β-hCG was monitored weekly until the β-hCG was undetectable. If the β-hCG level did not decline as described in the study protocol for tubal EP, or if the cardiac activity was still present, patient presents with abdominal pain and have obvious signs of hemoperitoneum, the medical treatment was considered to have failed and surgical procedures were performed.

Statistical Analysis

The descriptive statistics for continuous variables were expressed in mean ± standard deviation or median (minimum-maximum), while nominal variables were expressed in the number and percentage (%). The significance of the difference between the mean values of the groups was evaluated using the Student's t-test, while the significance of the difference in the median values was evaluated using the Mann-Whitney U test. Categorical data was compared by Chi-square distribution. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS for Windows version 22 software (SPSS Inc., Chicago, IL, USA).

Results

A total of 124 women were enrolled in this trial. Considering the all 124 patients, in 95 patients (% 76.6) EP was completely resolved with MTX administration and in 29 patients (% 23.4) there was a need for subsequent operations because of rupture of tubal EP or failure of MTX treatment. Therefore, the success rate of the single-dose MTX therapy for EP was 76.1% (95/124).

In the success group, 83 patients (%87.4) were cured with a single dose of MTX, and the remaining 12 patients (%12.6) were cured with a second/repeated dose of MTX. 29 patients (%23.4) underwent surgical treatment after an average of 4.5 ± 2.9 days (range 2-8 days). The second doses of MTX were administered after a mean of 7.6 ± 0.7 days when needed. Four of the patients (33.3%) who had received the second dose of MTX required surgical treatment.

There were no significant differences between two groups regarding maternal age (p=0.061), gravidity (p= 0.703), parity (p= 0.830), BMI (p=0.311) and gestational age (p=0.570) (Table 1).

The mean pretherapeutic β-hCG level for successfully treated with MTX (Group 1) was 2073.7± 751.5 mIU/mL. The doses of MTX used ranged from 75 mg to 95 mg with a mean of 82.2 ± 7.6 mg. In patients in whom medical treatment failed, the

β-hCG level at the first day of the injection was 3167 ± 316.7 mIU/mL, 3362.3 ± 378.0 mIU/mL at day 4 and 3002.5 ± 368.2 mIU/mL at day 7. β-hCG levels were statistically higher in Group 2 at day 1, day 4 and day 7 (p=0.012). Size of ectopic focus was greater in Group 2 as 38.4±23.7 mm vs 29.9 ± 14.8 mm (p= 0.033). There was also statistically significant difference between the two groups in terms of the presence or absence of fluid in the abdomen by TVUS (p=0.041). The rate of failure of medical treatment in patients with fluid detected during TVUS was 37.9% as seen in 11 patients, while 23.1% in the non-fluid group as seen in 22 patients (p = 0.041).

Table 1: Characteristics of the patients.

Characteristics	Group 1 (success group) n=95	Group 2 (failure group) n=29	p
Age (year) [μ]	34.6±4.9	30.8±5.4	0.061
BMI ((kg/m2) [μ]	29.4±4.3	28.2±8.2	0.311
Gravidity (n) [¥]	2 (1-5)	2 (1-5)	0.703
Parity (n) [¥]	1 (0-3)	1 (0-4)	0.830
Gestational ages (weeks) [μ]	6.0±1.7	6.5±1.2	0.570
D1 β-hCG level (mIU/mL) [μ]	2073.7±751.5	3167±316.7	0.012
D4 β-hCG level (mIU/mL) [μ]	2136.2±336.7	3362.3±377.9	0.012
D7 β-hCG level (mIU/mL) [μ]	1637.6±348.5	3002.5±368.2	0.012
Size of ectopic focus (mm) [μ]	29.9±14.8	38.4±23.7	0.033
Presence of fluid in the abdomen [α]	22 (23.1)	11(37.9)	0.041
Duration of hospital stay (day) [μ]	4.0±2.2	7.1±2.4	0.030

[μ]: mean ± standard deviation, [¥]: n (range), [α]: n (%), D1: 1st day of first MTX injection, D4: 4th day after MTX injection, D7: 7th day after MTX injection.

The mean duration of the hospital stay was 4.2 ± 1.9 days and 6.9 ± 2.1 days in Group 1 and Group 2, respectively (p= 0.030).

Cut-off values discriminating treated with MTX successfully from failure of MTX treatment by using Receiver Operating Characteristics (ROC) curve analysis of β-hCG levels at the first day of MTX treatment and size of ectopic focus were 2034 mIU/mL (AUC=0.628) and 25.5 mm (AUC=0.560), respectively (Figure 1).

Figure 1: ROC curves for the prognostic value of initial hCG level (mIU/mL) and size of ectopic focus (mm).

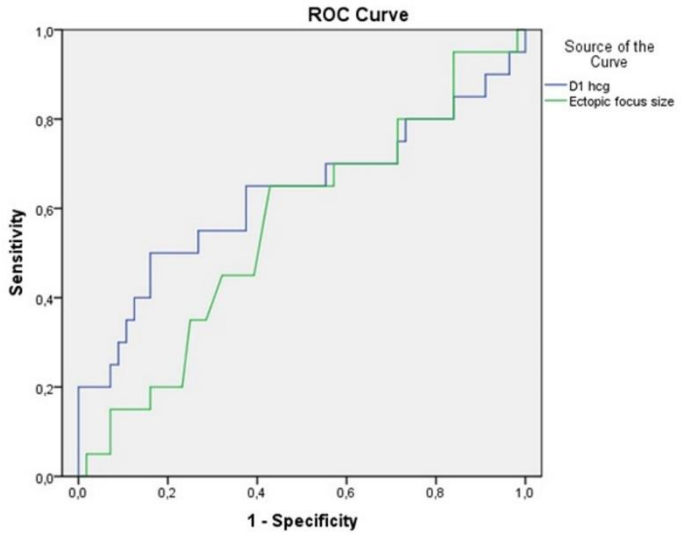

Table 2 represents sensitivity, specificity and the performance of β-hCG levels at the first day of MTX treatment, size of ectopic focus and the presence of fluid in the abdomen for assessing the diagnostic efficiency alone and joint screening of the three variables for discriminating successful MTX treatment and failure of MTX treatment. β-hCG levels at the first day of MTX treatment showed a moderate sensitivity with 56.9% and specificity of 59.1% while testing the size of ectopic focus alone indicated a moderate sensitivity with 43% and specificity of 68.1% and the presence of fluid in the abdomen showed a moderate sensitivity with 43.5% and specificity of 56.5%. Combining β-hCG levels at the first day of MTX treatment with size of ectopic focus and/or presence of fluid in the abdomen significantly increased the sensitivity, specificity and positive predictive values up to 70.3%, 86.3% and 80.0%, respectively (Table 2).

Table 2. Diagnostic performance of β-hCG level at the first of the treatment when combined with size of ectopic focus and presence of fluid in the abdomen discriminating successful MTX treatment.

Characteristics	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
D1 β-hCG level	56.9	59.1	53.4
Size of ectopic focus	43.0	68.1	59.4
Presence of fluid in the abdomen	43.5	56.5	51.5
D1 β-hCG level + Size of ectopic focus	66.1	77.2	71.1
D1 β-hCG level + Size of ectopic focus + Presence of fluid in the abdomen	70.3	86.3	80

D1: 1st day of first MTX injection.

Discussion

Medical treatment of EP with MTX has been performed since 1980 [16]. Success rates and factors affecting the success of medical treatment and have been shown by previous studies [17-19]. The overall success rate of single-dose MTX therapy in this study was 76.1%, which is comparable with the success rates reported in other studies. We found that initial serum β-hCG levels, size of ectopic focus and the presence of fluid in the abdomen were the most important predictors of successful medical treatment. Unlike other studies, we also evaluated the duration of hospital stay of patients, in which medical treatment was successful 4.03 day and 7.08 day for which MTX treatment failed. The long duration of hospital stay of patients associated with failure of medical management and subsequent surgical treatment.

Today, there is no consensus on the threshold of β-hCG above which MTX is contraindicated. Several studies found that initial β-hCG levels of 1000-5000 IU / ml are associated with treatment failure [5, 20, 21]. In our study, we found that the initial levels of β-hCG above 2000 mIU / ml were associated with failure of single dose MTX treatment. As with β-hCG, there is no consensus on the size of the ectopic focus that affects success rate of medical treatment [22, 23]. Some authors use the 25 mm ectopic focus size as the threshold while others use 35 mm to predict the success rate of medical treatment with single dose of MTX. In our study, we found that the size of ectopic focus greater than 25 mm related with failure of single dose MTX treatment.

Although there have been many studies evaluating the efficacy of the expectant, medical or surgical management options, there are only a small number of studies that have evaluated the cost of treatments for EP [24]. The ambulatory and hospital costs of care for ectopic pregnancy ranged from 1,700

euros to 1900 euros when the first-line treatment was surgical whereas these costs amounted to about 700 euros for subacute EP treated with MTX [9]. The cost of treating ectopic pregnancy depends on length of hospital stay. MTX resulted in a low rate of hospitalization and a short hospital stay and cost-effective [11].Some studies published in our country showed that the length of hospital stay varies between 4 and 10 days [12, 13]. Similarly in our study we found that the mean length of hospital stay was long for patients treated with MTX. Lecuru et al [11] followed 55 women treated with MTX and they found that management has naturally been significantly different for the medical and sugical treatment options, with a high rate of outpatient and ambulatory care in medically traeted group. Hospital stay was significantly shorter (0.6 ± 1.7/day) in medically treated group.

There is no established true cut-off initial β-hCG levels and size of ectopic focus for suitable candidate for outpatient medical management of ectopic pregnancies. The decision to proceed with medical or surgical management depends on the clinician's discussion with the patient [25]. In this study, we aimed to define the selection criteria to determine which patients can be treated as outpatient and shorten the length of hospital stay of hospitalized patients. We think that the combination of cut off values of the initial serum β-hCG levels, size of the ectopic focus and the absence of the abdominal fluid use for the prediction of successfully outpatient treatment for EP and represented study showed that; initial serum β-hCG ≤ 2000 mIU/mL, size of the ectopic focus ≤ 25 mm and if absence of the abdominal fluid successfully outpatient treatment of EP was feasible.

Retrospective nature and small sample size were the weaknesses of the study. We decided to focus on hospital stay in terms of cost in this study but it is important to know that there are other factors that may also affect the cost such as patient travel and time off work. There will be a need for prospective studies with larger populations to support our findings.

Conclusion

MTX therapy is simple and if initial β-hCG value less than 2000 mIU/mL, size of ectopic focus smaller than 25 mm and absence of abdominal fluid it does not require hospitalization. We can choose patients that will be good responder to MTX treatment of EP by initial serum β-hCG values, size of ectopic focus and presence of fluid in the abdomen. Better results can be expected from these patients and the outpatient MTX option may result in low consumption of resources.

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The role of COX-2 gene variants on the disease mechanism of inflammatory bowel disease in a Turkish population

Türk toplumundaki inflamatuar bağırsak hastalığının hastalık mekanizmasında COX-2 gen varyantlarının rolü

Elif Sinem İplik [1], Resul Kahraman [2], Barış Ertuğrul [3], Gonca Candan [3], Arzu Ergen [3], Bedia Çakmakoğlu [3]

Abstract

Aim: Inflammatory bowel disease has two major types: Crohn's disease and ulcerative colitis that occur in the gastrointestinal tract with unknown etiology. COX-2 has important role on carcinogenesis process including colon cancer supporting the tumor growth. COX-2 was also known due to its ability to change homeostasis on colonic mucosa in inflammatory cells on patients who have inflammatory bowel disease. In this study, we have aimed to find a linkage between inflammatory bowel disease and COX-2 in a Turkish population.

Methods:A total of 106 patients,42 with Crohn's disease and 64 with ulcerative colitis and 121 healthy control subjects were included the study. Gene variants of COX-2-765G→C and COX-2-1195A→G were analyzed by polymerase chain reaction and restriction fragment length polymorphism techniques.

Results: The results demonstrated that COX-2-1195A→G gene variants AA carriers were statistically found in high level on patients with both ulcerative colitis (p=0.001) and Crohn's disease (p=0.008). In contrast, AG genotype and G carriers were statistically found higher in control group (Crohn's disease, p=0.005 for AG and p= 0.008 for G; ulcerative colitis, p=0.001 for AG and p=0.001 for G).

Conclusion: In this research, we have observed important and questionable results between inflammatory bowel disease and COX-2, especially COX-2-1195A→G gene variants AA carriers in a Turkish population. Researches need to focus on their local roles on inflammatory bowel disease pathogenesis with large sample size.

Keywords: COX-2, gene variants, Crohn's disease, ulcerative colitis

Öz

Amaç: İnflamatuar bağırsak hastalığı, gastrointestinal sistemde etiolojisi tam olarak bilinmeyen bir hastalık grubu olup, Crohn hastalığı ve ülseratif kolit olmak üzere iki önemli tipe ayrılmaktadır. COX-2 kolon kanserinin de dahil olduğu karsinogenez prosesinde rolü olan ve tümör gelişimine katkı sağlayan bir mediatördür. Aynı zamanda, inflamasyon meydana geldiğinde kolonik mukoza üzerindeki stabiliteyi değiştirdiği bilinmektedir. Bu amaçla, çalışmamızda inflamatuar barsak hastalığı ile COX-2 ilişkisinin Türk kökenli kişiler üzerinde araştırılması amaçlanmıştır.

Yöntemler: Çalışmaya 42 Crohn ve 64 ülseratif kolitli hasta olmak üzere toplam 106 hasta) ve 121 sağlıklı kontrol dahil edilmiştir. COX-2 -765G→C ve COX-2 -1195A→G gen varyantları polimeraz zincir reaksiyonu ve restriksiyon parça uzunluk polimorfizmi teknikleri kullanılarak analiz edilmiştir.

Bulgular: COX-2-1195A→G gen varyantı AA taşıyıcılarının istatistiksel olarak hasta grubunda (Crohn hastalığı için p=0,008 ve ülseratif kolit için p=0,001) kontrol grubuna göre yüksek bulunmuştur. Buna karşılık olarak AG genotipi ve G taşıyıcıları da kontrol grubunda anlamlı olarak yüksek bulunmuştur (Crohn hastalığı: p=0,005 AG için ve p= 0,008 G için; ülseratif kolit: p=0,001 AG için ve p=0,001G için).

Sonuç: Çalışmada Türk kökenli kişiler üzerinde, inflamatuar bağırsak hastalığı ve COX-2 arasındaki ilişkiye dair COX-2-1195A→G AA taşıyıcıları gibi önemli ve araştırılması gerekli soruları beraberinde getiren bulgular elde edilmiştir. Hasta sayısının arttırılarak ek çalışmalar ile hastalık patogonezindeki rolünün tam olarak araştırılması gerektiği düşünülmektedir.

Anahtar Kelimeler: COX-2, gen varyantları, Crohn hastalığı, ülseratif kolit.

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Introduction

Inflammatory bowel disease (IBD) is a common condition and chronic inflammatory disease of the gastrointestinal tract with its unclear etiology such as environmental factors, genetics and immunity [1]. IBD has two major phenotypes which have been identified with their clinical and histopathological features: Crohn's disease (CD) and ulcerative colitis (UC). They have been also characterized by recurrent episodes of remission and exacerbation. According to recent studies, IBD could be resulted as colorectal cancer that's one of the reasons why the diseases have still some important questions to solve using genetic factors [2-4].

IBD has different processes in its types such as clinical course and response to the treatment. There are several studies that support these genetic differences could cause the diversities on CD and UC [5]. Nevertheless, UC and CD might be treatable by several medications and surgery [6-8].

To take precautions and prevent the colorectal cancer and related disease, researches still need to focus on underlying mechanisms of the diseases including their genetic roles. As discussed, it is important to understand and solve the etiology of IBD not only because it affects the daily life but also it could end up colon cancer.

Cyclooxygenase (COX) is an enzyme that has important role such as rate-limiting step on not only biosynthesis of prostaglandins and thromboxanes but also lipid mechanisms. COX has two major isoforms as COX-1 and COX-2. While COX-1 is to be found in normal tissues, COX-2 belongs to the expression of some hormones, cytokines and growth factors [8-10]. COX-2 and its relation to carcinogenesis are well known in several cancers including colon cancer. COX-2 leads to tumor growth by increasing the expression vascular endothelial growth factor (VEGF) of colon cancer cells [11]. COX-2-765G→C and COX-2-1195A→G are mostly studied as promoter gene variants. Their polymorphisms could cause to modify COX-2 transcription and mRNA levels [12].

We hypothesized that COX-2 gene polymorphisms which is well known for several cancers, might affect by facilitating immune response shift in tumor microenvironment and it might be associated with IBD by altering the inflammatory response. For this purpose, we aimed to show the relations of COX-2 -765G→C and COX-2 -1195A→G polymorphisms on IBD in a Turkish population for the first time.

Material and methods

Subjects

A total of 227 subjects including 106 patients suffering from IBD (42 CD and 64 UC) and 121 healthy control subjects were studied in our research after obtaining written informed consent from the participants and approval from Istanbul University's Ethics Committee based on World Medical Association Declaration of Helsinki.

Demographic data including age and gender were evaluated. Biochemical parameters i.e. serum albumin (mg/dL), C-reactive protein (CRP) (mg/L) and sedimentation rate (mm/h) were measured from the blood samples. In addition, pathological features of the patients with UC and CD in relation with the disease extension, localization and behavior were analyzed. Clinical and demographic data of the patients and the control group are given in Table 1.

Amplification of DNA and analysis of digested products

Blood samples from all patients and the control were collected and genomic DNA was extracted from peripheral whole blood by Invitrogen Purelink Genomic DNA technique. Polymerase chain reaction (PCR)/restriction fragment length polymorphism (RFLP) analysis was performed for the detection of the gene variants of COX-2 -765G→C and COX-2 -1195A→G. The primers to amplify genes and the enzymes to detect digested reaction are given in Table 2. The products were analyzed on 2% agarose gel stained with ethidium bromide and examined under transillumination.

Statistical analysis

The statistical analyses were performed using the SPSS 21.0 statistical software package (SPSS, Chicago, IL). P values lower than 0.05 were assumed to be statistically significant. We compared the cases and the controls in biochemical parameters using Student's t test. One-way Anova test was used to investigate the biochemical parameters between the genotypes. Categorical variables such as genotypes and alleles were compared using Chi- Square ($\chi 2$) test. The Odds Ratios and the confidence intervals were calculated as an estimate of the relative risk.

Table 1: Clinical and demographical parameters of the patients.

Clinical Parameters	UC (n=64)	CD (n=42)	All patients (n=106)	Controls (n=121)
Age (year) [β]	42.2±15.3	39.8±9.7	42.6±13.5	40.3±9.9
Sex(Male/Female)	31/33	19/23	50/56	30/91
CRP (mg/L) [β]	1.0±3.3	1.2±1.9	1.1±2.9	NA
Albumin (mg/dl) [β]	5.0±4.7	4.3±0.4	4.7±3.6	NA
Sedimentation (mm/h) [β]	26.6±20.4	27.8±21.7	27.1±20.8	NA
Demographical Parameters				
Disease extension in UC			NA	NA
Proctitis [α]	30 (47.6)	NA		
Left-sided colitis [α]	15 (23.8)	NA		
Extensive colitis [α]	18 (28.6)	NA		
Disease localization in CD			NA	NA
Ileal [α]	NA	16 (38.1)		
Ileocolonic [α]	NA	21 (50)		
Colonic [α]	NA	5 (11.9)		
Disease behavior in CD			NA	NA
Inflammatory [α]	NA	20 (47.6)		
Penetrating [α]	NA	9 (21.4)		
Stricturing [α]	NA	12 (28.6)		
Penetrating & stricturing [α]	NA	1 (2.4)		

[β]: mean±standard deviation, [α]: n(%)
n: number of subjects, CRP: C reactive protein, CD: Crohn's disease, UC: ulcerative colitis, NA: not applicable.

Results

There were no significant differences between the groups in terms of age (p=0.070).

In Table 3, the genotype and allele frequencies of COX-2-765 G→C and COX-2-1195A→G are given. Although there were no statistically significant differences on COX-2-765 G→C genotype and allele frequencies (p=0.)90, COX-2-1195A→G have come up statistically significant results on patients with both UC and CD that carrying the AA genotype compared with the control group [(all patient/control=(p=0,001; $\chi 2$ =16.70; OR=3.17; 95%Cl=1.80-5.58); CD/control=(p=0.008; $\chi 2$ =6.92; OR=2.71; 95%Cl=1.27-5.79); UC/control=(p=0.001; $\chi 2$ =14.06; OR=3.54; 95%Cl=1.79-7.00)].

In the control group, AG genotype and G allele carriers were statistically higher with respect to the patient groups [AG= (p=0.001; $\chi 2$ =19.63; OR=2.26; 95% Cl=1.52-3.35), G= (p=0.001; $\chi 2$ =16.70; OR=2.04; 95% Cl=1.41-2.95)] CD [AG=(p=0.005; $\chi 2$ =7.91; OR=1.95; 95% Cl=1.14-3.34), G=(p=0.008; $\chi 2$ =6.92; OR=1.82; 95% Cl=1.09-3.02)] and for UC [AG= (p=0.001; $\chi 2$ =16.61; OR=2.52; 95% Cl=1.50-4.22), G=(p=0.001; $\chi 2$ =14.06; OR=2.21; 95% Cl=1.38-3.57)].

When we examined the patient groups between UC and CD, there was no significant difference in terms of distribution of both genotypes (p=0.20). Each of the patient and control groups was checked for all polymorphisms by the Hardy-Weinberg equilibrium. According to Hardy-Weinberg equilibrium, the frequency of COX-2-1195A→G genotypes in the control subjects was not in the Hardy-Weinberg equilibrium.

Table 2. Procedure of the primers to amplify DNA and analysis of digested products.

Gene variants	COX-2 765G→C	COX-2 1195A→G
Primers	5'-TATTATGAGGAGAATTACTCGC-3'	5'-CCCTGAGCACTACCCATGAT-3'
	5'-GCTAAGTTGCTCACAGAGAT-3'	5'-GCCTTCATAGGAGATACTGG-3'
Enzyme	Aci I	Pvu II
Product	CC - 301 bp GG - 209 and 100 bp GC - 309, 209,100 bp	AA - 273 bp AG - 273 and 220bp GG - 220 bp

Table 3: Distribution of COX-2-765 G→C and COX-2-1195A→G gene variants in the study groups.

	UC (n=64)	**CD (n=42)**	**All Patients (n=106)**	**Controls (n=121)**
COX-2 765 G→C				
GG $^{\alpha}$	39 (60.)9	28 (66.7)	67 (63.2)	73 (60.3)
CC $^{\alpha}$	1 (1.6)	3 (7.1)	4 (3.8)	5 (4.1)
GC $^{\alpha}$	24 (37.5)	11 (26.2)	35 (33)	43 (35.5)
G $^{\alpha}$	102 (59.3)	67 (59.5)	169 (59)	189 (56.1)
C $^{\alpha}$	26 (40.6)	17 (40.4)	43 (40.5)	53 (43.8)
COX-2 1195 A→G				
AA $^{\alpha}$	49 (76.6)**	30 (71.4)***	79 (74.5)*	58 (47.9)
GG $^{\alpha}$	2 (3.1)	1/ (2.4)	3 (2.8)	1 (0.8)
AG $^{\alpha}$	13 (20.3)	11 (26.2)	24 (22.6)	62 (51.2)*,**,***
A $^{\alpha}$	111 (86.7)	71 (84.5)	182 (90)	178 (73.5)
G $^{\alpha}$	17 (13.3)	13 (15.5)	30 (10)	64 (26.5)*,**,***

$^{\alpha}$: n(%)
n=number of subjects, CD: Crohn's disease, UC, ulcerative colitis, *:all patients/control, **:CD/control, ***:UC/ control

Discussion

IBD is well known with their linkage between colorectal cancer [13, 14]. To have both UC and CD, this condition might lead to cancer in a long-term period [15, 16]. COX-2 is an enzyme that has a lot of regular activities in biosynthesis and lipid mechanisms. COX-2 also has the ability to let tumor growth by its potential of being expressed VEGF of colon cancer [11]. It is important to diagnose and have suitable treatments for IBD not only because it has not ignorable effect on daily life but also it has a big risk for colorectal cancer. COX-2 is lightening up with his potential for promising target to treatment options for colorectal cancer [17, 18]. COX-2 and IBD are underlined the colorectal cancer in somehow with their unclear role on the pathway. We have wanted to seek a correlation between them in Turkish patients.

There are several connections with IBD and colorectal cancer, colorectal cancer and COX-2, IBD and COX-2 in the way of directly or indirectly. If COX-2 might be potential of being the candidate for early prediction for colorectal cancer for whom suffering from IBD and have COX-2 related polymorphisms. In addition, polymorphisms are important for prediction not only because it results quickly in the laboratory analysis by simple samples of the patients such as blood; but, also it is cheaper than other analyzes such as biopsies. That is the reason of importance of finding a risk linkage for IBD and COX-2 to avoid colorectal cancer as prevention. One way of the mechanism with COX-2 and IBD is related with the inflammation. According to our results, it is hypothesized that tumor microenvironment and COX-2 interaction are related with IBD's etiology. COX-2 gene variants might affect the inflammatory response.

Due to our results, COX-2-1195A→G AA genotypes ended up statistically a risk factor not only for all patients but also between UC and CD. In addition, our results claim that AG genotype and G allele have protective role. There are studies that have supportive result for our study such as COX-2 was found to strongly induce the inflammatory cells of IBD patients on their colonic mucosa [19, 20]. Singer et al. [20] have worked on both COX-1 and COX-2 expression in all IBD cases (including UC, CD and healthy tissues). Their results ended up important results by COX-2 expression in UC and CD patients. Singer also hypothesized that COX-2 expression level could be linked to turn the healthy cells to carcinogenesis process [20]. When gastrointestinal homeostasis becomes weak, it results in adverse reaction of nonsteroidal anti-inflammatory drugs (NSAIDs) for users, which triggered the inhibition of prostaglandin syntheses such as COX-1 and COX-2 [21, 22]. In this weak condition, while COX-1 inhibition is started, COX-2 selective inhibitors may be expected to reduce the incidence of gastrointestinal adverse reaction while retaining the anti-inflammatory effects [22-24]. Although, it is known by some research that COX-2 and its related proteins help to recover the intestine when fistula needs healing process by working for angiogenesis [25-28].

Anderson et al. [29] have studied with COX-2 gene variants in a Scottish and Danish case-control study including 732 CD cases, 973 UC cases, and 1157 healthy controls. They have resulted with COX-2 A-1195G variant allele that had increased risk of UC and also they have claimed that carriers the variant have risk for UC before the age of 40. Zhang et al. [30] have also worked with both COX-2-1195G/A (A/A) and MnSOD9Ala/Val (V/V) in only 750 UC patients and 750 healthy subjects. Their results have ended up statistically increased results in UC patients with COX-2-1195G/A (A/A) genotype and they have also suggested that high-fat diet related the polymorphism in COX-2-1195G/A (A/A) for UC patients. De Vries et al. [31] have studied with COX-2 gene variants including COX-2 -1195 and COX-2 765 in Dutch IBD patients. They have only found the reduced association for risk of CD with COX-2 765 G C polymorphism.

COX-2 has the role to alter enzyme expression levels or impact biochemical function [32]. COX-2 might also be promoted by cytokines, growth factor, and oncogenes. When polymorphisms occur in COX-2, it could cause cellular over expression and effective to get failure the enzyme [33]. COX-2 has well understandable protective role in intestinal physiology [34] but its cellular and pathophysiological molecular mechanisms are remaining still unclear. That is the reason our study might have an answer for molecular way with Turkish patients by finding COX-2-1195A→G AA as a risk factor for all patients in both UC and CD.

The study has some potential limitations that make the study limited power even though the important results. Big sample size and further analyses might be helpful to find an answer for underlying mechanism of IBD and its relation with COX-2 genotypes.

Our study is ended up supportive and statistically important result for the literature with Turkish patients for the first time. The area needs to be lightened by further studies on pathophysiological molecular mechanism.

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Use of diagnostic modalities in the treatment of perianal fistula: A retrospective cohort study of 307 patients

Perianal fistül tedavisinde tanısal yöntemlerin kullanımı: 307 hastanın retrospektif kohort çalışması

Abdullah Şişik [1], Ali Kılıç [1]

Abstract

Aim: Deciding on the type of fistula and deciding on the most appropriate type of surgery is still a challenge for anal fistula disease. In this study, we aimed to evaluate whether magnetic resonance imaging (MRI), endoscopic examination and co-administration of both in preoperative preparations of anal fistulas are beneficial in this respect.

Methods: The study was retrospectively performed in patients treated surgically for perianal fistula between 2008 and 2017. The data of 307 patients operated for anal fistulas were reviewed with hospital records. Patients were grouped under the headings of preoperative MRI and non-MRI, endoscopic and non-endoscopic examination, and both performed and non-performed. The demographic data (age, sex), fistula type (simple or complicated), presence or absence of seton and the type of surgery were recorded. These parameters were compared with the groups.

Results: In the preoperative evaluation, 162 (53%) patients had MRI, 83 (27%) patients had endoscopic examination and 60 (20%) patients had both. There was a statistically significant correlation between the presence of preoperative MRI and the need for seton placement ($p < 0.05$ for all). Preoperative MRI, preoperative endoscopy and preoperative both modalities groups didn't show statistically significant correlation with patient's demographic data, fistula type and surgical method ($p > 0.05$ for all).

Conclusion: Preoperative modalities such as MRI and endoscopy are not sufficient in determining the type of fistula in an anal fistula and determining the surgical method to be applied. We believe that combining these studies with perioperative examination may be helpful in obtaining more effective results. Also, performing MRI preoperatively may help surgeons for decision of seton placement.

Key words: Perianal fistula, preoperative evaluation, fistula type, seton

Özet

Amaç: Anal fistül hastalığında fistül tipine karar vermek ve en uygun ameliyat tipine karar vermek ileri tetkiklerin kullanılmasına karşın halen içerisinde zorluklar barındırmaktadır. Bu çalışmada, anal fistül hastalarının ameliyat öncesi hazırlıklarında manyetik rezonans görüntüleme (MRG), endoskopik inceleme ve her ikisinin birlikte uygulanmasının bu konuda yararlı olup olmadığını değerlendirmeyi amaçladık.

Yöntemler: Çalışma 2008-2017 yılları arasında perianal fistül nedeniyle cerrahi tedavi uygulanan hastalarda retrospektif olarak yapıldı. Anal fistül nedeniyle ameliyat edilen 307 hastanın verileri hastane kayıtları ile gözden geçirildi. Hastalar ameliyat öncesi MRG yapılan ve yapılmayanlar, endoskopik inceleme yapılan ve yapılmayanlar ve her ikisi yapılan ve yapılmayanlar başlıkları altında gruplandırıldı. Hastaların demografik verileri (yaş, cinsiyet), fistül tipi (basit veya komplike), seton yerleşiminin olup olmadığı ve uygulanan cerrahi tipi kaydedildi. Bu parametreler gruplarla karşılaştırıldı.

Bulgular: Ameliyat öncesi değerlendirmede 162 (% 53) hastaya MRG, 83 (% 27) hastaya endoskopik inceleme ve 60 (% 20) hastaya da her ikisinin birden yapıldığı saptandı. Ameliyat öncesi MRG varlığı ile seton yerleştirilme gereksinimi arasında istatistiksel olarak anlamlı korelasyon saptandı ($p<0,05$). Ameliyat öncesi MRG, ameliyat öncesi endoskopi ve ameliyat öncesi her iki uygulamanın varlığı ile hastaların demografik özellikleri, fistül tipi ve uygulanan cerrahi tipi arasında istatistiksel olarak anlamlı ilişki saptanmadı ($p>0,05$).

Sonuç: Anal fistül hastalığında fistül tipini saptamada ve uygulanacak cerrahi şekline karar vermede MRG, endoskopi gibi preoperatif modaliteler yeterli olamamaktadır, bu incelemelerin peroperatif muayene ile birleştirilerek değerlendirilmesinin daha etkili sonuç elde etmede faydalı olacağı kanaatindeyiz. Ayrıca preoperatif MRG uygulamasının seton gereksinimi konusunda cerrahlara yardımcı olabileceğini düşünmekteyiz.

Anahtar sözcükler: Perianal fistül, preoperative inceleme, fistül tipi, seton

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Introduction

Anal fistula is a surgical disease that has been known and investigated for about 2500 years [1]. Although the cause is not known for certain; the crypto-glandular theory is the most accepted hypothesis [2, 3].

Diagnosis of the disease is done by physical examination and some additional examinations may be needed before surgery. Physical examination includes inspection of external orifice of anal fistula and digital rectal examination. The identification of the fistula tract and internal orifice with the anal probe ("stile") during the first examination is controversial [4-6]. Magnetic resonance imaging (MRI) and transanal ultrasonography (USG) are the most frequently used imaging methods. These tests are among the first choices to have knowledge about the complexity besides the diagnosis of the disease. Some studies argue that endoscopy should be performed in differential diagnosis. No study was found about the use of endoscopy (colonoscopy or flexible rectosigmoidoscopy (FRS)) routinely or when necessary, in literature [4, 5]. Another important point is that although several guidelines have been published on the standardization of colonoscopy requests, about 20-50% of the colonoscopy requests are unnecessary or inconsistent with the guidelines [7-9].

In the light of this knowledge, we tried to analyze the role of preoperative MRI and endoscopy in surgical treatment of anal fistula, in this study.

Materials and Methods

Patients who were operated on perianal fistula between 2008 and 2017 were included in the study. Information of the patients was received from the hospital records. Patient's demographic data, type of fistula, applied surgical method; presence of preoperative MRI and presence of preoperative endoscopy were recorded. Preoperative MRI and preoperative endoscopy in patient's record was noted as present or absent. The rationale of these modalities was not questioned because the decision about the selection of preoperative techniques depends on the attending surgeon. Fistula type is evaluated as simple or complicated according to Park classification. Superficial and intersphincteric fistulas were considered as simple fistulas, transsphincteric, suprasphincteric and extrasphincteric ones were considered as complex fistulas. The relationship with external sphincter and presence of multiple tracts were evaluated with physical examination, MRI and peroperative physical examination under anesthesia. Therefore the fistula type mentioned in this study was especially a postoperative decision. When patient's records were analyzed it was observed that various surgical methods were applied for treatment. We recorded the patients who were treated with seton placement due to the association of the fistula with the external sphincter.

Patients were grouped according to presence of preoperative MRI, presence of preoperative endoscopy and presence of both MRI and endoscopy. Preoperative modalities were evaluated as endoscopy +/-, MRI +/- and both +/- to determine the effect on parameters. These groups were compared each other according to demographic data, fistula type and seton requirement.

Patients operated for anal fistula due to Crohn's disease and patients who were operated for recurrent anal fistula were excluded from the study.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM, Armonk, NY, USA). Variables are expressed as mean ± standard deviations (SD) or as medians (range) depending on their distribution. Categorical variables were expressed as frequencies and percentages. Normally distributed variables were assessed using a t-test for paired groups. The Chi-square with Yates' correction method was used for comparison of continuous parametric variables. The statistical results were presented with a 95% confidence interval. The differences were considered statistically significant if the p-value was less than 0.05.

Results

After exclusion of 53 patients, 307 patients were included in the study. Five of 53 patients had Crohn's disease and 48 had recurrent anal fistula. Two hundred and forty six (80.2%) male and 61 (19.8%) female patients were analyzed. The mean age of the patients was 40.6 ± 11.2. Patients mostly had simple fistula (n=239, 77.8%). Surgical methods applied in the study are listed in table 1. Seton placement was performed in 32 (10.4%) patients. In preoperative examination MRI was present on 162 (53%) patients, endoscopy was present on 83 (27%) patients and both of these modalities were present on 60 (20%) patients. No significant difference was found when comparing the groups with age and gender ($p>0.05$ for all). There was no significant effect of preoperative endoscopy, MRI, or both in determining the type of perianal fistula ($p>0.05$ for all). There was a significant relationship between MRI use and seton placement, 81% of the seton placed patients had MRI preoperatively ($p<0.05$ for all) (Table1, Table 2).

In analysis of endoscopy group; no pathology was found in 66 (80%) of the endoscopic examinations. Sixteen patients (19%) had colonic polyps and histopathological examination of all polyps was benign in nature. Endoscopic examinations showed an internal orifice of fistula in only one patient (1%).

Table 1: Operation types performed for anal fistula treatment

Operation	All/ n (%)	Endoscopy	p	MRI	p	Both	p
Fistulotomy – fistulectomy	225 (73.3)	61	0.944	108	0.247	42	0.344
Seton placement	32 (10.5)	8	0.485	26	0.001	8	0.479
Mucosal flep	8 (7.2)	2	n/a	6	n/a	1	n/a
LIFT	11 (9.7)	4	n/a	5	n/a	2	n/a
FiLaC	7 (4.6)	1	n/a	4	n/a	2	n/a
Combined procedures	27 (8.7)	7	0.847	13	0.107	5	0.912
Total	307						

LIFT: Ligation of intersphincteric fistul tract, FiLAC: Fistula laser coagulation, n/a: not applicable

Discussion

Anal fistula is defined as the pathway connecting two distinct epithelial surfaces formed between the anal canal and perianal skin texture [5, 10].The commonly accepted cause is abscess formation after obstruction of anal gland ducts and epithelialization of the tract after opening of the abscess to the skin [2-4, 11]. The incidence of anal fistula as a common disease in European countries is reported to be between 1.04 and 2.32 per 10,000/year [12]. Fistula disease can be a source of stress for the patient and the surgeon, although diagnosis and treatment are often simple. For the correct treatment of the anal fistula, it is necessary to know the etiology of the disease and its relation to sphincter muscles.

Table 2: Comparison of the imaging techniques on the variables of the study group according to presence or absence of each technique.

	All, n=307	Endoscopy	Endoscopy absent	p	MR	MR absent	p	Endoscopy and MR	Endoscopy and MR absent	p
	n (%)	83(27)	224 (73)	n/a	162 (53)	145 (47)	n/a	60	247	n/a
Age	40.6±11.2	41.1±11.3	40.4±11.2	0.637	39.5±11.5	41.7±10.8	0.880	40.6±11.8	40.6±11.1	0.971
Gender										
Male	246 (80)	65 (26.4)	181 (73.6)	0.368	128 (52)	118 (48)	0.668	48 (20)	198 (80)	1.000
Female	61 (20)	18 (29.5)	43 (70.5)		34 (56)	27 (44)		12 (20)	49 (80)	
Fistula type n, (%)										
Simple	239 (78)	60 (25.1)	179 (74.9)	0.103	120 (50)	119 (50)	0.100	41 (28)	198 (72)	0.057
Complicated	68 (22)	23 (33.8)	45 (66.2)		42 (62)	26 (38)		19 (28)	49 (72)	
Seton requirement										
Yes	32 (10)	8 (25.0)	24 (75.0)	0.485	26 (81)	6 (19)	0.001	8 (25)	24 (75)	0.479
No	275 (90)	75 (27.3)	200 (72.7)		136 (49)	139 (51)		52 (19)	223 (81)	

n/a: not applicable

According to the relationship with sphincters, fistulas are classified as superficial, intersphincteric, transsphincteric, suprasphincteric and extrasphincteric. Intersphincteric and transsphincteric fistula constitute the majority of the fistula [6, 13]. Anal fistulas are also classified as simple or complicated [14, 15].Complicated anal fistulas include transsphincteric fistulas containing 30% of the external sphincter, suprasphincteric, extrasphincteric, horseshoe fistulas, inflammatory bowel disease-related fistulas, fistulas caused by radiation damage, anteriorly located fistulas in women, malignancy-associated fistulas [4].

Since the surgeons know the difficulties of fistula surgery, they make the necessary examinations to understand the type of the fistula in the preoperative period. Sometimes this can result in excessive use of available facilities. Occasionally, history and physical examination may reveal whether the fistula is a simple or complicated fistula, but the doubt of secondary tracts leads to the desire for additional tests for diseases such as Crohn's disease and rectum cancer. MRI is considered to be the most useful method in evaluating the relationship between the fistula and the sphincter complex [5, 16]. While useful for recurrent and complicated fistulas, the contribution is fairly small for simple fistulas.

We could not find a study in the literature about the use of colonoscopy and FRS in fistula operations. There have been many studies on the use and indications of colonoscopy, most of them related to malignancy scans and inflammatory bowel disease. Fistula-related articles rarely mention this topic referring that it is used routinely in some clinics and only for inflammatory bowel disease and malignancy suspicion in some others.

In this study we evaluated the impact of preoperative diagnostic techniques i.e. endoscopy and MRI on the type and treatment of perianal fistula. Many studies had already mentioned about the importance of preoperative MRI on the treatment of anal fistula [16]. In our study the patients who were treated with a seton placement had more MRI preoperatively than non-seton placed patients significantly. This result may reflect that seton placed fistulas are mostly associated with external sphincter and may be considered as complex fistula. Also more MRI application in this group might have directed the surgeon for seton placement. The patients who were performed both MRI and endoscopy did not show any significance in fistula type and seton placement. We may attribute this to the retrospective nature of the study and to the preoperative diagnostic modalities being surgeon-dependent and non-homogeneous. In this study, 27% of patients who underwent surgery for fistula received endoscopy. These data are based on hospital records. The rate may be lower than the actual value, because the patients who had endoscopy in another hospital couldn't be evaluated. We estimate that FRS or colonoscopy has been done to over 50% of the patients. This issue can be recognized as the limitation of the study, it has to be revealed with prospectively designed new studies.

In our study, inner orifice of fistula was seen in only one patient's endoscopy. Therefore endoscopy may be considered to be ineffective in determining the fistula tract or the internal orifice. The inner orifice of simple fistulas is usually at the level of anal crypts, and the sight of the inner orifice with a flexible colonoscope is almost impossible. Examination with rigid rectoscope / proctoscope is recommended in the literature for inner orifice evaluation. None of the patients had evidence of a malignancy with endoscopy and the most common finding was diminutive benign polyps. The detection rate of polyps was also the same as the normal population [17].

In the prospective study performed by Buchanan and colleagues comparing with physical examination, endoanal ultrasonography and MRI; MRI was found to be the most effective method in determining the secondary fistula tracts and fistula internal orifices. They reported that all patients went through FRS, but no FRS results were reported [5].We can understand from the literature that anamnesis, physical examination, MRI, and examination under anesthesia can be sufficient for determining the treatment of a fistula patient.

One of the limitations of this research study was the constitution of the sample. First, patients were not randomly selected from a larger population to participate in the study, because of the retrospective design. This might be considered as a bias. The results might not generalize to other populations, particularly those with greater diversity in ethnicity and social class in respect to disease distribution.

In conclusion, our suggestion with this study's findings for the impact of preoperative diagnostic techniques on the type and treatment of perianal fistula is as follows; preoperative categorization and decision of treatment modality for anal fistula should not be generalized. Depending on the patient; physical examination, radiological examination, and endoscopic examination should be performed alone or together. Additionally, performing MRI preoperatively may help the surgeon for decision of seton placement.

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A study to use hematological and biochemical parameters as a key in the diagnosis of acute mesenteric ischemia

Akut mezenterik iskemi tanısında hematolojik ve biyokimyasal parametrelerin bir anahtar olarak kullanımına yönelik bir çalışma

Mikail Çakır [1], Doğan Yıldırım [1], Ahmet Kocakuşak [1], Okan Murat Aktürk [1], Leyla Tigrel [1]

Abstract

Aim: Acute mesenteric ischemia is still fatal in 59-92% of cases. Delay in diagnosis of acute mesenteric ischemia can cause dramatic increase in morbidity and mortality rates. However several diagnostic and disease related factors have been widely studied. Controversy still remains. In this study, we evaluated hematological and biochemical parameters in patients with acute mesenteric ischemia.

Methods: 46 patients (study group) who underwent emergent surgery for acute mesenteric ischemia and 46 patients (control group) operated for acute abdomen with another etiology other than acute mesenteric ischemia and internalized to intensive care unit were included in this study. Medical records and clinical data of acute mesenteric ischemia patients between January 2008 and December 2014 were evaluated with regard to 8 parameters; age, amylase, white blood cell count, mean platelet volume, creatine kinase, lactate dehydrogenase, lactate and D-dimer. These parameters were selected for their increased levels in acute mesenteric ischemia patients according to many published medical studies. Control group was formed randomly from patients followed in intensive care unit for their co-morbidities after acute abdomen operation in the same period. Gender was included in the table but was not taken into account as a parameter for the study.

Results: Mean values of age, white blood cell count, creatine kinase, lactate dehydrogenase, lactate and D-dimer were significantly higher in acute mesenteric ischemia group than the control group. Mean platelet volume was significantly lower in acute mesenteric ischemia group. The p values were for age (p=0.009), for amylase (0.475), for white blood cell (p=0.001) for mean platelet volume (0=0.001), for creatinine kinase (p=0.017), for lactate dehydrogenase (p=0.001), for lactate (p=0.001), for D-dimer (p=0.001) respectively.

Conclusion: White blood cell count, creatine kinase, lactate dehydrogenase, lactate and D-dimer levels increase; mean platelet volume decrease in acute mesenteric ischemia patients significantly.

Keywords: Acute mesenteric ischemia, hematological parameters, biochemical parameters.

Öz

Amaç: Akut mezenterik iskemi %59-92 oranından ölümcül seyretmektedir. Tanıda gecikme morbidite ve mortalitede ciddi artışa sebep olabilmektedir. Bu konuyla ilgili pek çok tanısal çalışma yapılmıştır. Bu çalışmada, akut mezenterik iskemisi olan hastalarda hematolojik ve laboratuar parametrelerin değerlendirilmesi amaçlandı.

Yöntem: Bu çalışmaya akut mezenterik iskemi tanısıyla acil cerrahiye giden 46 hasta ile akut abdomen sebebiyle opere edilen ve yoğun bakım ünitesine alınan 46 hasta dahil edildi. Ocak 2008 ve Aralık 2014 tarihleri arasında akut mezenterik iskemi hastalarının dosyaları tarandı. Sekiz parametre ile ilgili tablolar oluşturuldu: amilaz, beyaz küre sayısı, ortalama trombosit hacmi, kreatinin kinaz, laktat dehidrogenez, laktat ve D-dimer. Bu parametreler daha önce çeşitli çalışmalarda akut mezenterik iskemide yükselmiş olarak bulunan parametrelerdir. Kontrol grubu aynı dönemde akut abdomen sebebiyle opere edildikten sonra yoğun bakıma alınmış olan hastalardan randomize olarak seçildi. Cinsiyet tablolarda yer almakla birlikte bu çalışmada bir parametre olarak kullanılmadı.

Bulgular: Ortalama yaş, amilaz düzeyi, beyaz küre sayısı, kreatinin kinaz, laktat dehidrogenez, laktat ve D-dimer akut mezenterik iskemi grubunda kontrol grubuna oranla daha yüksek olarak tespit edildi. Ortalama trombosit volumu akut mezenter iskemisi grubunda istatistiksel olarak anlamlı derecede daha düşüktü. P değerleri yaş için 0,009, amilaz p=0,475, beyaz küre sayısı için 0,001, kreatinin kinaz için 0,017, laktat dehidrogenaz için 0,001, laktat içim 0,001 ve D-dimer için 0,001 idi.

Sonuç: Akut mezenterik iskemi hastalarında beyaz küre sayısı, kreatin kinaz, laktat dehidrogenez, laktat, D-dimer sayıları artarken ortalama trombosit hacmi belirgin olarak azalmaktadır.

Anahtar kelimeler: akut mezenterik iskemi, kan parametreleri, D-dimer

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Introduction

Acute mesenteric ischemia (AMI) accounts for approximately 1% of all causes of acute abdomen and is associated with very poor prognosis. The mortality rate is between 59% and 92% [1]. Although diagnostic methods have advanced in recent years, laboratory findings are still an area of investigation. A 24-hour delay in diagnosis and surgical intervention reduces the survival rate of AMI patients by 20% [2]. Physical examination findings in emergency unit are similar to other causes of acute abdomen. Laboratory findings are usually non-specific in routine examination. In cases with a strong suspicion for AMI, more specific markers such as lactate, lactate dehydrogenase (LDH) and D-dimer may be studied. Duplex ultrasonography and computerized tomography angiography are useful but not specific for distal vascular pathologies [3,4]. Angiography performed by interventional radiology is the best imaging method but most of the emergency units don't have a possibility of angiography. From the literature review there is no sensitive and specific laboratory test for an early diagnosis of bowel infarction and the diagnosis is often delayed. Therefore blood measurements of various hematologic and biochemical markers are widely studied. The most popular ones are white blood cell (WBC) count [1], creatine kinase (CK), mean platelet volume (MPV) [5], neutrophil to lymphocyte ratio (NLR)[6-8], red cell distribution width (RDW)[7], lactate dehydrogenase (LDH), lactate, D-dimer, procalcitonin, phosphorus [1,2,8]. AMI is an acute inflammatory process depending on ischemia. Bacterial infiltration of intestinal wall causes sepsis and sepsis related biomarkers such as C-reactive protein, procalcitonin, MPV and neutrophilia are used as indicators of inflammation. The main etiologic factors are embolic or thrombotic arterial occlusion in 60-70% of cases, non-occlusive ischemia and infarction in 20-30% of cases and mesenteric venous thrombosis in 5-10% [1]. Since the delay in diagnosis increases mortality rates, measurement of several biomarkers in blood may give important clues for diagnosis.

The aim of this study was to evaluate the association of WBC, CK, LDH, lactate and D-dimer in patients with AMI with regard to their diagnostic efficacy.

Materials and Methods

From January 1st 2008 to December 31st 2014; 46 patients operated for AMI at Haseki Research and Training Hospital Emergency General Surgery Clinic were analyzed retrospectively. The study was approved by Haseki Research and Training Hospital Ethical Committee with a number of 17R/2018 with confirmation of Helsinki declaration. Written consent of the patients for using their clinical data was taken before the operation. Control group was formed from the patients operated for acute abdomen other than AMI and internalized to intensive care unit (ICU) for their co-morbidities. A total of 8 parameters (age, gender, amylase, WBC, CK, LDH, lactate, D-dimer) were recorded for 2 groups. Imaging modalities, operation findings, survivors and non-survivors were also evaluated. Control group was chosen randomly from the patients operated for acute abdomen in ICU. To provide similarity between groups, all of the patients in the control group were chosen randomly from the patients operated for acute abdomen and sent to intensive care unit due to co-morbidities in the same period. All of the patients with AMI were followed in the intensive care unit (ICU) after the operation.

Statistical analysis

Detection of AMI in the study group was regarded as the main outcome. All statistics were performed using SPSS 20.0 for Windows (SPSS Inc, Chicago, IL, USA). Normally-distributed continuous variables were expressed as mean ± standard deviations (SD) Categorical variables were expressed as frequencies and percentages.

The patients with and without AMI were regarded as AMI and control groups, respectively. Patients' demographics (age and sex) and laboratory parameters (WBC (103/mm3), MPV (fentoliter), amylase (U/L), LDH (U/L), CK (IU/L), lactate (mg/dL), D-dimer (µg/L)) were analyzed based on this grouping. Fischer's exact test and Mann-Whitney U test were used for normally and non-normally distributed parameters, respectively. Categorical variables were analyzed using Pearson's chi square test.

The patients were analyzed based on the serum levels of the parameters as increased or non-increased according to the upper normal levels reported by the laboratory and analyzed by using Pearson's chi square test (Table 1).

The analysis of receiver operating characteristics (ROC) curve associated with the area under the curve (AUC) was used to discover the optimal cut-off values with their specificity and sensitivity numbers to predict the development of AMI.

All tests were two sided and p value less than 0.05 were considered statistically significant.

Table 1. The upper and lower limits of laboratory paramaters

Laboratory parameter	Lower limits	Upper limits	Unit
Amylase	28	100	U/L
WBC	4.320	10.200	$10^3/mm^3$
MPV	6.8	10.8	Fl (fentolitre)
CK		<171	IU/L
LDH		<217	U/L
Lactate	0.5	1.6	mg/dL
D-dimer		<500	µg/L

WBC: White blood cell, MPV: Mean platelet volume, CK: Creatine kinase, LDH: Lactate dehydrogenase

Results

A total of 46 AMI and 46 control patients were enrolled. There were 22 47.8%) male and 24 (52.2%) female patients in AMI group. There were 24 (52.2%) male and 22 (47.8%) female patients in control group. Male/female ratio was similar in groups. Gender difference wasn't important statistically. Mean ages were 67.2 and 60.4 years for AMI and control groups respectively and age was significantly higher in AMI group (p=0.009). Amylase levels in both groups were not significantly different, (p=0.475). WBC (p=0.001), CK (p=0.017), LDH (p=0.001), lactate (p=0.001), D-dimer (p=0.001) mean levels were significantly higher in AMI patients than control group patients. MPV mean values were 9.6±2.59 fentoliter (fL) in AMI group and 10.4±1.3 fL in control group (Table 2).

Table 2. Comparison of parameters in regard to the groups.

	Mesenteric Ischemia		Control		
	n	%	n	%	
Male	22	47.8	24	52.2	
Female	24	52.2	22	47.8	
	Mean±SD	Median	Mean±SD	Median	p
Age	67.2±17.7	71.5	60.4±8.6	59.5	0.009
Amylase	110.4±104.1	78	72.9±24.8	64.4	0.475
WBC	17365.2±7769.8	15850	7428.9±2169.6	7325	0.001
MPV	9.6±2.5	9.1	10.4±1.3	10.1	0.001
CK	396.9±680.6	105.5	91.6±52.3	78	0.017
LDH	474.3±282.3	386.5	191.8±37.8	185.6	0.001
Lactate	6.6±2.8	6.6	0.8±0.4	0.8	0.001
D-dimer	1316.4±362.4	1341	346.8±94.4	355	0.001

WBC: White blood cell, MPV: Mean platelet volume, CK: Creatine kinase, LDH: Lactate dehydrogenase

Five parameters (WBC, LDH, CK, lactate, D-dimer) increased significantly in blood of AMI patients. The frequencies of elevated values were detected as cumulative percentages for amylase in 68(73.9%), for WBC in 47(51.1%), for MPV in 75(81.5%), for CK in 70(76.1%), for LDH in 50(54.3%), for lactate in 47(51.1%) for D-dimer in 45(48.9%) of all patients (n=92). It was seen that MPV increase is more prominent in acute abdomen patients other than AMI. There was no significant relationship between the parameters evaluated in AMI (Table 3).

Table 3. Mesenteric ischemia and relationship among the parameters.

		Age	Amylase	WBC	MPV	CK	LDH	Lactate
Amylase	rho	0.165						
	p	0.274						
WBC	rho	-0.210	-0.101					
	p	0.161	0.503					
MPV	rho	0.025	0.270	0.096				
	p	0.871	0.069	0.525				
CK	rho	-0.209	-0.056	0.051	-0.242			
	p	0.164	0.714	0.736	0.105			
LDH	rho	0.122	0.150	0.245	-0.164	0.108		
	p	0.420	0.320	0.100	0.277	0.476		
Lactate	rho	0.128	-0.014	-0.046	0.055	-0.087	-0.004	
	p	0.398	0.929	0.761	0.716	0.565	0.980	
D-dimer	rho	0.058	-0.114	0.058	-0.089	0.249	-0.084	-0.057
	p	0.702	0.451	0.703	0.558	0.095	0.577	0.705

WBC: White blood cell, MPV: Mean platelet volume, CK: Creatine kinase, LDH: Lactate dehydrogenase

The examples of ROC curves for WBC and lactate are shown in (Table 4, 5) (Figure 1, 2). Cut-off value of WBC as 11,405 103/mm^3 revealed "Area Under Curve" value of 0.959. Similarly, 1.9 mg/dL cut off value of lactate revealed "Area Under Curve" of 0.994.

Table 4. Interpretation of the curve of the parameters

Parameter	Area Under Curve	SE	p	95% Confidence Interval	
Amylase	0.542	0.065	0.475	0.416	0.671
WBC	0.959	0.019	0.001	0.922	0.997
MPV	0.737	0.051	0.001	0.655	0.855
CK	0.646	0.060	0.017	0.529	0.763
LDH	0.935	0.030	0.001	0.878	0.995
Lactate	0.994	0.007	0.001	0.981	1.000
D-dimer	1.000	0.001	0.010	0.998	1.000

WBC: White blood cell, MPV: Mean platelet volume, CK: Creatine kinase, LDH: Lactate dehydrogenase

Table 5. Cut-off values of the parameters.

	Cut-off value	Sensitivity	1-Specificity
WBC	11,405	0.804	0.043
MPV	9.65	0.804	0.304
LDH	213.75	0.957	0.217
Lactate	1.9	0.978	1.000
D-dimer	481.5	1.000	0.022
CK	78.35	0.652	0.477

WBC: White blood cell, MPV: Mean platelet volume, CK: Creatine kinase, LDH: Lactate dehydrogenase

Other than our main aim of this study, we would like to give also clinical data for these patients and groups. In AMI group CT and CT angiography were the main imaging modality to put the initial diagnosis. According to causes there were arterial occlusion in 34 (73.9%), venous occlusion in 8 (17.4%) and non-occlusive mesenteric ischemia in 4 (8.7%) of patients, respectively. Ischemia was detected in only the small intestine in 24 (52%) patients, while both the small intestine and colon were ischemic in 22 (48%) patients. The patients underwent resection of ischemic segments except one patient. For this patient revascularization of SMA was performed successfully after open embolectomy. Twenty-seven (58.7%) patients died, 19 (41.3%) patients survived after the operation. Mean ages of patients who died and survived were 71.3 and 61.7 years, respectively. Control group was consisting of patients operated for acute abdomen and internalized to intensive care unit due to co-morbidities. 18 (39%) appendicitis (11 perforated, 7 non-perforated), 7 (15%) peptic ulcer perforation, 11 (24%) incarcerated inguinal hernia (6 with small intestine resection, 5 without resection), 7 (15%) colorectal tumor perforation (4 resection and anastomosis, 3 resection and ostomy formation), 3 (7%) brid ileus were the operation findings (Table 6). Mortality rate for this group was 15.2%.

Table 6. Control Group

	Number	%	Mortality (%)
Acute Apendicitis (perforated 11, non-perforated 7)	18	39	3
Peptic Ulcer Perforation	7	15	1
Incarcerated inguinal hernia (resection 6, without resection 5)	11	24	1
Colorectal tumor perforation (resection and anastomosis 4, resection and ostomy formation 3)	7	15	2
Brid Ileus	3	7	0
Total	46	100	7 (15.2%)

Figure 1. The ROC curve of white blood cell.

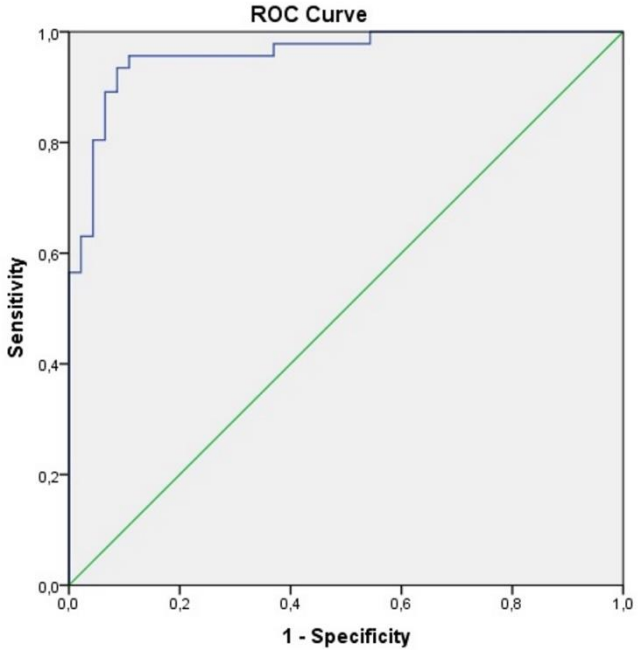
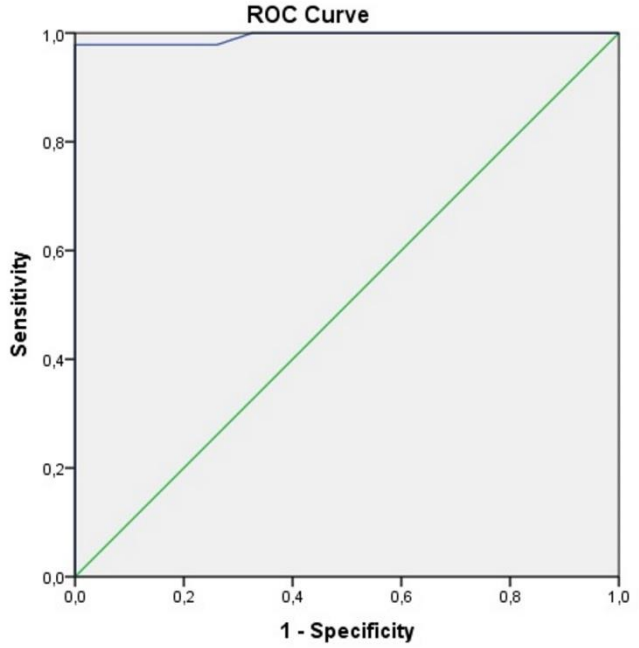


Figure 2. The ROC curve of lactate.



Discussion

The main pathophysiologic changes in AMI are systemic inflammatory response, bacterial translocation and reperfusion injury. Intestinal wall microcirculation deteriorates, capillary permeability increases and bacterial translocation

occurs. Progression will finally cause peritonitis and perforation. Early diagnosis, early surgical intervention; resection of necrotic intestinal segments and restoration of blood flow are essential. A high index of suspicion with prompt diagnostic evaluation may reduce the delay prior to surgical intervention. Therefore to find a specific and sensitive biomarker related to AMI is still an area of investigation. Most of retrospective trials suggest some biomarkers to increase in AMI but also add that they are not specific and sensitive because those biomarkers increase in other acute abdomen causes [1, 5, 8, 9, 10]. Concerning this in our study we studied that 5 relatively more increasing parameters in AMI compared with other causes of acute abdomen. These parameters also increase in other causes of acute abdomen. But our results showed that increase is more evident in AMI. The patients with AMI have leukocytosis, metabolic acidosis, an elevated D-dimer and elevated serum lactate, LDH and CK [10, 11]. Increased WBC count exceeding 20X10^9/L have been reported but these finding has not been associated with the extent of necrosis or distinguishing AMI from other diagnosis [1, 10]. CK isoenzyme BB has been demonstrated in the mucosa and muscularis throughout the entire gastrointestinal system. Isoenzyme CK-BB levels are increasing with intestinal ischemic pathologies [12, 13] but total CK level has not been found to increase in most of studies. In our study total CK was found higher significantly in AMI patients (p=0.017). D-dimer is the one of the most studied parameters in AMI. It is an enzyme degradation product of fibrin that is released during intravascular coagulation and fibrin deposition which may be present in AMI. In most of the studies D-dimer is an important marker showing intestinal ischemia [14, 15] and some studies say its level doesn't differ significantly between AMI and other causes of acute abdomen [10]. We found that it is higher in AMI patients (P=0.001). LDH is also an increasing parameter. Its increase is also controversial. Some studies report that the difference is not significant [1]. In our study LDH increase was found significant on comparison with other acute abdomen causes (p=0.001). Lactate is associated with late stage mesenteric ischemia with extensive transmural infarction, body tissue hypoperfusion, anabolic metabolism and death [15]. Lactate is elevated after advanced mesenteric damage [6]. But its increase is not specific to AMI. Some studies report that increase in lactate level doesn't differ in AMI compared with other causes of acute abdomen [10, 16]. In our study lactate level was significantly higher in AMI patients (p=0.001). MPV findings were conversely related to literature knowledge. We reviewed several studies reporting MPV increase in AMI patients. MPV value was higher in acute abdomen patients than AMI [5, 9].To measure a single parameter is not sufficient to diagnose AMI. These parameters should be evaluated altogether.

Limitation of the study was its retrospective design. Besides, the selection of control group might be biased due to lack of uniformity of criteria for acceptance of patients to ICU.

In conclusion, AMI has still high morbidity and mortality. Diagnostic delay must be prevented by means of laboratory findings and imaging modalities especially computed tomography and computed tomography angiography so that early diagnosis may ensure timely surgery. As in other reported studies, increasing levels of WBC, LDH, CK, lactate and D-dimer could help the diagnosis of AMI. Early surgery and proper management will increase survival especially in hospitals with limited radiologic facilities.

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Arch Clin Exp Med 2018;3(2):57-62. e-ISSN: 2564-6567

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Laringeal skumaöz hücreli karsinomlarda lenfatik damar yoğunluğu ve mikrodamar yoğunluğunun değerlendirilmesi

The evaluation of lymphatic vessel density and microvessel density in laryngeal squamous cell carcinoma

Ganime Çoban [1], Ebru Akay [2], Kemal Deniz [3], İmdat Yüce [4], Süleyman Balkanlı [3]

Öz

Amaç: Larinks karsinomlarında boyun lenf nodlarına metastaz, sağ kalımı önemli oranda azaltan bir etkendir. Bu çalışmanın amacı; larinksin skuamöz hücreli tümörlerinde tümör içi ve tümör dışı alanlarda lenfatik damar yoğunluğu ve mikrodamar yoğunluğunun lenf nodu metastazı ile ilişkisini ortaya koymaktır.

Yöntemler: Çalışmamızda 2000-2006 yılları arasında Erciyes Üniversitesi Tıp Fakültesi Patoloji Ana Bilim Dalı'nda larinks skuamöz hücreli karsinom tanısı almış 86 olgu incelemeye alındı. Tümör içi ve tümör dışı alanlarda immünhistokimyasal bir belirteç olan D2-40 ile lenfatik damar yoğunluğu ve CD34 ile mikrodamar damar yoğunluğu değerlendirildi. Sonuçlar tümör derecesi, tümör yerleşim yeri, lenf nodu metastazı ile karşılaştırıldı.

Bulgular: Olguların tümör içi ve tümör dışı lenfatik damar yoğunluğu sırası ile 8,93±12,5 ve 24,1±20,1 idi (p=0,001). Tümör içi mikrodamar yoğunluğu değeri 217,53±89,8 ve tümör dışı mikrodamar yoğunluğu değeri 330,43±92,4 olarak sayıldı (p=0,001). İyi diferansiye tümörlerde tümör içi lenfatik damar yoğunluğu değeri, iyi diferansiye olmayan tümörlere göre yüksekti, fakat anlamlı sonuç elde edilemedi (p=0,100). Kötü diferansiye tümörlerde tümör dışı mikrodamar yoğunluğu değeri anlamlı olarak yüksek bulundu (p=0,050). Tümör içi mikrodamar yoğunluğu değeri lenf nodu metastazı olan tümörlerde anlamlı olarak düşüktü (p=0,028). Lenf nodu metastazı olan ve olmayan her iki grupta da tümör dışı lenfatik damar yoğunluğu değeri yüksekti, istatiksel olarak anlamlı bir sonuç elde edilemedi (p=0,084).

Sonuç: Bu çalışmada iyi diferansiye tümörlerde tümör içi mikrodamar yoğunluğu ve kötü diferansiye olgularda tümör dışı mikrodamar yoğunluğu daha yüksek idi. Lenfatik damar yoğunluğu değeri ile diferansiasyon arasında bir ilişki saptanmadı. Metastaz yapmayan grupta tümör içi ve tümör dışı mikrodamar yoğunluğu değeri yüksek bulundu. Metastaz ile lenfatik damar yoğunluğu değeri arasında bir ilişki izlenmedi.

D2-40 ve CD34 'ün birlikte kullanımı ile lenfatik damar yoğunluğunun değerlendirilmesinin, metastazın erken belirlenmesinde daha önemli olabileceğini düşünmekteyiz.

Anahtar Kelimeler: D2-40, anjiogenez, CD34, larinks, skuamöz hücreli karsinom

Abstract

Aim: Metastasis to the cervical lymph nodes in laryngeal carcinomas is a factor reducing survival significantly. The present study aimed to reveal the association of lymph node metastasis with lymphatic vessel density and microvessel density in the intratumoral and extra-tumoral areas of laryngeal squamous cell carcinoma.

Methods: Eighty-six cases diagnosed with laryngeal squamous cell carcinoma in Pathology Department of Erciyes University Faculty of Medicine between 2000-2006 were included in the present study. Lymphatic vessel density and microvessel density were assessed with D2-40 which is an immunohistochemical marker in intratumoral and extra-tumoral areas and CD34, respectively. The results were compared with tumor grade, tumor localization, and lymph node metastasis.

Results: Intratumoral and extra tumoral lymphatic vessel density value were 8.93±12.5 and 24.1±20.1, respectively (p=0.001). Mean intra tumoral microvessel density was calculated as 217.53±89.8 while extra tumoral microvessel density was calculated as 330.43±92.4 (p=0.001). Intratumoral lymphatic vessel density value was higher in the well-differentiated tumors compared to the poorly differentiated tumors but no significant result was obtained (p=0.100). Extra tumoral microvessel density value was found to be significantly higher in the poorly differentiated tumors (p=0.05). Intratumoral microvessel density value was significantly lower in tumors with lymph node metastasis (p=0.028). Extra-tumoral lymphatic vessel density value was higher in both groups with and without lymph node metastasis, however, no statistically significant result could be obtained (p=0.084).

Conclusion: In the present study, intratumoral microvessel density was higher in well differentiated tumors whereas extra tumoral microvessel density was determined to be higher in poorly differentiated cases. No significant association was noted between lymphatic vessel density and differentiation. Extra tumoral and intra tumoral microvessel density values were found to be higher in the group without metastasis. No association was detected between metastasis and lymphatic vessel density value.

We suggest that assessing lymphatic vessel density with the co-administration of D2-40 and CD34 may be more important for early detection of metastasis.

Keywords: D2-40, angiogenesis, CD34, larynx, squamous cell carcinoma

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Giriş

Larinks karsinomları, baş boyun bölgesinin en sık görülen neoplazmlarıdır [1]. Özellikle erkeklerde sık görülmektedir. En sık yerleşim yerleri glottik bölge olup, ikinci sırada supraglottik bölge gelmektedir. Skuamöz hücreli karsinomlar (SHK) larinksin en sık görülen malign tümörüdür [1]. SHK, diferansiyasyon derecesi, sellüler pleomorfizm ve mitotik aktivite temel alınarak iyi, orta ve kötü diferansiye olmak üzere üç gruba ayrılır. Çoğu glottik karsinomlar, iyi-orta diferansiye iken, özellikle subglottik alan olmak üzere diğer lokalizasyondakiler orta-kötü diferansiyedir. Tümörün prognozunda klinik evre ve yerleşim yeri, büyüklüğü, lenf nodu tutulumu, Ki-67 proliferasyon indeksi, lenfovasküler ve perinöral invazyon, lenf nodunda ekstrakapsüler yayılım ve rezeksiyon sınırlarının durumu önemlidir [1, 2].

Larinks karsinomları en sık servikal bölge lenf nodlarına metastaz yapmaktadır. Son yıllarda tümör vaskülarizasyonu ve tümör progresyonu hakkında ilişkiyi gösteren çalışmalar vardır. Bilindiği gibi solid tümörlerin gelişimi ve metastaz yapmasında yeni damar oluşumu önemli rol oynar [3].Kan damarları iki farklı süreç ile oluşur; bunlar vaskülogenez ve anjiogenezdir [4]. Anjiogenez, tümörlerin gelişimi, invazyonu, metastazı ve prognozu ile ilişkilidir [5-7]. Solid kanserlerin gelişiminde kan damarlarının yanı sıra lenf damarları da önemli role sahiptir [8]. Lenfanjiogenez tümörün lenf nodu metastazı yapıp yapmayacağı konusunda önemli bir göstergedir. Metastazların erken tanınabilmesi mikrodamar yoğunluğu (MDY) ve lenfatik damar yoğunluğunun (LDY) gösterilebilmesi ile mümkün olabilir [3, 5, 9]. Artmış MDY'nin meme kanserlerinde bağımsız prognostik belirleyici olduğu gösterilmiştir [10]. Histolojik kesitlerde lenfatik ve kan damarlarının tanınması çok önemlidir. Ancak lenfatik endotelyal hücrelerin Hematoksilen-Eozin (HE) ile boyalı rutin histolojik kesitlerde tanınması zor olmaktadır. Lenf damarlarını göstermede birçok immünohistokimyasal belirleyici bulunmaktadır. Bu antikorlar LYVE-1, Prox-1, podoplanin ve D2-40 olarak sıralanabilir [11, 12]. D2-40, 40kDa ağırlığında siyaloglikoprotein özelliğinde monoklonal bir antikordur [13]. Onkofetal membran antijeni olup, testiküler gonositlerin yüzey hücrelerinde, germ hücreli tümörlerde, lenfatik endotelde ve mezotel hücrelerinde bulunur [14]. D2-40, lenfatik endotelyal hücreleri göstermede oldukça duyarlı ve özgüldür [15-17]. D2-40 sitoplazmik boyanma paternine sahiptir. Lenfatik dokudan kaynaklanan tümörlerde ve lenf nodlarındaki tümör invazyonunu göstermede oldukça faydalıdır [18]. CD 34, yaklaşık 116 kDa ağırlığında tek zincir transmembran proteinidir. Hematopoetik hücreler, dermis ve yumuşak dokudaki dendritik hücreler ve fibroblastik hücreler, endotel hücreleri, kemik iliğinin stromal hücrelerinin öncüllerinde reaksiyon gösterir [19]. D2-40 lenfatik endotelyal belirleyicisi ile CD34 gibi panendotelyal bir belirleyicinin birlikte kullanımı lenf ve kan damarlarının ayırt edilmesinde önemli katkı sağlar. Literatürde çeşitli tümörlerde tümör içi (Tİ) ve tümör dışı (TD) alandaki lenfatik invazyon alanları karşılaştırılmış olup, prognozla ilişkisi değerlendirilmiştir [20-22].

Biz bu çalışmada, larinksin SHK'de, D2-40 ve CD34 kullanarak Tİ ve TD alanlarda lenfatik ve damar sayılarını değerlendirdik. Elde edilen sonuçlar ile tümör diferansiyasyonu, yerleşim yeri ve lenf nodu metastazı arasındaki ilişkiyi göstermeyi amaçladık.

Gereç ve yöntemler

Çalışmamızda, Erciyes Üniversitesi Tıp Fakültesi Patoloji Ana Bilim Dalı'nda larinks SKH tanısı almış 86 olgu retrospektif olarak değerlendirildi. Lokal etik kuruldan çalışma için onam alındı. Çalışma Helsinki Deklerasyonu Prensipleri'ne uygun olarak yapıldı. Çalışmanın retrospektif yapısından dolayı hastalardan yazılı onam alınamadı.

Hastaların dosya kayıtlarından ve patoloji raporlarından yaş, cinsiyet, tümör yerleşim yeri, tümör çapı ve uygulanan tedaviler hakkında veriler toplandı.

Patolojik değerlendirme

HE boyamasında Tİ ve TD alanların en iyi görüldüğü bloklar saptandı. HE boyalı preparatlarda tümör histolojik tipi ve diferansiyasyonu değerlendirildi. Histolojik derece, tümör hücrelerinin pleomorfizm, keratin yapıp yapmaması, mitozun seyrek ya da sık olmasına göre iyi diferansiye, orta derece diferansiye ve kötü diferansiye olmak üzere üç gruba ayrıldı. Hafif pleomorfizm, belirgin keratin varlığı, seyrek mitoz varlığı olan vakalar iyi diferansiye, belirgin pleomorfizm, keratinin yokluğu ve sık mitoz içeren vakalar kötü diferansiye olarak yorumlandı. İyi ve kötü diferansiye arasında kalan vakalar orta derece diferansiye olarak değerlendirildi. İmmünohistokimyasal boyama için %10'luk formalin fiksasyonu sonrası hazırlanmış parafine gömülü dokulardan 3-5 mikronluk kesitler yapıldı. Primer antikorlar olarak D2-40 (Dako, Klon D2-40, 1/80 dilüsyonda) ve CD34 (Dako 1/200 dilüsyonda) kullanıldı. İmmünohistokimyasal boyamada streptavidin-biotin kiti kullanarak avidin-biotin peroksidaz metodu uygulandı.CD34 ve D2-40 için sitoplazmik boyanma dikkate alındı. Çalışmada Olympus mikroskop kullanılarak damar ve lenfatiklerin en yoğun olduğu 200 büyütmede 4 saha değerlendirildi.MDY'de, TD ve Tİ alanlarda CD34 pozitif boyanan damarlar, LYD için TD ve Tİ alanlarda D2-40 boyanan lenfatik kanallar sayıldı.Bu parametreler; tümörün yerleşim yeri, diferansiyasyonu ve lenf nodu metastazı ile ilişkileri karşılaştırıldı.

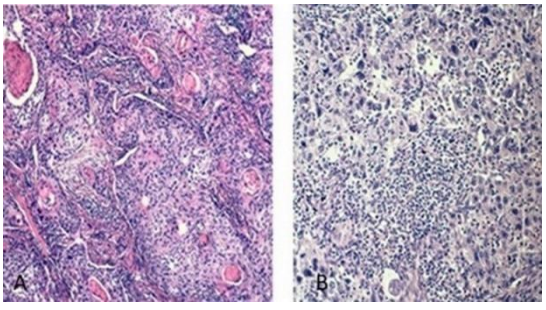
İstatistiksel analiz

Çalışma verileri değerlendirilirken tanımlayıcı istatistiksel metodlar (Ortalama, standart sapma, ortanca, frekans, yüzde oran) kullanıldı. Bulguların istatiksel olarak değerlendirilmesinde, karşılaştırmalarda ki kare testi, t testi ve varyans analizi kullanıldı. P değerinin 0,05 altındaki değerleri anlamlı kabul edildi.

Bulgular

Çalışmada değerlendirmeye alınan 86 olgunun 85'i (%98,8) erkek, 1'i(%1,2) kadındı. Yaş ortalaması 60,1±9,8 yıl idi. Tümörler en sık glottik (%52,3) ve supraglottik (%39,5) yerleşimli idi. Histopatolojik incelemede olguların 33'ü (%38,4) iyi diferansiye, 35'i (%40,7) orta diferansiye, 18'i (%20,9) kötü diferansiye olarak değerlendirildi (Resim 1). Ellibir olguda (%59,3) lenf nodu metastazı tespit edilemedi. Hastalara ait demografik veriler ve tümör özellikleri Tablo 1'de özetlendi (Tablo 1).

Resim 1: İyi diferansiye skuamöz hücreli karsinom (A). Kötü diferansiye skuamöz hücreli karsinom (B) (HEx200).



Olguların diferansiyasyonlarına göre metastaz oranları karşılaştırıldığında orta derece ve kötü diferansiye tümörlerin metastaz oranının daha yüksek olduğu görülmüş olup, istatiksel

olarak anlamlıydı (p=0,03). Tümörlerin yerleşim yerlerine göre metastaz oranları Tablo 2'de özetlendi.

Tablo 1: Demografik veriler ve tümör özellikleri.

Parametre	Özellik	n
Yaş (yıl) [β]		60,1±9,8
Cinsiyet	Erkek/kadın	85/1
Tümör çapı (cm) [β]		3.1±1,3
Tümör dağılımı [μ]	Supraglottik	34 (39,5)
	Glottik	45 (52,3)
	Subglottik	7 (8,2)
Histopatoloji [μ]	İyi diferansiye	33(38,3)
	Orta differansiye	35 (40,6)
	Kötü diferansiye	18 (20,9)
Lenf nodu metastazı [μ]	Var	35 (40,7)
	Yok	51 (59,3)

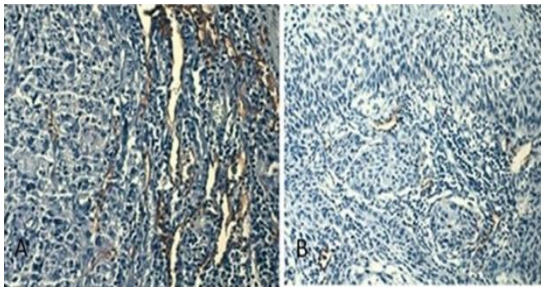
[β]: ortalama standart sapma
[μ]: n(%)

Tablo 2: Olguların yerleşim yerleri ve metastaz durumlarına göre dağılımları (p=0,032).

	Supra-glottik	Glottik	Sub-glottik	Toplam
Olgu Sayısı	34	45	7	86
Lenf nodu metastazı (+)	16 (%47,1)	15 (%33,3)	4 (%57,1)	35
Lenf nodu metastazı (-)	18 (%52,9)	30 (%66,7)	3 (%42,9)	51

Olguların Tİ ve TD lenfatik damar sayıları karşılaştırıldığında, Tİ LDY değeri ortalama 8,93±12,5 olup, TD LVD'nin ortalama değeri 24,1±20,1 idi (P =0.001). Olguların diferansiyasyonu ile Tİ ve TD lenfatik damar sayıları arasında anlamlı bir sonuç elde edilemedi (Resim 2) (p=0,996).

Resim 2: Skuamöz hücreli karsinomda D2 40 ile tümör çevresindeki (A) ve tümör içerisindeki (B) lenfatiklerde boyanma (X200).



Lenf nodu metastazı durumuna göre, Tİ ve TD alanların LDY ve MDY oranları Tablo 3'de özetlendi. Her iki grupta da TD LDY'nin fazla olduğu görüldü. Tİ ve TD LDY ile metastaz arasında anlamlı bir ilişki saptanamadı (p>0.05).

Tümörlerin yerleşim yerlerine göre Tİ LDY karşılaştırıldığında, Tİ LDY'nin ortanca değerinin subglottik yerleşimli 7 olguda 6, glottik yerleşimli 45 olguda 4 ve supraglottik yerleşimli 34 olguda 5 olarak değerlendirildi. P değeri 0,281 olup yerleşim yerleri ve Tİ LDY arasında anlamlı bir sonuca varılamadı. Tümörlerin yerleşim yerlerine göre TD LDY karşılaştırıldığında supraglottik bölgede yerleşen 34 (%39,5) vakanın ortanca TD LDY değeri 21, glottik bölgedeki 45 vakanın (%52,3) 16 ve subglottik yerleşimli 7 vakanın (%8,1) 25'ti. Yerleşim yerleri ve TD LDY arasında anlamlı bir fark bulunamadı (p = 0,168).

Olguların Tİ ve TD MDY değerleri karşılaştırıldığında, Tİ alanlarda MDY değeri ortalama 217 ±89, TD alanlarda 330±92 olarak değerlendirildi (p= 0,001). Olguların diferansiyasyonu ve TD MDY karşılaştırıldığında iyi diferansiye tümörlerde (33 vaka) 333,2±78,9, kötü diferansiye tümörlerde (18 vaka) 374,2±80,1 olarak değerlendirildi. Kötü diferansiye tümör ile iyi diferansiye tümörlerin TD MDY değerleri arasında anlamlı bir fark bulundu (p=0,03).

Tablo 3: Olguların lenf nodu metastaz durumuna göre tümör içi-tümör dışı lenfatik damar ve mikrodamar yoğunluğu

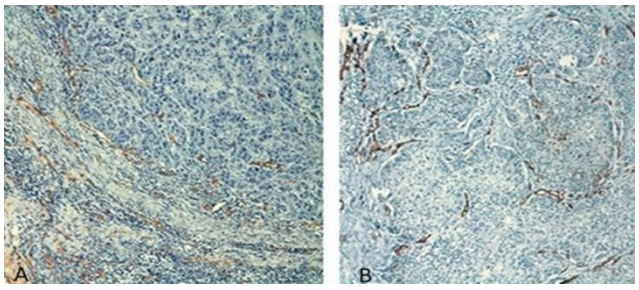
Parametre	Lenf nodu met(+)	Lenf nodu met (-)
Tİ LDY	10,28	23,85
TD LDY	8	24,78
Tİ MDY	191,97	235,07
TD MDY	307,10	346,07

Tİ: tümör içi, TD: tümör dışı, LDY: lenfatik damar yoğunluğu, MDY: mikrodamar yoğunluğu.

Olguların diferansiyasyonları ve Tİ MDY karşılaştırıldığında, iyi diferansiye olgularda Tİ MDY değeri ortalama 243,6±90,3, orta derece diferansiye vakalarda 210,7±81,4 ve kötü diferansiye tümörlerde 183±95,2 olarak saptandı (p= 0,058) (Resim 3). Olguların lenf nodu metastaz durumuna göre MVD durumu Tablo 2'de özetlendi. Lenf nodu metastazı olmayan grupta Tİ ve TD MDY değeri daha yüksekti (p = 0,058).

D2-40 ile olguların 33'ünde (%38,4) tümöral dokuda farklı oranlarda pozitif boyanma izlendi. 53 vakada (%61,6) boyanma izlenmedi. Olguların diferansiyasyonuna göre tümördeki boyanma oranları karşılaştırıldığında iyi diferansiye 33 olgunun 17'sinde, orta derece diferansiye 35 olgunun 9'unda ve kötü diferansiye 18 olgunun 7'sinde D2-40 ile boyanma görüldü (p= 0,125).

Resim 3: Kötü diferansiye skuamöz hücreli karsinomda CD34 ile tümör çevresinde (A) ve tümör içerisinde (B) boyanan vasküler yapılar (X200).



Tartışma

Larinks karsinomları baş boyun bölgesinin en sık görülen neoplazmlarıdır. Erkeklerdeki tüm kanserlerin %2,2' si, kadınlarda %0,4' ünü oluşturur. Çoğu hasta 4.dekat veya daha ileri yaştadır, fakat daha genç yaşlarda da görülebilir. Sigara başlıca risk faktörüdür. Bazı ülkelerde kadınlarda sigara kullanımının artmasına bağlı olarak görülme sıklığı artmaktadır [1]. Diğer risk faktörleri arasında, sesin kötü kullanımı, keratosis [1], Human Papilloma Virüs [23], Ebstein Barr Virüs [24] gibi viral nedenler, radyasyon [25], Bloom's sendromu [26], Li-Fraumeni sendromu[27], beslenme, gastroözefagial reflü ve asbest yer almaktadır. Sebze ve meyvelerde bulunan C vitamini, folat ve flavonoidler gibi antioksidanların larinks kanseri riskini azalttığı gösterilmiştir [2].

Anjiogenez, tümörlerin gelişimi, invazyonu, metastazı ve prognozunda önemli role sahip temel mekanizmalardan biridir

[5-7].Larinks neoplazmları metastazlarını en sık servikal lenf nodlarına yapmaktadır. Genellikle lenf nodu metastazı primer tümör alanındaki lenfatik damar invazyonunun gerçekleşmesi ile başlamaktadır. Daha sonra kanser hücreleri lenfatik yol ile lenf nodlarına tümör embolisi olarak taşınırlar. Lenfanjiogenez tümörün lenf nodu metastazı yapıp yapmayacağı konusunda önemli bir göstergedir. Özellikle de Tİ lenfanjiogenezin tümörün prognozu ve metastaz yapmasında önemli olduğu bildirilmiştir [28-29].Çeşitli malignitelerde CD34 ve D2-40 birlikte kullanılarak, Tİ lenfatik ve damar sayıları, TD lenfatik ve damar sayılarının metastaz ile ilişkisi gösterilmiştir. Çalışmamızda lenf nodu metastazı olan ve olmayan her iki grupta da TD LDY, Tİ'den daha yüksekti.

Kolon kanserinde yapılan bir çalışmada, D2-40 ile HE boyamaya oranla lenfatik invazyon saptanmasında %19 oranında artış olduğu gösterilmiştir. Bu çalışmada ayrıca kolorektal karsinomlarda Tİ lenfanjiogenezisin, lenfatik invazyon, lenf nodu ve karaciğer metastazı ile korelasyon gösterdiği saptanmıştır [30]. Kolon adenokarsinomlarında yapılan bir başka çalışmada, Tİ alanda lenfatik kanallarda azalma görülmüştür. LDY ile klinikopatolojik parametreler arasında korelasyon izlenmemiştir [31].

Erken evre serviks skuamöz hücreli karsinomlarında Tİ'de normal servikal dokuya göre LDY'nin fazla olduğu, D2-40 ile reaksiyon veren Tİ'deki lenfatiklerin lümenlerinin kapalı tümör çevresindeki lenfatiklerinin lümenlerinin açık olduğu görüldü. Ayrıca tümör çevresindeki lenfatiklerin sayılarının artışı ile lenfatik invazyonun korele olduğu saptandı [32]. Çalışmamızda da, Tİ'deki çoğu lenfatik kanal kapalı olup yarık benzeri görünümde iken TD alandaki lenfatik kanallar daha büyük ve lümenlerinin açık olduğu izlendi. Tümör içindeki kanalların kapalı olmasında tümör dezmoplasisinin rolü olabilir.

Gastrik karsinomlarda D2-40 ve CD31 kullanılarak yapılan bir çalışmada LDY ve MDY oranları değerlendirilmiştir. TD LDY'nin Tİ LDY' ye göre yüksek olduğu ve lenf nodu metastazı ile direkt ilişkili olduğu saptanmıştır. Ayrıca TD alandaki lenfatiklerin açık ve geniş lümenli olduğu görülmüştür [33]. Prostat adenokarsinomlarında D2-40 belirteci kullanılarak yapılan bir çalışmada, TD alanların TD alana göre daha fazla lenfatik içerdiği gösterilmiştir. TD lenfatik invazyonun lenf nodu metastazı ile ilişkili olduğu ve Gleason grade yükseldikçe TD LVD' nin de yükseldiği saptanmıştır [34].

Bizim çalışmamızda metastazı olan ve olmayan her iki grupta da TD MDY, Tİ MDY'den istatistiksel olarak anlamlı şekilde daha fazladır. Tİ ve TD MDY, metastaz olan grupta metastaz olmayan gruba göre düşük olarak bulunmuştur. Bu değerler istatistiksel olarak anlamlıdır. Veriler literatür ile korele değildir.

Larinkste D2-40 ile yapılan 40 vakalık bir çalışmada, TD D2-40 pozitif lenfatik damarların normal mukozadan daha fazla sayıda olduğu saptandı. Metastaz olan grupta metastaz olmayana göre TD lenfatik sayısı daha fazlaydı. TD LDY'nin tümör progresyonu ve invazyonunda önemli olduğu görüldü [35]. Endometrium adenokarsinomlarında CD31 ve D2-40 ile yapılan bir çalışmada lenfatik invazyonun kan damarı invazyonundan daha fazla olduğu gösterilmiştir. Ancak kan damarı invazyonun, prognozda daha önemli olduğu bildirilmiştir [36].

Larinksin lenfatik sistemi bölgelere göre farklılık göstermektedir. Supraglottik bölge en fazla lenfatik sisteme sahip olup, lenf nodu metastazı en sık bu bölge tümörlerinde görülmektedir [37]. Çalışmamızda lenf nodu metastazı olan 35 vakanın %45,7'si supraglottik, %42,9'u glottik ve %11,4'ü subglottik yerleşimliydi. Tİ ve TD LDY en yüksek subglottik, en düşük glottik bölge tümörlerinde izlendi. Tİ damar sayıları supraglottik bölgede yüksek saptandı. TD damar sayısı en yüksek subglottik en düşük glottik bölgede görüldü. Glottik bölge lenfatik sistemin çok az olduğu bölge olmasına rağmen çalışmamızda glottik bölgede yerleşen tümörlerde metastaz oranı yüksek bulundu. Bu tümörlerin ileri evre tümörler olduğunu düşünmekteyiz. Supraglottik bölge yerleşimli tümörlerde metastaz oranı yüksek olup literatur ile uyumludur.

Larinks karsinomlarında yerleşim yerleri ve lenf nodu metastazları arasında yapılan bir çalışmada supraglottik bölge yerleşimli tümörlerde glottik bölge yerleşimli tümörlere göre lenf nodu metastaz oranı daha yüksek olarak bulundu [38]. Larinksin supraglottik skuamöz hücreli karsinomlarında yapılmış 108 vakalık bir çalışmada damar yoğunluğu ve lenf nodu arasında korelasyon izlenmedi. Klinikopatolojik parametreler ve yaşam oranı ile MDY arasında ilişki saptanmadı [39].

Çalışmamızda, Tİ MDY iyi diferaniye tümörlerde, TD MDY orta derece ve kötü diferansiye tümörlerde yüksek saptandı. Diferansiyasyon kötüleştikçe TD damar sayısı artmaktaydı.

Kyzas ve arkadaşları, baş boyun bölgesindeki SHK' de CD105 ile yaptıkları bir çalışmada yüksek MDY'nin kötü dereceli tümör ile ilişkili olduğunu saptamışlardı [40].Çalışmamızda tümör diferansiyasyonu ile TD veTİ lenfatik sayıları arasında istatiksel olarak anlamlı sonuç elde edilemedi. Tümör derecesi ile Tİ ve TD lenfatik sayılarının karşılaştırıldığı bir çalışmada ise, tümör derecesi ile LDY arasında anlamlı bir ilişki saptanamadı [41].Dil skuamöz hücreli karsinomlarında yapılan bir başka çalışmada ise yaşam süreleri ile LDY arasında ilişki saptanmadı [42].

D2-40 lenfatik endotelyal bir belirleyici olmasına rağmen, çalışmamızda tümöral dokuda ve kıkırdak dokusunda D2-40 ile değişen oranlarda boyanma görüldü. Tümör boyanması ile diferansiyasyon karşılaştırıldığında iyi diferansiye olguların %51,5'u, orta derece diferansiye tümörlerin %27,3'ü, kötü diferansiye tümörlerin %21,2'sinde boyanma izlendi. İstatiksel olarak anlamlı sonuç elde edilemedi, ancak iyi diferansiye tümörlerde daha yüksek oranda pozitif boyanma saptandı.

Literatürde kondroid neoplazmlar ve kordoma ayrımında D2-40 kullanılarak yapılmış çalışma mevcuttur. Enkondromların %100'ünde, grade 1 ve 2 kondrosarkomların %94'ünde pozitif boyanma izlenirken kordomalarda boyanma görülmemiştir [43].

D2-40, malign mezotelyoma ve adenokarsinom ayrımımında da faydalıdır. D2-40 mezotelyomalarda pozitif reaksiyon vermektedir. Ancak benign mezotelyal proliferasyon ve malign mezotelyoma ayrımında yarar sağlamamaktadır [18]. Ayrıca epiteloid mezotelyomaların tanısında en özgül ve duyarlı belirleyicilerden biridir [44,45]. Vasküler tümör tiplerinin karşılaştırıldığı bir çalışmada, Kaposi sarkomu, kaposiform hemanjioendotelyoma, hobnail hemanjiyomada D2-40 salınımının yüksek olduğu görülmüştü [46].Shotaro Iwakiri ve arkadaşlarının yaptığı çalışmada küçük hücre dışı akciğer karsinomlarında ve lenfatik endotel hücrelerinde D2-40 ile pozitif boyanma görülmüştür. Skuamöz hücreli karsinomlarda adenokarsinomlara göre daha yüksek oranda boyanma izlenmiştir. Ayrıca artmış LDY'nin kötü prognozla ilişkili olduğunu belirtmişlerdir [47].

Bizim çalışmamızda vakaların yeterli klinik verileri temin edilemediğinden D2-40 ve CD34 ile saptanan Tİ ve TD LDY ve MDY değerlerinin prognozla ilişkisi çalışılamadı.

Sonuç olarak, bu çalışmada larinks karsinomlarında D2-40 ile Tİ ve TD lenfatikler değerlendirildi ve tümör dışında daha çok lenfatik bulunduğu saptandı; fakat metastaz ile ilişkisi bulunamadı. Metastaz yapmayan grupta Tİ ve TD'de LDY daha fazla izlendi. TD ve Tİ alandaki LDY ve MDY difeansiyasyon, lenf nodu metastazı, yerleşim yeri ve tümör boyanmasının durumuna göre karşılaştırıldı. LDY ve MDY'nin larinks

kanserlerinde diferansiyasyon ve lenf nodu metastaz ile ilişkisi saptanamadı. Lenf nodu metastazlarının erken değerlendirilmesi, tedavinin belirlenmesinde ve prognozda önemlidir. LDY ve MDY'nin metastaz ile ilişkisini değerlendirmek için, daha fazla çalışma ile desteklenmesi gerektiğini düşünmekteyiz.

Teşekkür

Bu çalışma TST-08-619 no'lu proje olarak Erciyes Üniversitesi Bilimsel Araştırma Projeleri Birimi tarafından desteklenmiştir.

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Arch Clin Exp Med 2018;3(2):63-66. e-ISSN: 2564-6567

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Computed tomography assessments of pancreatic steatosis in association with anthropometric measurements: A retrospective cohort study

Pankreatik steatozun antropometrik ölçümler ile ilişkisinin bilgisayarlı tomografi değerlendirmesi: Retrospektif kohort çalışma

Yeliz Aktürk[1], Serra Özbal Güneş [1]

Abstract

Aim: Pancreatic steatosis is the fat accumulation in the pancreatic parenchyma. It is suggested that pancreatic fat infiltration may play an important role in the prognosis of diseases such as diabetes, malignancy and pancreatitis, leading to some inflammatory processes and fibrosis, and may even play an etiological role in the progress of pancreas-related diseases. However, a limited number of studies on pancreatic steatosis are available in the literature.

The aim of this study was to investigate the relation of pancreatic steatosis with age, sex, hepatic steatosis, subcutaneous fat tissue and visceral fat tissue thickness.

Methods: Hundred patients without a history of previously known pancreas disease or diabetes mellitus were included in the study. All patients had gone under abdominal tomography scan for a suspected kidney stone. Pancreas density, visceral and subcutaneous fat tissue thickness were reviewed retrospectively. The presence of coexisting hepatosteatosis was investigated.

Results: Pancreatic steatosis was detected in 54% of 100 cases examined. There were no significant difference between the pancreatic steatosis and normal pancreas groups in terms of gender and subcutaneous fat tissue thickness (p=0.115 and p=0.511, respectively). Pancreatic steatosis increased significantly with increasing age and visceral fat tissue thickness (p=0.001 and p = 0.001, respectively). The incidence of hepatic steatosis was 42% in patients with pancreatic steatosis.

Conclusion: According to our results, pancreatic steatosis increases with age and increased visceral fat tissue thickness. Thus, elderly patients with increased visceral fat tissue must be investigated for pancreatic steatosis.

Key-words: pancreas, steatosis, visceral, subcutaneous, fat tissue

Öz

Amaç: Pankreatik yağlanma, pankreas parankiminde yağ birikimidir. Bazı inflamatuar süreçlere ve fibrozise yol açarak diyabet, malignite, pankreatit gibi hastalıkların prognozunda etkili olabileceği ve hatta pankreasla ilgili hastalıkların gelişiminde etiyolojik rol oynayabileceği öne sürülmektedir. Pankreatik yağ birikiminin yaşla, cinsiyetle ve obeziteyle artış gösterdiği düşünülmektedir. Ancak literatürde pankreas yağlanması ile ilgili sınırlı sayıda çalışma mevcuttur.

Bu çalışmada pankreas yağlanmasının; yaş, cinsiyet, subkutan yağ doku kalınlığı, visseral yağ doku kalınlığı ve hepatosteatoz ile ilişkisini araştırmak amaçlandı.

Yöntemler: Araştırmaya; bilinen pankreas hastalığı ve diabetes mellitus öyküsü bulunmayan, üriner sistem taşı araştırılması amacıyla tomografi incelemesi yapılan 100 olgu dahil edildi. Retrospektif olarak yeniden değerlendirilen tomografi görüntüleri üzerinden pankreas parankim dansitesi, visseral ve subkutan yağ doku kalınlıkları ölçüldü. Eşlik eden hepatosteatoz varlığı araştırıldı.

Bulgular: Çalışmaya dahil edilen 100 olgunun %54'ünde pankreatik yağlanma saptandı. Pankreatik yağlanma olan ve olmayan olgular karşılaştırıldığında; cinsiyet ve subkutan yağ doku kalınlığı açısından fark yoktu (sırası ile p=0,115 ve p=0,511). Pankreas yağlanması yaş ve visseral yağ doku kalınlığı arttıkça istatistiksel olarak anlamlı şekilde artmıştı (sırası ile p=0,001ve p = 0,001). Pankreatik yağlanması olan olgularda karaciğer yağlanması insidansı %42 olarak bulundu.

Sonuç: Bulgularımıza göre; yaş ve visseral yağ doku kalınlığı arttıkça pankreas yağlanması da artış göstermiştir. Bu nedenle visseral yağ doku kalınlığı artmış, ileri yaştaki olgular pankreas yağlanması açısından da araştırılmalıdır.

Anahtar kelimeler: pankreas, yağlanma, visseral, subkutan, yağ doku

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Introduction

Pancreatic steatosis (PS) is a clinical condition that occurs as a result of accumulation of free fat acids and triglycerides in the pancreatic parenchyma [1]. Although it typically affects the entire pancreas homogeneously, it is possible to observe focal and irregular uptake in the parenchyma [2]. Focal steatosis is a clinically insignificant condition, but it is important because of its ability to imitate the mass lesion [3]. Pancreatic fat infiltration was first discovered in 1993 by Ogilvie through the study of cadavers. In this study, Ogilvie showed that more pancreatic fat accumulates in overweight cadavers (17% to 9%) compared to underweight ones [4].

Infiltration of any organ with fat can lead to some inflammatory processes [5]. Non-alcohol-induced hepatic steatosis can develop pathological processes leading to steatosis, fibrosis and cirrhosis. Similarly, it has been suggested that PS may develop diabetes and malignancy due to inflammatory processes initiated by fat accumulation followed by fibrosis [6, 7]. In addition, it has been proved that steatosis in pancreas aggravates the pancreatitis due to lipotoxicity [8]. It has been thought that PS may be effective in prognosis and play an etiological role in pancreas-related diseases. However, there are limited numbers of studies available on PS, which is an important entity in the literature.

In this study, we aimed to detect the cases with PS among the cases examined with unenhanced abdominal computed tomography (CT) on suspicion of urinary stones and to investigate the relation of PS with age, sex, hepatic steatosis, subcutaneous fat tissue and visceral fat tissue thickness in these cases.

Material and Methods

After obtaining the necessary authorization from the ethics committee, the abdominal CTs taken at our hospital between January 2017 and March 2017 without contrast material were retrospectively reevaluated. The study was performed according to the Declaration of Helsinki. Written consent could not be taken due to the retrospective design of the study. All CT scans were standardized on the same device with 128-section CT (Optima CT660, General Electric Healthcare Systems, Milwaukee, USA).

A total of a hundred patients who went under noncontrast abdominal tomography scan for a suspected urinary system stone were consecutively included in the study after the application of exclusion criteria. In all cases, a tomography examination was performed in order to investigate the urinary stones, but no stone was detected. Diabetes mellitus and history of pancreatitis were the exclusion criteria.

All CT imaging was evaluated by two blinded radiologists.

Fatty infiltration of the pancreas, liver and spleen was assessed by attenuation, which was measured in Hounsfield units (HU). The raw data set was reconstructed at a thickness of 1.5 mm.

The degree of pancreatic parenchymal attenuation was measured in 4 regions of interests (ROIs) at different locations in the head, neck, body and tail of the pancreas on unenhanced CT images (Figure 1). Each ROI was a round area of 0.5 cm^2, modified according to the thickness of the pancreatic parenchyma. We considered the mean value of 4 ROIs to indicate the extent of pancreatic attenuation [9]. Pancreatic lesions and vascular structures were excluded from the measurement. We were also careful not to include the peripheral margin of the pancreas to avoid the influence of the partial volume effect. We also measured splenic attenuation on unenhanced CT images by averaging the measurements in HU from one 1cm^2 ROI. From the aforementioned pancreatic and splenic attenuation measurements, P-S, where P indicates the pancreatic attenuation and S indicates the splenic attenuation, was calculated. The differences between the mean values of them were determined. If this difference was -5 or lower, it was classified into the fatty pancreas group and the rest were classified into the non-fatty pancreas group [10].

The liver steatosis was assessed by CT scan. For each patient, the average CT attenuation values in 4 sectors (one in the left lobe, two in the right lobe, and one in the caudate lobe) of the liver and in one region of the spleen were monitored (Figure 2). Each ROI was a circular area with a diameter of 1 cm^2. Liver steatosis was assessed by averaging the four ROI measurements and we calculated the liver-to-spleen attenuation ratio on CT and the difference between hepatic and splenic attenuation on CT. Hepatic steatosis was defined as a liver-to-spleen attenuation ratio less than 0.9 or a hepatic attenuation value at least 10 HU lower than the splenic attenuation value [11, 12].

Figure 1: Extent of pancreatic parenchymal attenuation was measured in 4 regions of interest (black circles) at different locations in the head, neck, body and tail of the pancreas on unenhanced computed tomography images

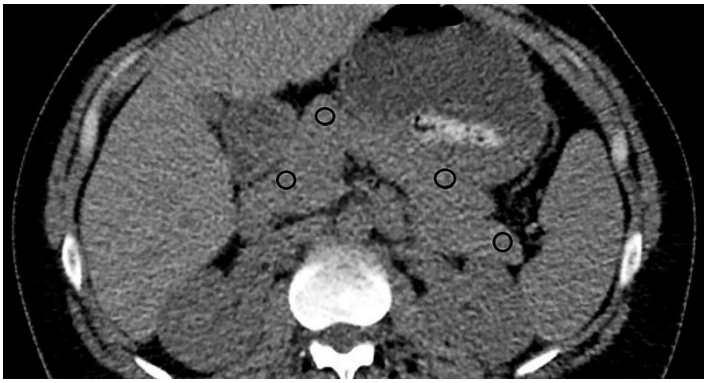
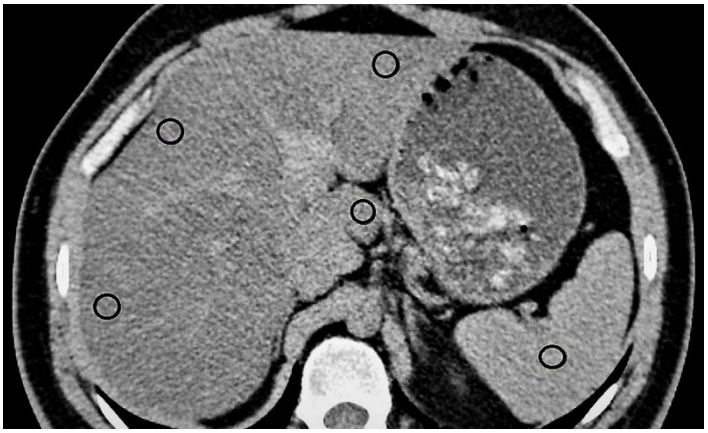
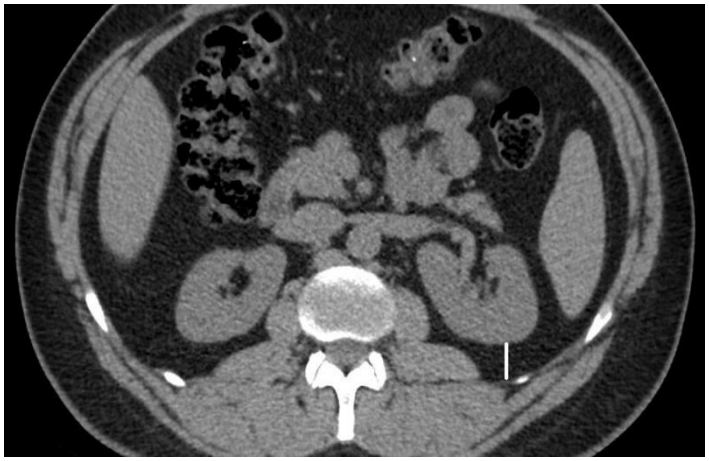


Figure 2: The degree of liver attenuation was measured in 4 regions of interest (black circles) in different sectors in the liver. The degree of spleen attenuation was measured in 1 region of interest in the spleen.



Abdominal subcutaneous fat tissue was measured bilaterally at the point 5 cm lateral to the umbilicus [13]. As an indicator of visceral obesity, the perirenal fat pad was measured in millimeter as the vertical distance between the left posterior renal capsule and the junction of the abdominal wall and paraspinal musculature (Figure 3) at the level of the left renal vein [14].

Figure 3:. The perirenal fat pad was measured in mm as the vertical distance between the left posterior renal capsule and the junction of the abdominal wall and paraspinal musculature (white line) at the level of the left renal vein



The cases were divided into two groups according to CT findings: Group 1 as those with PS and Group 2 as those without PS. The two groups were compared in terms of visceral and subcutaneous fat tissue thickness, age and gender.

Statistical analysis was performed with SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± standard deviation (SD). The student t test was used to compare fatty pancreas and non-fatty pancreas group. Independent samples t test was used to compare the age, subcutaneous and visceral fat thickness and gender data between two groups, whereas the qualitative and the coexistence of PS and hepatosteatosis data of two groups were compared using the Chi square test. Statistical significance was set at $p<0.05$.

Results

Meanage of the patients was 47±11.2 years with a range from 20 to 90 years 52 (52%) of the cases were male and 48 (48%) were female.

PS was detected in 54 cases (54%) of the cases examined (Group 1). There were 46 cases (46%) in Group 2. The mean age of the patients in Group 1 (52±8.7 years) was significantly higher than the patients in Group 2 (41±6.3 years) (p=0.001). In group 1, there were 32 male (59%) and 22 (41%) female patients. The groups were similar with regard to gender distribution (p=0.115). The demographic data and anthropometric measurements are given in Table 1.

There was no significant difference between the the groups in terms of subcutaneous fat tissue thickness (p=0.511). However, visceral fat tissue thickness was found to be significantly increased in Group 1 compared to Group 2(p=0.001).

The rate of coexistence of hepatic steatosis and PS was 42% (n=23). There were 33 cases (33%) of hepatic steatosis in the whole patient group. In the group 1 of 54 patients with PS, 23 (46%) patients had co-existing hepatic steatosis. In the group 2 of 46 patients without PS a total of 10 (22%) patients had hepatic steatosis (p=0.027).

Table 1. The demographic data and measurements of the two groups

	Group 1 (n=54)	Group 2 (n=46)	p
Age (year)	52±8.7	41±6.3	0.001
Male/female (n/n)	32/22	20/26	0.115
Average subcutaneous fat tissue thickness (mm)	26.2±2	25±4	0.511
Average visceral fat tissue thickness (mm)	13.6±3	6.2±1	0.001
Hepatic steatosis	23	10	0.027

Discussion

It has been suggested that obesity and associated insulin resistance may play a role in pancreatic adipocyte infiltration and that PS may develop in obesity cases as a consequence. Similar to non-alcohol-induced hepatic steatosis resulting from peripheral lipolysis, the term of “non-alcohol-induced PS” has been suggested [15]. PS is a process that begins with fat accumulation in pancreas and leads to inflammation. Similar to fibrosis that can occur in case of hepatosteatosis, to cirrhosis that may develop due to it and to possible formation of hepatocellular cancer, PS is also thought to play a role in the formation of fibrosis and adenocarcinoma [16]. Pancreatic cancer ranks near the top in mortality rates due to cancer [17]. It has been observed that a high body mass index (BMI) increases the relative risk of pancreatic cancer formation and the structure of fat distribution in central obesity is an independent risk factor for pancreatic cancer [18, 19].

CT is an important tool in measuring the amount of solid organs and intraabdominal fat tissue [20]. A high amount of fat accumulation in the visceral adipose tissue is known as visceral obesity. This body structure has been associated with metabolic syndrome, cardiovascular diseases and cancers such as prostate, breast and colon [21].

The ethiogenesis of PS is unknown and may be associated with the direct toxic effect of fat replacement in acinar and islet cells [22]. There is no specific biomarker for detecting PS [23]. At the present time, the gold standard for quantitative assessment of intraabdominal fat tissue is CT and magnetic resonance imaging [24].

Obesity is the main risk factor and etiological reason for PS [25]. Lipotoxicity is a cause of dysfunction of the pancreas beta cells [26]. There are views about the onset of exocrine pancreas deficiency after fat deposition in pancreas acinar cells [27]. There are studies which correlate insulin resistance to PS [28].

CT is one of the most popular and useful methods for measuring visceral lipidosis [29]. There are studies claiming that the fat accumulation in pancreas may differ between individuals with the same BMI [30, 31]. Another study in the literature found that PS is significantly associated with systolic hypertension, hyperglycemia, dyslipidemia and obesity comparing the two groups with normal and fatty pancreas [32]. Similar to our study, as a result of his autopsy studies, Ogilvie found that the visceral lipidosis and PS are significantly associated [4].

When evaluated age-wise, the patient group with PS was older. In an autopsy study including 394 cases, a significant correlation was found between PS and age. In this study, which was divided into 4 levels according to the severity of steatosis, it was found that severe PS was reduced in people who had a long-term disease and this finding was interpreted as PS may be partially reversible [33]. There are studies showing increased accumulation of pancreatic fat, especially in patients over 60 years of age. However, this has not been proven by prospective studies [34, 35]. The rate of coexistence of hepatic steatosis and PS can be as near as 67% according to some studies in the literature [10, 15]. In another ultrasonographic study, 68% of patients with PS had fatty liver, but 97% of patients with fatty liver had fatty pancreas [3]. In a study by Patel et al, they found a positive correlation between the level of steatosis in liver and the pancreas in a group of patients who were diagnosed with nonalcoholic fatty liver disease by liver biopsy [36].The incidence of hepatic steatosis was 42% in patients with PS in our study. This situation can be interpreted as that the PS can be observed before hepatic steatosis as a precursor of metabolic syndrome. Although it has been stated in the literature that it is

often associated with hepatic steatosis, our study and some other studies observed that this association rate may not be as high. As a different clinical entity than hepatic steatosis, PS may be a precursor of hepatic steatosis. However, there is a need for new large-scale studies in this subject.

Since the height and weight information of the subjects participated in our study could not be reached, no comparison was made in terms of BMI. In addition, cases were evaluated based only on CT findings and biochemical parameters such as lipid and glucose were not included in the study. These were the limitations of our study.

In conclusion, according to our study, PS increases as the age and visceral fat tissue thickness increase. Visceral fat thickness has been found to be larger in patients who have fat accumulation in pancreas. Thus, it may be said that the visceral fat accumulation, may also cause fat accumulation in pancreas.

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Stent placement after flexible ureterorenoscopy for renal stones can improve stone-free rate on final follow-up: A retrospective single center study

Böbrek taşlarına uygulanan fleksibl üreterorenoskopi sonrası stent yerleştirilmesi son takipte taşsızlık oranını arttırabilir: Retrospektif tek merkezli çalışma

Onur Kaygısız [1], Gökhun Özmerdiven [2], Kadir Ömur Günseren [1], Hakan Kılıçarslan [1]

Abstract

Aim: Although the advantage of ureteral double j (D/J) stenting has been shown in reducing post- operative pain after ureteroscopic surgery, its contribution to stone clearance for additional treatment has not been fully assessed. In this study we aimed to evaluate the effect of stenting on stone free rates at the end of the additional treatment.

Methods: We reviewed the medical records of all patients who underwent flexible ureterorenoscopy (FURS) for kidney stones between October 2009 and January 2015. Patients with malignant ureteral stricture, severe skeletal malformation, renal unit malformation, non-opaque renal stone or lost to follow-up were excluded. 47 of 289 patients (stenting 24 patients, non-stenting 23 patients) assessed. The perioperative and postoperative parameters and stone-free rates were compared in patients whether they had intraoperative D/J stent (group 1) or not (group 2).

Results: No differences were found between groups according to age, gender, body mass index, operation history, preoperative stenting history, shockwave lithotripsy history, ureteral stricture, stone size, access sheath rate, retreatment, or additional treatment number and stone location. Operation time was significantly higher in group 1. Those who refused additional treatment were insignificantly lower in group 1. Although the stone-free rates were similar for the two groups at the end of the first month, the stone-free rates after the additional treatments were significantly higher in group 1.

Conclusion: Stenting during FURS, improved the stone-free rate on final follow-up, if residual stones remain.

Keywords: Stents, kidney stone, ureteroscopy

Öz

Amaç: Her ne kadar üreteroskopik cerrahi sonrası üreteral çift J uçlu (Double J-D/J) stent yerleştirilmesinin postoperatif ağrıyı azaltmaktaki avantajı gösterilmiş olsa da taşların temizlenmesi ve ek işlem için hasta uyumuna etkisi tam olarak değerlendirilmemiştir. Biz bu çalışmada stent takılmasının ek tedaviler sonunda taşsızlık oranlarına olan etkisini araştırdık.

Yöntem: Kasım 2009 ve Ocak 2015 tarihleri arasında fleksibl üreterorenoskopi (FURS) uygulanan hastaların tıbbi kayıtları gözden geçirildi. Maling üreteral darlık, ileri derecede iskelet malformasyonu, böbrek malformasyonu olan hastalar ve takipten çıkan hastalar çalışmadan çıkarıldı. 289 hastanın 47'si (24 stent takılan, 23 stent takılmayan) değerlendirilmeye alındı. Operasyon sırasında D/J stent takılan (grup 1) ve takılmayan (grup 2) hastaların perioperatif ve postoperatif parametreleri ve taşsızlık oranları karşılaştırıldı.

Bulgular: Gruplar arasında yaş, cinsiyet, vücut kitle indeksi, operasyon öyküsü, operasyon öncesi stent yerleştirilmesi, şok dalga litotripsi hikayesi, üreteral darlık, taş boyutu, akses kılıfı kullanım oranı, tekrar tedavi, ek tedavi taş sayısı ve lokalizasyonu açısından fark yoktu. Stent uygulanan grupta anlamlı olarak operasyon süresi uzun izlendi. Ek tedavileri red etme oranı grup 1'de daha düşük izlendi. İlk ay sonunda taşsızlık oranları iki grup için benzer olmasına rağmen, ek tedavilerden sonra taşsızlık oranları grup 1'de anlamlı olarak yüksek izlendi.

Sonuç: FURS sırasında stent yerleştirilmesi, rezidüel taşların kalması durumunda son takipte taşsızlık oranını arttırmaktadır.

Anahtar kelime: Stent, böbrek taşı, üreterorenoskopi

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Introduction

Ureteral double-J (D/J) stents are often placed during many urological procedures. Ureteral D/J stent placement for urinary diversion could relieve renal obstruction and prevent ureteral stricture while reducing pain and improving stone-free rates. However, the procedure provides no benefits for uncomplicated ureteroscopic lithotripsy with lower urinary tract symptoms [1].

Flexible ureterorenoscopy (FURS) has an increasing role in active treatment of kidney stones with advanced equipment. D/J stent placement after FURS is controversial, however it has been shown that postoperative D/J stenting can decrease postoperative pain in FURS [2, 3]. In non-complicated FURS for a small stone, no D/J stenting is preferred, yet the effect of stenting for stone-free status has not been widely investigated [2, 3]. One recent study found that ureteral stents did not improve stone-free rates at the postoperative first month and did not decrease operation time [3].

In the treatment of renal stones with FURS, additional treatments just like extracorporeal shock wave lithotripsy (ESWL) and percutaneous nephrolithotomy (PCNL) may be needed for residual fragmentation after FURS treatment. No studies have investigated the effect of stenting on stone-free rates with additional treatment. Our aim was to evaluate the impact of intra-operative stenting on operative time and stone free-rates at the end of the treatment.

Material and Methods

Following local ethical committee approval, we reviewed medical records of 289 patients who underwent FURS for kidney stones between October 2009 and January 2015 in a single center. Study procedures followed the ethical standards of the Helsinki Declaration and all patients gave written informed consent of this study. Exclusion criteria were malign ureteral stricture (n=2), severe skeletal malformation (n=16), renal unit malformation (n=46), presence of non-opaque renal stones (n=18), conversion to percutaneous nephrolithotomy (PCNL) (n=13), failure to report for follow-up (n=109) and patients under 18 years old (n=37). Therefore, a total of 47 patients were evaluated after applying exclusion criteria. Patients with D/J stent placement after FURS were designated as belonging to the stented group (Group 1) while patients without intra-operative stenting comprised the non-stented group (Group 2).

Patient demographics (age, gender, body mass index (BMI)) and preoperative clinicopathological features including stone location, mean stone area (cm^2), use of computed tomography, use of preoperative D/J stents, previous intervention and surgical treatments for stone disease were recorded. BMI was calculated as weight in kilograms divided by the square of the height in meters. The stone was determined with urinary ultrasound, X-ray of kidney, and ureter and bladder X-rays (X-ray KUB). In doubtful cases, a CT scan was performed.

Perioperative data included operation time, operation side, use of ureteral access sheath, and use of D/J stent at the end of the operation. Operation time was also grouped as <60 minutes and ≥ 60 minutes. Hospitalization time (days), Complication rate and patients who had febrile urinary tract infection were recorded.

After the operation, the stone status was evaluated in the second week and in the first month. If any residual stones were observed after the first month, additional treatment had been planned. D/J stent would have removed at the end of the additional treatment. The status of the stones was assessed by physical examination, urinalysis, X-ray KUB and urinary ultrasound. In ambiguous cases, non-contrast computed tomography was used to assess the status. Patients that required additional treatment for residual fragments were evaluated one month following their last procedure. Additional treatments for residual stones were extracorporeal shock wave lithotripsy (ESWL), retrograde intrarenal surgery (RIRS), percutaneous nephrolithotomy (PCNL) and ESWL+RIRS. Patients who refused the additional therapy for residual stones with known final stone status was included the study and they were classified as refused additional treatment.

Flexible ureterorenoscopy (FURS) Technique

FURS was performed in a dorsal lithotomy position under general anesthesia. Semi-rigid double lumen 8.5 F ureterorenoscope was used for guide wire insertion and assessment of the ureters. After a guide wire was inserted into the ureter under fluoroscopic image, ureteral obstruction or stones were assessed with visual and fluoroscopic images. A 7.5F flexible ureterorenoscope was used. The 9.5 F access sheath was used according to ureteral diameter and stone burden. Stone fragmentation was performed with holmium laser lithotripsy. The stones were fragmented until they were less than 2mm in size. Small fragments were left for spontaneous passage. A 4.7 F D/J stent was inserted at the end of the operation.

Statistical analysis

Statistical analysis was performed with the SPSS version 22 software. The Shapiro-Wilk test was used to test the normality of variables. The normally distributed variables are presented as mean ± standard deviation and were compared with Student's t test. The non-normally distributed variables were presented as median (minimum-maximum) and were compared with the Mann-Whitney U test. Nominal data were presented as number and percentage and were compared to the Fisher's Exact test. A finding of p less than 0.05 was considered statistically significant.

Results

The mean age was 49.3±13.9 years in group 1 and 47.8±13.8 years in group 2. The rate of preoperative D/J stent (prestenting) was 4.3%. The stones were mostly observed in lower pole of kidney (29.2% in group 1 and 39.1% in group 2) in all groups. ESWL treatment was applied more than other treatments, before FURS (29.2% in group 1 and 34.8% in group 2) in all groups. Ureteral stricture was not seen in both groups.

There were no differences between the groups according to age, gender, BMI, operation history, mean stone area, preoperative CT scan, side and localization of the stones, preoperative D/J stent history, previous ESWL, operative history and ureteral stricture ($p>0.05$ for all) (Table1).

Use of access sheath rate, need for additional treatments, number of additional treatments and hospitalization time were similar for the two groups (Table 2). Seven patients (29.1%) had febrile urinary tract infection in Group 1 and inpatient treatment was applied for one patient because of urosepsis. 4 patients (17.3%) had febrile urinary tract infection in Group 2. Overall complication rate are similar in two groups ($p=0.646$) (Table 2).

Although refusals of the additional treatment rate were more prevalent in the Group 2, the difference was not statistically significant (Table 2). The stone-free rate was 45.8% at the first postoperative month and 83.3% with the additional therapy in Group 1. In Group 2, the stone-free rate was 21.7% at the first postoperative month and 30.4% with additional therapy. The stone-free rate in the first month was higher in Group 1, but not statistically significant. However, the stone-free rate after the additional therapy was significantly lower in Group 2 and operation time was significantly higher in Group 1 ($P=0.029$ and $P=0.049$, respectively) (Table 2).

Table 1. Comparison of the patients' demographics and preoperative data.

		Group 1 (n=24)	Group 2 (n=23)	P
Mean age (year) [β]		49.3±13.9	47.8±13.8	0.711
Gender	Female (n=26) (%)	41.7	47.8	0.772
	Male (n=21) (%)	58.3	52.2	
Mean BMI (kg/m^2) [µ]		27 (19-40)	29 (21-55)	0.190
Mean stone area (cm^2) [µ]		1.8 (0.5-4.5)	1.5 (0.4-7.7)	0.309
Preoperative CT scan [¥]		13(54.2)	9 (39.1)	0.385
Right sided stones (%)		49.8	54.2	0.832
Location of stone [¥]	Pelvis	7 (13.0)	3 (13.0)	0.597
	Upper	2 (7.2)	4 (16.7)	
	Mid	4 (16.7)	3 (13)	
	Lower	7 (29.2)	9 (39.1)	
	Multiple including lower calyx	4(16.7)	5 (21.7)	
Multiple location (%)		16.7	21.7	0.724
Preoperative D/J [¥]		1(4.2)	1(4.2)	1
Preoperative ESWL history (%)		29.2	34.8	0.760
Ureteral stricture		0	0	NA
Operation history [¥]	None	15 (62.5)	16 (69.6)	0.539
	Open	3 (12.5)	3 (13.0)	
	RIRS	0	1 (4.3)	
	PCNL	2 (8.3)	1 (4.3)	
	URS	4 (16.7)	2 (8.7)	

[β]: Mean ± standard deviation, [µ]: mean (range), [¥]: mean (%),%: percentage in group
D/J: Double J stent, ESWL: Extracorporeal shock wave lithotripsy, RIRS: Retrograde intrarenal surgery, PCNL: Percutaneous nephrolithotomy, URS: Ureterorenoscopy, CT: Computed tomography, NA: Not applicable

Table 2. Comparison of two groups with respect to the perioperative and follow up parameters.

		Group 1 (n=24)	Group 2 (n=23)	P
Use of access sheath rate (%)		50	39.1	0.561
Operative time (min) [µ]		90 (40-170)	55 (40-180)	0.049
Operative time [¥]	<60 min	4 (16.7)	12 (52.2)	0.045
	≥ 60 min	20 (83.3)	11(47.8)	
Hospitalization time (day) [µ]		2 (2-19)	2 (2-5)	0.282
Febrile urinary tract infection [¥]		7 (29.1)	4 (17.3)	0.061
Complication rate (%)		29.1	26	0.646
Additional treatment [¥]	None	20 (83.3)	17 (73.9)	0.301
	SWL	2 (8.3)	5 (21.7)	
	RIRS	0	1 (4.3)	
	PCNL	1(4.2)	0	
	RIRS with SWL	1 (4.2)	0	
Total treatment number [µ (range)]		1.21±0.72 (1-4)	1.26±0.90 (1-5)	0.947
Refused the additional treatment [¥]		1 (4.2)	3 (12.5)	0.100
Stone free rate (1st month) [¥]		11 (45.8)	5 (21.7)	0.650
Stone free rate (at the end of additional treatment) [¥]		20 (83.3)	7 (30.4)	0.029

[β]: Mean ± standard deviation, [µ]: mean (range), [¥]: mean (%),%: percentage in group
D/J: Double J stent, ESWL: Extracorporeal shock wave lithotripsy, RIRS: Retrograde intrarenal surgery, PCNL: Percutaneous nephrolithotomy.

Discussion

Although ureteral stents may support ureteral healing and relieve ureteral obstruction, they cause significant morbidity, including pain, irritating voiding symptoms, hematuria and infection [4, 5]. For these reasons, routine D/J after FURS stenting is controversial.

The insertion of a D/J stent after URS was widely investigated, contrary to FURS. Routine stenting after ureteroscopy was not shown to improve the stone-free rate when accompanied by increased lower urinary symptoms, pain and operative time [6]. Even a greater stone diameter was not found to be a factor in making a ureteral stenting decision when there were similar stone-free and complication rates after uncomplicated ureteroscopic lithotripsy [7].

Although D/J stent placement at the end of the FURS procedure is optional, nearly 50% of surgeons prefer to insert it routinely [8]. Others make the decision according to intra-operative factors [8]. Miernik et al. [9] reported that complication rates were found to be 9.1% due to the use of wider access sheath and so an intraoperative D/J stent was inserted in 57% of patients undergoing FURS.

Nevertheless, a few studies have investigated the effect of intra-operative D/J stent placement on the stone-free rate following additional treatment. It was shown that D/J stent insertion could lessen the pain in FURS, although there was no benefit for stone free-status at first postoperative month [2, 3]. However ureteral stent could be used for pain relief with a shorter operative time [10]. These studies did not support the use of a D/J stent for all FURS cases. However, these studies also didn't emphasize the role of D/J stenting on residual stone treatment after FURS, as is the focus of our study.

Potential benefits of a D/J stent are support of the passage of urine and stone fragments and hydronephrosis healing. Jones et al. [11] reported a higher success rate following failed ureteroscopic management of ureteric calculi with ureteral stent insertion. Also, Chu et al. [12] stated that prestenting decreased operative time and the reoperation rate in patients with ureter stones larger than 1 cm. Moreover Lumma et al. [13] reported prestenting improved stone-free rates in patients with mid- or upper-ureter stones as distinct from distal ureter stones. Rubenstein et al. [14] point out prestenting can result in better stone-free rates. Preoperative D/J stent placement also has been shown to improve the success rate for URS for nephroureterolithiasis [15]. Preoperative ureteral stenting may facilitate the ureteral access sheath insertion [16]. These studies could explain the better stone-free rate at the end of additional therapy in patients with perioperative stenting. However, stenting before SWL did not increase the stone-free rate with lower urinary tract symptoms [17].

It has been reported that stenting after ureteroscopic stone management caused longer operative time [6]. However stenting after FURS led to the shorter operative times in the previous research [3], in our study operative time was longer in group 1.

Patient compliance is essential for FURS because retreatment and additional treatment are required, especially for large stones. The rate of refusals of additional treatment was higher in group 2 (12.5% vs. 4.2%) but the difference was not statistically significant. Stone-free rate with an additional treatment was significantly higher in group 1. So, we believe that stenting encouraged patients to seek further treatment and stenting should be the part of minimal invasive surgery for kidney stones, if additional treatments are necessarily considered.

As the limitation of this study, the exclusion criteria were too many, but the exclusion criteria had a high stent placement rate. Therefore, a comparable small sample size has been realized.

In conclusion, stenting intraoperatively after FURS improved the stone-free rate on the final follow-up. However, stenting caused the prolonged operative time. We suggest that intraoperative stenting after FURS is on surgeon's mind if

surgeon consider that residual stones will be at the end of the first month. Prospective studies with a larger number of patients could give a definite judgment on these issues.

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Is metabolic syndrome related to postmenopausal osteoporosis? A retrospective study

Metabolik sendrom postmenopozal osteoporoz ile ilişkili midir? Retrospektif bir çalışma

Elif Turan [1], Hafize Kızılkaya [2], Yalçın Aral [1]

Abstract

Aim: To evaluate the difference between postmenopausal women with and without osteoporosis in terms of metabolic syndrome.

Methods: A total of 98 postmenopausal women younger than 65 years, were enrolled in the study. According to the bone mineral density examination; 49 participants who had T-score>−2.5 at the spine or/and femoral neck were included in the group without osteoporosis (Group 1), and 49 participants who had T-score≤−2.5 at the spine or/and femoral neck were included in the osteoporosis group (Group 2). Patient's profile which included all demographic data, particularly anthropometric evaluation and medical history was obtained. Serum fasting glucose, lipid profiles and 25 OH vitamin D levels were also recorded.

Results: Age (p=0.001), menopausal age (p=0.003), systolic blood pressure (p=0.004) and diastolic blood pressure (p=0.001) of Group 2 were significantly higher than Group 1. There were no significant difference in terms of body mass index, weight, lipid profiles, serum calcium and serum 25 OH vitamin D levels among the groups (p>0.05 for all). Twenty five (51%) of 49 women in Group 1 and 36 (73%) of 49 women in Group 2 had metabolic syndrome. There was a statistically significant relationship between osteoporosis and the metabolic syndrome (p=0.037).

Conclusion: Our results demonstrated that osteoporosis is related with the metabolic syndrome in postmenopausal women.

Keywords: Metabolic syndrome, menopause, osteoporosis.

Öz

Amaç: Postmenopozal kadınlarda, osteoporoz ile metabolik sendrom arasındaki ilişkiyi değerlendirmek.

Yöntemler: 65 yaşın altında toplam 98 postmenopozal kadın çalışmaya dahil edildi. Kemik mineral dansitometre sonucuna göre; lumber ve/veya femur boyun T skoru>-2.5 olan 49 hasta postmenopozal osteoporoz olmayan gruba (Grup 1), T skoru≤-2.5 olan 49 hasta postmenopozal osteoporoz grubuna (Grup 2) dahil edildi. Tüm demografik verileri içeren hasta profili, antropometrik değerlendirme ve tıbbi öykü kaydedildi. Serum açlık glukozu, lipit profili ve serum 25 OH D vitamin seviyesi de kaydedildi.

Bulgular: Grup 1 ve Grup 2 karşılaştırıldığında; yaş (p=0.001), menopoz yaşı (p=0.003) sistolik kan basıncı (p=0.004) ve diyastolik kan basıncı (p=0.001) Grup 2'de Grup 1'e göre anlamlı şekilde daha yüksekti. Vücut kitle indeksi, boy, kilo, lipid profili, serum 25 OH vitamin D düzeyleri açısından gruplar arasında anlamlı fark yoktu (p>0.05). Osteoporozu olan 49 hastanın 36'sında (%73), osteoporozu olmayan 49 hastanın ise 25'inde (%51) metabolik sendrom tespit edildi. Osteoporoz ile metabolik sendrom arasında istatistiksel olarak anlamlı ilişki tespit edildi (p=0.037).

Sonuç: Postmenopozal kadınlarda osteoporoz ile metabolik sendrom arasında anlamlı ilişki olduğu tespit edilmiştir.

Anahtar Kelimeler: Metabolik sendrom, menopoz, osteoporoz.

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Introduction

Metabolic syndrome is a cluster of systemic disorders and is well known to increase the risk of endocrinopathy. Insulin resistance plays a central role and is related to the all components of metabolic syndrome, defined by the presence of central obesity, dyslipidemia, glucose intolerance or diabetes mellitus, and hypertension [1]. National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) criteria and International Diabetes Federation (IDF) criteria are used for diagnosis of metabolic syndrome [2]. According to the ATP III criteria, metabolic syndrome is reported to be present in 30% of men and 41.8% of women in Turkey [3]. The same study also showed an increase in the prevalence of the metabolic syndrome, especially over the age of 45 years.

Osteoporosis is one of the most common diseases worldwide. Due to its prevalence, osteoporosis is considered as an important public health concern. Approximately 30% of all postmenopausal women have osteoporosis in the United States and in Europe [4]. Osteoporosis and cardiovascular disease are age-related conditions that affect mortality and morbidity. The relation of coronary artery atherosclerosis and calcification with osteoporosis is reported in women [5]. Atherosclerosis and hyperlipidemia were also reported to be associated with osteoporosis [6].

The data about the association between osteoporosis and the metabolic syndrome is limited [7, 8]. There is no data in the literature, concerning the relation of postmenopausal osteoporosis and metabolic syndrome in Turkish population. Therefore, we aimed to probe the relation of osteoporosis and metabolic syndrome in postmenopausal women.

Material and Methods

The study was approved by Bozok University ethics committee. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 and informed consent was obtained from all participants for being included in the study. Written consent could not be taken due to the retrospective design of the study.

A total of consecutive 98 postmenopausal women who were younger than 65 years living in Yozgat area/Turkey were enrolled in the study between ??? and ????. All participants were postmenapousal for at least one year. Patients suffering from ischemic heart disease, chronic systemic inflammatory disorders, patients with renal failure, patients suffering from thyroid and parathyroid related disorders and patients above 65 years of age were excluded from the study.

Participants were assigned in two groups based on their bone mineral density (BMD) score; 49 participants who had T-score>−2.5 at the spine or/and femoral neck were included in the group without osteoporosis (Group 1) and 49 participants who had T-score ≤−2.5 at the spine or/and femoral neck were included in the osteoporosis group (Group 2).

Personal medical history, including age and menopause duration was obtained. Weights (kg) and heights (m) of the participants were measured. Body mass index (BMI) as kg/m^2 was calculated by the formula of (weight in kg) / (height in meters^2). Waist circumference (WC) of the participants was measured to evaluate abdominal obesity. Blood pressure (mmHg) was measured using with standard mercury manometer. The normal limit was 130 mmHg for systolic blood pressure and 85 mmHg for diastolic blood pressure, consistent with NCEP-ATP III cut points for blood pressure in the definition of the metabolic syndrome [2]. Patients taking antihypertensive medications were also classified as hypertensive. Blood samples for fasting glucose, serum calcium (mg/dL), 25 OH vitamin D (ng/mL) and lipid parameters including total cholesterol (mg/dL), HDL (mg/dL), LDL (mg/dL) and triglyceride (mg/dL) were centrifuged at room temperature for 5 minutes at 3000 RPM. The extracted serum was kept in ice bags and put in deep freezers at -80 °C.

Metabolic syndrome was defined with the NCEP ATP III criteria. This definition requires the presence of at least three or more of the five components of the following categorically defined risk factors: Abdominal obesity; waist circumference greater than 88 cm, hypertension (130/85 mmHg or greater, taking antihypertensive medications), high triglycerides (150 mg/dL or greater), low HDL cholesterol (less than 50 mg/dL in women), hyperglycemia (100 mg/dL or greater or taking antidiabetic medication) [2].

Statistical analysis

The findings were analyzed statistically using the Statistical Package for the Social Sciences, version 18.0 (Chicago, IL). The distribution was evaluated with the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation and non-normally distributed variables were expressed as median with minimum and maximum values. Mean values of the two groups were compared by independent samples T test for variables distributed normally and Mann-Whitney U-test for variables distributed non-normally. Chi square test was used for categorical variables. The value of $p < 0.05$ was considered statistically significant.

Results

Descriptive characteristics are summarized in Table. When compared with Group 1, mean age (54.5±5.7 vs. 58.2±4.6; p=0.001), menopausal duration [7 (1-20) vs. 10 (1-24); p=0.003)], systolic blood pressure (121.1±10.9 vs. 128.7±13.7; p=0.004) and diastolic blood pressure (76.7±7.8 vs. 81.7±7.8; p=0.001) were significantly higher in Group 2. Lumbar spine BMD (-1.68±0.59 vs. -3.03±0.49; p=0.001) and femur neck BMD (-1.19±0.65 vs. -1.95±0.84; p=0.001) were significantly lower in Group 2.

There were no significant difference between the groups in terms of menopause age (p=0.997), weight (p=0.324), height (p=0.388), BMI (p=0.541), fasting glucose (p=0.539), total cholesterol (p=0.628), HDL (p=0.444), LDL (p=0.732), triglyceride (p=0.198), and serum 25 OH vitamin D (p=0.707) levels (Table).

The prevalence of the metabolic syndrome was 62% (61 of 98 participants) in all study population. The metabolic syndrome was detected in 25 (51%) of 49 participants and 36 (73%) of 49 participants in Group 1 and Group 2, respectively.

There was a statistically significant relationship between osteoporosis and the metabolic syndrome (p=0.037).

Table: Descriptive features

Parameter	Group 1 (n=49)	Group 2 (n=49)	p
Age (year) β	54.5±5.7	58.2±4.6	0.001
Height (m) β	1.56±0.06	1.55 ±0.05	0.388
Weight (kg) β	80.4±12.1	78.0±12.6	0.324
Body mass index (kg/m^2) β	32.9±5.3	32.2±5.5	0.541
Waist circumference (cm) β	103.4±12.3	104.8±10.6	0.523
Lumbal spine BMD (g/cm^2) β	-1.68±0.59	-3.03±0.49	0.001
Femur neck BMD (g/cm^2) β	-1.19±0.65	-1.95±0.84	0.001
Menopause age (year) β	47.3±6.2	47.9±3.9	0.997
Menopausal duration (year) μ	7 (1-20)	10 (1-24)	0.003
Fasting glucose (mg/dL) μ	101 (71-310)	109 (73-301)	0.539
Total cholesterol (mg/dL) β	203.7±35.6	207.6±42.4	0.628
HDL (mg/dL) β	51.0±10.6	52.8±11.0	0.444
LDL (mg/dL) β	123.4±30.7	125.7±33.4	0.732
Triglyceride (mg/dL) β	127(39-427)	143 (57-451)	0.198
Serum calcium (mg/dL) β	9.5±0.5	9.5±0.4	0.824
25 OH vitamin D (ng/mL) μ	14 (4-68)	14 (4.1-134)	0.707
Mean sistolic pressure (mm/Hg) β	121.1±10.9	128.7±13.7	0.004
Mean diastolic pressure (mm/Hg) β	76.7±7.8	81.7±7.8	0.001
Metabolic syndrome (n (%))	25 (51%)	36 (%73)	0.037

β: mean ± standard deviation, μ: median and range

Discussion

In this study, a significant relation has been found between metabolic syndrome and osteoporosis in postmenopausal women.

Obesity is commonly seen in postmenopausal women. Silva et al. reported that about 50% of postmenopausal women are obese [9]. Previous studies have demonstrated that body fat mass and BMI were higher in postmenopausal women than perimenopausal women [10]. In this study, mean BMI in both groups were above 30 kg/m2 as obese. However, there were no significant differences in BMI, WC and weight between the groups.

A several number of studies have supported that osteoporosis and cardiovascular diseases have a link because of common pathophysiological and genetic risk factors [11-13]. Recent studies also proved that estrogen deficiency is an independent risk factor for osteoporosis and coronary heart disease [12, 13]. Estrogen level has been found to be positively correlated with BMD and HDL [14, 15]. Barengolts et al. compared the lipid profile in postmenopausal women with and without osteoporosis [16]. No significant difference was found between the groups. Same as the literature, in our study, there was no significant difference in lipid profiles in postmenopausal women with and without osteoporosis. On the other hand, the prevalence of both cardiovascular disease and osteoporosis increase with advanced age [17]. All postmenopausal patients included the study were under 65 years of age, because the risk of cardiovascular disease was expected to increase with age progression, especially above 60.

The components of metabolic syndrome, such as high blood pressure, increased triglycerides, and reduced HDL are also related to osteoporosis while other components such as obesity are not. It is demonstrated that osteoporosis is related to inflammation. It was recently shown that, participants with high insulin resistance have more inflammation than participants with low insulin resistance [18, 19]. Some studies advocated that low chronic inflammation may affect bone health [20]. According to a study, the prevalence of DM and insulin resistance in postmenopausal women was higher than in premenopausal women [21]. Gundoğan et al. reported that women who were between 50-59 ages had higher prevalence of the metabolic syndrome than normal population [3]. They found the metabolic syndrome rate as 40.4%, according to NCEP-ATP III criteria and as 48.3% according to IDF criteria. The impact of risk factors of the metabolic syndrome on bone health has been regarded as controversial in the literature [22-24].

A study showed that there was an association between metabolic syndrome features and prevalent osteoporotic fractures in a cross-sectional analysis, and metabolic syndrome was related to lower BMD [24]. The opposite results have also been reported [22, 23]. Especially in some studies, the authors suggested that obesity, diabetes and the metabolic syndrome have protective effects for osteoporosis [22]. On the other hand, a meta-analysis indicated that the metabolic syndrome is associated with a 15% reduced risk of fractures in adults [23].

In the present study, the rate of the metabolic syndrome was higher in patients with osteoporosis. Also mean systolic and diastolic blood pressures were higher in patients with postmenopausal osteoporosis. Sedentary lifestyle can potentially contribute to insufficient sun exposure and individual components of metabolic syndrome. Age of the patients with postmenopausal osteoporosis was significantly higher than the patients without postmenopausal osteoporosis. Therefore, we thought that significant differences in the prevalence of the metabolic syndrome between the groups may be related to higher age, and also sedentary lifestyle in the postmenopausal osteoporosis group.

Our study has several limitations; because of cross-sectional study design, we cannot assess reasons between metabolic syndrome and low BMD. Secondly, our group consists of female patients who refer to the endocrine clinic. Population generalization cannot be done because it does not include male patients.

In conclusion, in our study, the prevalence of the metabolic syndrome was found to be higher as 62% in all the postmenopausal participants. Our result showed that rate of the metabolic syndrome was higher in patients with osteoporosis than the patients without osteoporosis in the postmenopausal patients under 65 years of age.

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Arch Clin Exp Med 2018;3(2):75-78. e-ISSN: 2564-6567

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Non-epileptic paroxysmal events in early childhood and role of EEG: A single center experience

Erken çocukluk çağında epileptik olmayan paroksismal olaylar ve EEG'nin rolü: Tek merkez deneyimi

Serkan Kırık [1], Mehmet Yaşar Özkars [2]

Abstract

Aim: Non-epileptic paroxysmal events are the most frequently movement disorders mimicking epilepsy. Our aim in this article is to increase awareness among physicians by sharing our clinical experience; to reduce unnecessary anti-epileptic use and the number of examinations.

Methods: In total 73 patients were included in the study. Patients were evaluated according to detailed anamnesis, video recordings, laboratory findings and electroencephalography (EEG) findings.

Results: The most common diagnosis in patients involved in the study was breath holding spells. The youngest age group was benign sleeping myoclonus. None of the patients had epileptiform activity in the EEG.

Conclusion: Non-epileptic paroxysmal events commonly involve the unnecessary use of anti-epileptic medications due to mimicking of epilepsy. This study has shown that detailed anamnesis, EEG findings, and increasinguse of mobile phone video reduce unnecessary treatment and examination in these patients.

Keywords: Paroxysmal, electroencephalography, children

Öz

Amaç: Epileptik olmayan paroksismal olaylar, epilepsi ile en sık karıştırılan hareket bozukluklarıdır. Bu yazıdaki amacımız klinik deneyimimizi paylaşarak hekimler arasında farkındalığı arttırmak; gereksiz anti-epilepik kullanımını ve tetkik sayısını azaltmaktır.

Yöntemler: Çalışmaya 73 hasta dahil edildi. Hastalar ayrıntılı anamnez, video kayıtları, laboratuvar bulguları ve elektroensefalografi (EEG) bulgularına göre tanı açısından değerlendirildi.

Bulgular: Çalışmaya dahil edilen hastalarda en sıktanı katılma nöbetiydi. En küçük yaş grubu benign uyku myoklonisiydi.Hastaların hiçbirinin EEG'sinde epileptiform aktivite saptanmadı.

Sonuç: Epileptik olmayan paroksismal olaylar, epilepsi ile sık karıştıklarından sıklıkla gereksiz anti-epileptik tedavi kullanımı söz konusu olmaktadır. Bu çalışma, ayrıntılı anamnez, EEG bulguları ve giderek yaygınlaşan video kullanımının böylesi hastalarda gereksiz tedavi ve tetkik gereksinimini azalttığını göstermiştir.

Anahtar Kelimeler: Paroksismal, elektroensefalografi, çocuk

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Introduction

Non-epileptic paroxysmal events (NEPE) in early childhood as a complicated case involving the intermittent repetitive motor movements, behavioral changes and somatic symptoms cause disquiet among parents and physicians in most of the time [1]. Symptoms diminish with age, even disappear before the school ages, and often do not require treatment which is the most important characteristic in most of the cases. Additionally, some patients are subjected to treatment due to misdiagnosis of epilepsy. For differentiating these symptoms from epileptic seizures, the absence of electroencephalographic (EEG) epileptiform changes in the event of an epileptic seizure proves itself useful in diagnosis. The most crucial step for diagnosis is the detailed anamnesis. Frequent NEPE in early childhood have a wide spectrum and are composed of benign sleeping myoclonus (BSM), benign paroxysmal vertigo (BPV), breath-holding spell (BHS), night terrors (pavornocturnus) and infantile masturbation [2, 3]. Less commonly observed symptoms include chills, hyperekplexia and paroxysmal tonic upgaze. Nowadays, with the widespread use of camera devices such as mobile phones, the correct diagnosis of such events can be established easily [4].

In this particular study, we aimed to raise awareness of pediatric physicians by showing the clinical characteristics, EEG findings and established diagnoses of the patients who applied to pediatric neurology clinics; thus, making contributions to reduction of misdiagnosis, unnecessary examination, excessive costs of treatment.

Material and Methods

In our study, the files of the patients who had BSM, BPV, BHS, pavornocturnus and infantile masturbation were reviewed retrospectively in Kahramanmaraş Sütçü İmam University Medical School Pediatric Neurology Clinic between June 2017 and April 2018. The study was performed according to the declaration of Helsinki. Written consent was taken from parents of the patients.

The study included patients admitted our pediatric neurology clinic, normal neuromotor development, at least one family member or guardian who was able to identify habitual events. Patients' diagnoses consisted of BHS (cyanotic type-pallid type), BSM, pavornocturnus, BPV and infantile masturbation. Patients with pathologic neurological examination, patients with neuromotor growth retardation and patients whose file information was not available were excluded from the study.

We retrospectively reviewed the medical records of a total of 87 cases. Fourteen patients were excluded from the study; so, a total of 73 patients were included in the study.

The detailed anamnesis of patients, duration of complaints, EEG records, laboratory findings, physical examination findings and images obtained by families and/or findings acquired during EEG were recorded. Two types of BHS are present based on the color of the child during the apneic episode following the end of prolonged expiration either pale (pallid attacks) or blue (cyanotic attacks) [4]. The 3rd Beta criteria determined by the International Headache Society for BPV were taken into consideration [5]. Patients with low hemoglobin concentration and low ferritin levels than (<10 ng/dL) were evaluated for iron deficiency anemia. Dallman anemia criteria for hemoglobin concentration were taken as reference according to age (6 months-4.9 years= 11 g/dL, 5-11.9 years= 11.5 g/dL) [6].

Statistical Analysis

Data analysis was done by the SPSS 22.0 package program. Normally-distributed continuous variables were expressed as mean ± standard deviation. Continuous variables without normal distribution and categorical variables were expressed as median and frequencies with percentages, respectively.

Results

There were a total of 73 patients included in the study. The average age of these patients was 14.42 ± 10.24 months (45 days-49 months). Thirty nine (53.4%) of the patients were male and 34 (46.5%) were female. Female to male ratio was higher in patients diagnosed with infantile masturbation (F / M: 2/1) contrary to the other patients in which higher male to female ratios were present.

The most commonly established diagnosis was BHS (n= 51) followed by pavornocturnus (n= 9). The patients with BSM constituted the youngest age group (mean= 53.2 ± 12.8days) and the infantile masturbation group had the oldest age group (mean= 41± 8.6 months) (Table).

All of the patients' EEG records were examined. Non-epileptic paroxysmal activity was detected in EEG in 8 patients (10.9%). None of the patients showed any epileptic abnormalities on EEG.

Table: Demographic and clinical characteristics of the patients due to non-epileptic paroxysmal events.

Diagnosis		n (%)	Male sex (%)	Age (M/D) β	Attack frequency (D/M/Y)	Duration of Symptoms (min)	Sleep-awake
BHS		51 (69.8)	52.9	19.5±11.6 M	7.6±4.3 M	3±4.6	Awake
	Cyanotic	32 (43.8)	53.1	20.2±7.4 M	8.1±5.2 M	3±4.3	Awake
	Pallid	19 (26)	52.6	17.4±8.3 M	7±3.4 M	3±5.2	Awake
Pavor nocturnus		9 (12.3)	55.5	38 ±10.7 M	8.3±6.3 M	10±8.3	Sleep
BSM		7 (9.5)	57.1	52.3±12.8 D	4±4.8 D	1±2.3	Sleep
BPV		3 (4.1)	66.6	22.3±9.3 M	4.2±3.5 Y	5±4.1	Awake
IM		3 (4.1)	33.3	41±8.6 M	5.2±8.2 D	5±3.8	Awake

β: mean±standard deviation, BHS: Breath-holding spell, BSM: Benign sleep myoclonus, BPV: Benign paroxysmal vertigo, IM: Infantile masturbation, D: day, M: month, Y: year, min: minutes

Neuroimaging was performed on 3 patients with BPV diagnosis. Pathology was not observed in imaging findings. Iron-replacement therapy was administered to 43 patients who applied for breath-holding spell and to those who had iron deficiency anemia. Eight patients without anemia were recommended and treated with piracetam (Nootropil®, 5-10 mg/kg/dose, per oral, three times a day, UCB Pharma, Istanbul, Turkey). A significant decrease in complaints was observed in 3-month follow-ups of the patients.

In pavornocturnus, the attack interval was one time during the day. Families were given recommendations. All of the patients had regression in their symptoms after 3 months. Complaints of patients diagnosed with BSM ended before the patients were 3 months old. Cyproheptadine (Sipraktin®, 2-4 mg/dose, per oral, twice a day, I.E. Ulagay, Istanbul, Turkey) therapy was initiated for all BPV patients. At the end of the third month of the test, there was a decrease in the frequency of attacks. All patients with infantile masturbation had diaper dermatitis and patients' families were given recommendations. There was a decrease almost %90 in the interval of attacks during the 3-month follow-up period in BSM patients. Also, the number of attacks in patients with BSM and infantile masturbation was significantly higher than the other patients.

Discussion

Non-epileptic paroxysmal events include an episodic phenomenon, a motor phenomenon with a variable duration and a generally stereotypical character. The diagnosis is based on detailed anamnesis and attentive observation. Clinical spectra are quite extensive. Frequencies reported in various studies that were carried out by Kotagal et al. [7] was at 15% while the study carried out by Patel et al. [8] demonstrated as 3.5%. Duration, location, shape, time of occurrence, state of consciousness of the attacks; between the epilepsy and the NEPE diagnosis, may cause hesitance among physicians. In this case, differential diagnosis can be established by recording the seizure through a video recording device and evaluating the EEG at the same time [1, 2].

BHS is a paroxysmal disorder that is triggered by emotional and / or physical stimuli that occurs approximately at 4.6% during early childhood. It is more commonly observed among males. The reported age range varies between the 3rd month and up to 6 years, but in most of the cases range is between 6 months and 36 months [4, 9]. The majority of patients presenting with BHS have a seizure of cyanotic type followed by pallid type seizures. BHS begins with a warning period, followed by crying. The triggering factors during the stimulation differ according to the types of seizures. BHS, a cyanotic type, is a psychogenic stimulus that induces seizure, whereas the pallid type of trauma is anterior [10, 11]. In our study, the number of male patients was higher and cyanotic type seizures were detected in the majority of patients in accordance with the literature. The vast majority of patients were composed of individuals younger than 3 years of age. No epileptic abnormality was observed during any EEG recording. In particular, most patients benefit from iron therapy.

Pavornocturnus is a sleep disorder that occurs in the non-REM sleep period, followed by screaming, cold sweating, crying and hallucinations about 1.5-2 hours into sleeping. It is most commonly seen between 4-6 years of age and in males. It is typically observed once in the night. As it may be limited to a few minutes, the time may be longer than expected. Patients may not recognize their family during the time of the attack and do not remember any of them the next day [12]. EEG recordings of all patients in our study were normal. Suggestions such as reducing the duration for watching television, and not watching videos from mobile phones were made. There was a decrease in the number of attacks in the follow-up time.

The International Headache Society described BPV as a group of periodic syndromes in childhood and stated that it was a leading symptom of migraine [5]. BPV begins during the infancy period; as episodes of sudden onset of dizziness and not exceeding a few minutes. Attacks usually begin to be observed at 1-2 years after walking and may last up to six years. Nausea, vomiting, paleness is usually evident. During events the child is awake, exhibits panic-like behavior and suddenly scared and refuses to move until the event is over. If the child is tried to be carried during this period, unbalanced movement and behavior is usually observed. Electroencephalography and magnetic resonance imaging are normal. Cyproheptadine and diphenhydramine treatment were reported to be beneficial [13]. In our study, magnetic resonance imaging and EEG findings of three patients were normal and patients benefited from cyproheptadine treatment.

Infantile masturbation is defined as the child's self-stimulating pleasure behaviors. The age of onset is between 3 months and 5 years and it is observed more frequently in females. When the patient is sitting or lying down, stretches legs, compresses breath, blushing occurs. The event lasts a few minutes and can be interrupted. It can be repeated 15-20 times a day. When infections of the urinary tract, such as diaper dermatitis, cause itching, the child accidentally discovers that he or she is pleased with the movements he or she makes in order to get rid of the irritation. With behavioral therapy, this can be eliminated [14, 15]. The number of female patients in our study was high and neurological examinations and EEG recordings were normal. Diaper dermatitis was mentioned in 3 of the patients. The parents were warned and informed about diaper dermatitis and urinary tract infection. A decrease in the number of complaints in the control was detected.

BSM is a myoclonic beat during the newborn and premature infantile period, especially when sleeping, repetitive, high frequency, for seconds or for minutes. It is thought that the neuronal structure that provides motor control during sleep is not mature and is caused by genetic factors. When the child wakes up, episode ends. The most important characteristic is not seen outside sleep. These attacks usually disappear when the child is 4-6 months old. Treatment is unnecessary [16]. Patients involved in our study constituted the youngest age group of patients. Neuromotor development of the patients was evaluated as normal. EEG examinations showed no epileptiform abnormality with movement. In patients with tumors, neuromotor development was consistent with months, and when they were 3 months old, movements disappeared.As a result, during early childhood it is disquieting for both parents and physicians because it can get involved with NEPE, especially epilepsy. With the increasing EEG requirements in recent years and the increasing use of mobile camera phones, great convenience has been provided to these patients. Accurate diagnosis and treatment costs are at the least. Misdiagnosis can cause the child to change his or her life style or future plans. This is an intense source of stress for both the child and the family in the long run. The best way to reduce this is to communicate properly with the family and to inform them that these situations are benign.

Limitations of the study were, as would be expected with any retrospective study. In a retrospective study, we were constrained by the information from the medical records.The results do not represent the actual incidence of NEPEs in the general population

As a result, during early childhood it is disquieting for both parents and physicians because it can get involved with NEPE, especially epilepsy. With the increasing EEG requirements in recent years and the increasing use of mobile camera phones, great convenience has been provided to these patients. Accurate diagnosis and treatment costs are at the least. Misdiagnosis can cause the child to change his or her life style or future plans. This is an intense source of stress for both the child and the family in the long run. The best way to reduce this is to communicate properly with the family and to inform them that these situations are benign.

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Assessment of the role of EGF +61A/G and EGFR R497K polymorphism in patients with inflammatory bowel disease: A case-control study

İnflamatuar bağırsak hastalığında EGF +61A/G ve EGFR R497K polimorfizm rolünün değerlendirilmesi: Bir olgu-kontrol çalışması

Resul Kahraman [1], Elif Sinem İplik [2], Turan Çalhan [1], Abdurrahman Şahin [1], Bedia Çakmakoğlu [3]

Abstract

Aim: Epidermal growth factor (EGF) and epidermal growth factor receptor (EGFR) play an important role in the regulation of cell growth, survival, migration, apoptosis, proliferation, and differentiation. We aimed to investigate the presence of EGF (+61A/G) and EGFR R497Kpolymorphisms in patients with inflammatory bowel disease (IBD) and their associations with clinical features of the patients.

Methods: This case-control study included 91 IBD patients (45 Crohn's disease (CD) patients and 46 ulcerative colitis (UC) patients) and 129 healthy controls (HC).EGF and EGFR were genotyped by polymerase chain reaction and restriction fragment length polymorphism techniques to elucidate their association with clinical outcomes. The disease activity for UC and CD were assessed by Truelove-Witts index (TW) and Crohn's disease activity index (CDAI), respectively. The Montreal classification was used for disease involvement and behavior.

Results: EGFR497 AA genotype was significantly decreased in patients with UC compared with CD and HC. In addition, the patients with UC who had EGF +61 A allele had increased risk of moderate and severe disease (p=0.28; OR= 3.13; 95% CI=0.34-28.73). The patients with CD who had the EGF61 AG genotype were found to increased risk for the presence of penetrating disease (p=0.14; $\chi 2$=5.59; OR=5.00; 95% CI=1.26-19.83). EGF +61 A genotype carriers also had higher CDAI scores (p=0.19; OR=4.00; 95% CI=0.44-36.14). In addition, A+ carriers were also found to have higher requirement for anti-TNF treatment (p=0.11; OR=5.0; 95% CI=0.56-44.4).

Conclusion: In this study, EGFR 497 AA genotype was found to decrease significantly in patients with UC compared to HC and CD patients. To enlighten the mechanism, further studies with larger sample groups are needed to clarify the role of the EGF (+61A/G) and EGFR R497K genes polymorphism, and development of the etiology and pathogenesis of IBD.

Keywords: EGF61, EGFR497, inflammatory bowel diseases, Crohn's disease, ulcerative colitis

Öz

Amaç: Epidermal büyüme faktörü (EGF) ve epidermal büyüme faktörü reseptörü (EGFR), hücre büyümesi, canlılığı, migrasyonu, apoptoz, proliferasyon ve farklılaşmasının düzenlenmesinde önemli bir rol oynamaktadır. İnflamatuar barsak hastalığı (İBH) olan hastalarda EGF (+61A/G) ve EGFR R497K polimorfizmlerinin varlığını ve hastalığın klinik özellikler ile ilişkisini araştırmayı amaçladık.

Yöntemler: Bu vaka kontrol çalışmasında 91 IBD hastası (45 Crohn hastalığı (CD) hastası ve 46 ülseratif kolit (UC) hastası) ve 129 sağlıklı kontrol (HC) vardı. EGF ve EGFR, polimeraz zincir reaksiyonu ve restriksiyon fragman uzunluğu polimorfizm teknikleri ile hastalık ve sağlıklı control grubu genotiplendirildi. Genotiplerinhastalık ve klinik özellikleri ile ilişkileri incelendi. UC ve CD için hastalık aktivitesi sırasıyla Truelove-Witts indeksi (TW) ve Crohn hastalığı aktivite indeksi (CDAI) ile değerlendirildi. Montreal sınıflandırması hastalık tutulumu ve davranışı için kullanılmıştır.

Bulgular: Ulseratif kolit hastalarında EGFR497 AA genotipi CD ve HC'ye göre anlamlı olarak azaldığı saptanmıştır. Ek olarak, EGF +61 A alleli olan UC'li hastalarda orta ve ciddi hastalık riski artmıştır (p = 0.28; OR = 3.13; % 95 CI = 0.34-28.73). EGF +61 AG genotipine sahip olan CD'li hastalarda penetran hastalık varlığı açısından artmış risk bulundu (p = 0.14; $\chi 2$ = 5.59; OR = 5.00; % 95 CI = 1.26-19.83). EGF +61 A alleli taşıyıcılarında daha yüksek CDAI skor riski saptandı (p = 0.19; OR = 4.00; % 95 CI = 0.44-36.14). Ek olarak, CD hastalarında EGF +61 A alleli taşıyıcılarının anti-TNF tedavi gereksinimi için artmış riske sahip olduğu bulunmuştur (p = 0.11; OR = 5.0; % 95 CI = 0.56-44.4).

Sonuç: Bu çalışmada, UC'li hastalarda EGFR497 AA genotipinde HC ve CD'li hastalara kıyasla, anlamlı azalma saptandı. EGF +61A allele sahip hastalarda artmış aktivite riski saptanmıştır.IBD'nin etiyolojisi ve patogenezinde EGF (+ 61A / G) ve EGFR R497K gen polimorfizminin rolünü açıklığa kavuşturmak için daha geniş örnek gruplarıyla daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: EGF +61A/G, EGFR R497K, inflammatuar bağırsak hastalığı, Crohn's hastalığı, ülseratif kolit

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Introduction

The inflammatory bowel diseases (IBD) are chronic relapsing inflammatory disorders of the alimentary tract with unknown etiology. Interactions between genetic and environmental factors and exaggerated immunologic response against several antigens have been accepted as included in the etiopathogenesis of IBD [1]. IBD mainly consists of two diseases according to clinical and histopathologic features: Crohn's disease (CD) and ulcerative colitis (UC).

The intestinal epithelial layer is a barrier that prevents the transport of several toxins, allergens, and microorganisms from the gut lumen into the circulation. Dysfunction of this barrier is associated with increased gut permeability, which is claimed as one of the factors in the etiopathogenesis of IBD. Several growth factors maintain gut mucosal integrity, including transforming growth factor β (TGF- β), insulin-like growth factor (IGF), and epidermal growth factor (EGF) [2].

Epidermal growth factor (EGF) is a mitogenic polypeptide that has 53 amino acids except for alanine, phenylalanine, and lysine [3]. EGF has been detected in a variety of body fluids and plays an important role in regulating cell growth, survival, migration, apoptosis, proliferation, and differentiation [4]. Another important function of EGF in the gastrointestinal tract (GI) is mucosal protection associated with intestinal maturation and maintenance of epithelial cell homeostasis in the small intestine [4]. Experimental studies have shown that EGF plays an important role in protecting the intestinal barrier function, and wound healing in necrotizing enterocolitis and ischemia-reperfusion injury models [5, 6]. It has been shown that EGF has anti-inflammatory effects in human fetal intestinal and colonic cells [7]. It has been determined that a single nucleotide polymorphism located in the 5' untranslated region at position 61 of the EGF gene affects expression levels of EGF [8, 9]. Shahbazi et al. [10] demonstrated that cells of individuals with the EGF 61 AA genotype produce less EGF compared with those with EGF 61 AG and GG genotypes. In addition, Wu G, et al. [11] noted an important role between EGF +61 GG genotype and the +61 G allele with the risk of colorectal cancer. Inflammation has been shown to induce genetic or epigenetic changes in cells, resulting in overexpression or persistent activation of endothelial growth factor receptors, thereby activating oncogenesis-related pathways [11].

EGF receptor (EGFR) is a 170-kDa transmembrane glycoprotein encoded by a gene located on chromosome 7p13-q22. EGFR serves as the common receptor for EGF and transforming growth factor-α (TGF-α) [5,12]. EGFR is a tyrosine kinase that manages cell survival, proliferation, barrier function, and ion transport of colon epithelial homeostasis [13]. The receptors could be found on a variety of cells such as fibroblasts, cornea, lens, glial cells, and epithelium of the small intestine [14, 15].

One of the major receptors of polymorphic EGFR has been identified; it plays its role as a single nucleotide change (G-A) belonging to an arginine to lysine substitution in codon 497, which is also called R497K, in the extracellular domain [16]. The EGFR R497K polymorphism has been shown to reduce EGFR activation and downregulate EGFR target genes. This has been demonstrated to be an important marker for the reduction of tumor recurrence in patients with colorectal carcinoma [17]. Animal models and cell culture studies revealed the anti-inflammatory role of EGF an EGFR in intestinal inflammation models [7, 18].

In the present study, we aimed to investigate the presence of EGF +61A/G and EGFR 497 polymorphisms in patients with IBD and the association of these polymorphisms with the clinical features of the patients with CD and UC compared with healthy subjects.

Material and Methods

Subjects

In total, 220 Turkish subjects, 91 patients with IBD (45 CD and 46 UC) and 129 healthy control subjects were enrolled consecutively in the study. The characteristics of the patients with CD (Group 1) and UC (Group 2) and control group (Group 3) and demographic data are given in Table 1. This study was designed as a case-control study. The patient group was selected from patients diagnosed with UC and CD according to European Crohn's and Colitis Organization (ECCO-2010) criteria and followed up at the Gastroenterology Clinic of the Umraniye Education and Research Hospital (Istanbul-Turkey) between January 2012 and December 2013 [19]. The control group included age- and sex-matched volunteers from hospital staff and volunteers from among individuals who admitted to the Gastroenterology Clinic for dyspeptic complaints. Subjects in the control group were individuals not having an inflammatory disease or systemic disorder. After obtaining written informed consent from the participants and approval from Istanbul University's Ethics Committee, blood specimens were collected in tubes containing EDTA. DNA was ex¬tracted from peripheral blood lymphocytes using the salting-out procedure. Disease activity and severity were evaluated using the Truelove-Witts index (TW) in patients with UC and with the Crohn's Disease Activity Index (CDAI) in patients with CD [20]. Patients with CD were divided into three groups as mild (CDAI= 150-220), moderate (CDAI= 220- 450), and severe activity (CDAI> 450). The location and behavior of disease are classified according to the Montreal classification. [21]. The CD location is classified as L1 terminal ileum with or without cecum involvement (L1), colon (L2), ileocolon (L3). According to the CD behavior, three groups were separated as nonstricturing, nonpenetrating (B1), stricturing (B2) and penetrating (B3). Patients with UC were divided into three groups according to the extent of disease: distal (proctosigmoiditis) colitis was determined as inflammation limited to the rectum and sigmoid colon; left-sided colitis, determined as inflammation limited to distal of the splenic flexure; and extensive colitis, involvement exceeding the splenic flexure. Patients were also divided into two groups according to whether they had surgery or not. The patients were also divided into mesalazine, azathioprine and anti-tumor necrosis factor alpha drugs (infliximab and adalimumab) according to their treatment.

Polymorphism analysis and RFLP for EGFR R497K and EGF +61A/G

Genomic DNA was extracted from isolated lymphocytes using a standard nonorganic procedure. The

extracted DNA was used for characterization of the subsequent polymorphic genes. Polymerase chain reaction (PCR), followed by restriction fragment length polymorphism (RFLP), was used for genotyping. Initially, PCR was performed to determine the polymorphic regions using suitable primers. PCR products of EGFR R497K and EGF +61A/G were further subjected to digestion using BstN1 and AluI restriction enzymes, respectively (Table 2). The PCR products were visualized using electrophoresis through a 3% agarose gel. The relative size of the PCR products was determined by comparison of the migration of a 50–1000 bp DNA molecular weight ladder. A permanent visual image was obtained using an ultraviolet (UV) illuminator. Two independent researchers read all genotypes. In the event of any conflicts, the genotypes were repeated.

Statistical analysis

SPSS 11.0 software was used for statistical analysis. The Chi-square test and Fisher's test were used to assess the differences of genotype and allele frequency between the two groups. Comparison of intergroup demographic data was determined using Student's t-test. ANOVA and t-test were used to compare averages of variables in more than two groups. The calculation of differences between sexes was made using the Chi-square test. For the assessment of correlation between the variables, Pearson's and Spearman's correlation analyses were conducted for parametric and nonparametric variables, respectively. Quantitative variables were expressed as mean ± SD (standard deviation) and median (Minimum / Maximum), and categorical variables were expressed as n (%). Variables were examined at 95% confidence interval. A p value of <0.05 was considered statistically significant.

Results

The demographic and laboratory data of patients with CD, UC, and the control group are presented in Table 1. There were no significant differences between the three groups in terms of age and sex. Patients with UC and CD did not differ in terms of the disease duration. Table 3 summarizes the distributions of genotypes and alleles of EGF +61A/G and EGFR R497K genes in patients with IBD including CD and UC and healthy controls.

The EGFR497 AA genotype was significantly decreased in patients with UC compared with HC (p=0.002 and CD (p=0.027). Nevertheless, there was no statistically significant difference in EGF +61 genotype frequencies between the three groups (all p>0.05). EGF +61A/G and EGFR497 polymorphisms were compared in terms of disease localization, severity, anti-TNF drug use, and operative status in both disease groups (Table 4, 5). The patients with CD who had EGF +61 AG genotype were found to have a 5-fold increased risk for the presence of penetrating disease (p=0.14; $\chi 2$=5.59; OR=5.00; 95% CI=1.26-19.83). EGF +61 A allele carriers also had higher CD activity index (CDAI >220) scores (p=0.19; OR=4.00; 95% CI=0.44-36.14). In addition, A+ carriers were also found to have five times higher requirement for anti-TNF treatment (p=0.11; OR=5.0; 95% CI=0.56-44.4). Based on the extension of CD, EGF +61 AG genotype carriers had a 2.5-fold higher risk of ileocolonic involvement (p=0.14; OR=2.56; 95% CI=0.66-9.96). The patients with UC who had the EGF +61 A allele had increased risk of moderate and severe disease (p=0.28; OR= 3.13; 95% CI=0.34-28.73).

Table 1: Characteristics of patients with CD and UC and control.

	Group1	Group 2	Group 3	P1	P2	P3
Number (n)	45	46	129			
Age (year) [β]	39.4±11.6	42.0±11.8	42.8±14.8	0.182	0.085	0.560
Sex (Female/Male)	23/22	26/20	79/50	0.540	0.060	0.190
Disease duration (month) [β]	38.2±47.0	56.1±50.0		0.085		
BMI (kg/m^2) [β]	24.4±6.4	25.3±5.6	26.3±3.8	0.264	0.084	0.498
CRP (mg/dl) [β]	1.57±3.56	0.74±1.0	0.47±0.3	0.084	0.046	0.140
CD Behavior			NA			
Nonstr-nonpenet.	22	NA				
Stricturing	11	NA				
Penetrating	12	NA				
CD Location			NA			
Ileal	20	NA				
Ileocolon	18	NA				
Colon	7	NA				
Disease Activity Mild/Moderate /Severe	23/14/8	22/21/3	NA			
UC Location			NA			
Proctitis	NA	14				
Left-sided	NA	11				
Extensive	NA	21				
Treatment (n (%))			NA			
Mesalazine [α]	38 (77)	56 (100)				
Azathioprine [α]	39 (80)	18 (32)				
Anti-TNF [α]	13 (20)	0				

[β]:Mean±standard deviation, [α]: n(%)

Group1: Crohn's disease group, Group 2: ulcerative colitis group, Group 3: healthy control, CD: Crohn's disease, CRP: C-reactive protein, BMI: body mass index, p1: p value between group 1 and group 2, p2: p value between group 1 and group 3, p3: p value between group 2 and group 3.

Table 2: Polymerase chain reaction and restriction fragment length polymorphism methods

Gene Variants	Primers	Enzymes
EGFR R497K	5'-TGCTGTGACCCACTCTGTCT-3'5'CCAGAAGGTTGCACTTGTCC-3'	BstN1
EGF +61	5′-TGTCACTAAAGGAAAGGAGGT-3′, 5′-TTCACAGAGTTTAACAGCCC-3′	AluI

EGF: epidermal growth factor, EGFR: epidermal growth factor receptor

Table 3: Distributions of genotypes and alleles of EGF61 and EGFR497

Polymorphism	Group 1 n=45		Group 2 n=46		Group 3 n=129		p_1	p_2	p_3
	n	%	n	%	n	%			
EGF(+61A/G)									
GG	11	24.4	13	28.3	28	21.7	0.704	0.367	0.680
AA	17	37.8	14	30.4	34	26.4	0.147	0.595	0.460
GA	17	37.8	19	41.3	67	51.9	0.102	0.215	0.731
GG+AG vs AA	28	62.2	32	69.6	95	73.6	0.147	0.595	0.460
AA+AG vs GG	34	75.6	33	71.7	101	78.3	0.704	0.367	0.680
EGFR R497K									
AA	7	15.6	1	2.2	25	19.4	0.569	0.002	0.027
GG	20	44.4	20	43.5	57	44.2	0.976	0.934	0.926
AG	18	40.0	25	54.3	47	36.4	0.670	0.034	0.170
AA+AG vs GG	25	55.6	26	56.5	72	55.8	0.976	0.934	0.926
GG+AG vs AA	38	84.4	45	97.8	104	80.6	0.569	0.002	0.027

Group1: Crohn's disease group, Group 2: ulcerative colitis group, Group 3: healthy control group, EGF: epidermal growth factor, EGFR: epidermal growth factor receptor, p1: p-value between healthy control group and CD group, p2: p-value between healthy control group and UC group, p3: p-value between CD group and UC group

Discussion

EGF exerts effects on cell proliferation and differentiation by binding to a tyrosine kinase receptor EGFR. It is well known that EGF and its receptor have roles on the immune system, cell proliferation, and apoptosis. The interaction of EGF and its receptor activates intracellular signaling pathways and has a mitogenic effect. The disruption of this regulation causes various cancers including colon cancer.

Table 4: Evaluation of EGF +61A/G and EGFR 497 polymorphisms in patients with CD in relation to disease type, localization, activity, treatment and operative status.

	EGF61		GG N%		GA+AA N%		p
CD	Localization	Ileal	7	35.0	13	65.0	0.172
		Ileocolonic	4	22.2	14	77.8	
		Colonic	0	0.0	7	100.0	
CD	Disease	Non-stricturing, non-penetrating	5	22.7	17	77.3	0.529
	behaviour	Stricturing	4	36.4	7	63.6	
		Peetrating	2	16.7	10	83.3	
CD	Disease	Mild	7	30.4	16	69.6	0.178
	Activity	Moderate	1	7.1	13	92.9	
	(CDAI)	Severe	3	37.5	5	62.5	
CD	Surgery	No	7	23.3	23	76.7	0.709
		Yes	4	28.6	10	71.4	
CD	Anti-TNF	No	8	25.0	24	75.0	0.607
	treatment	Yes	3	23.1	10	76.9	
CD	Azathioprine	No	6	37.5	10	62.5	0.130
		Yes	5	17.2	24	82.8	
	EGFR497		AA N	AA %	GG+AG N	GG+AG %	p
CD	Localization	Ileal	3	15.0	17	85.0	0.555
		Ileocolon	2	11.1	16	88.9	
		Colon	2	28.6	5	71.4	
CD	Disease	Non-stricturing, non-penetrating	4	18.2	18	81.8	0.723
	Behavior	Stricturing	2	18.2	9	81.8	
		Penetrating	1	8.3	11	91.7	
CD	Disease	Mild	3	13.0	20	87.0	0.715
	Activity	Moderate	2	14.3	12	85.7	
		Severe	2	25.0	6	75.0	
CD	Surgery	No	4	13.3	26	86.7	0.392
		Yes	3	21.4	11	78.6	
CD	Anti- TNF	No	5	15.6	27	84.4	0.680
	treatment	Yes	2	15.4	11	84.6	
CD	Azathioprine	No	3	18.8	13	81.2	0.484
		Yes	4	13.8	25	86.2	

CD, Crohn's disease; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor, TNF, tumor necrosis factor; CDAI, Crohn's disease activity index

Table 5: Evaluation of EGF +61A/G and EGFR 497 polymorphisms in patients with UC in relation to disease type, localization, activity, treatment and operative status.

EGF61		GG		GA+AA		p
		N	%	N	%	
Localization	Proctitis	4	28.6	10	71.4	0.224
	Left-sided	1	9.1	10	90.9	
	Extensive	8	38.1	13	61.9	
Disease Activity (TW)	Mild	6	27.3	16	72.7	0.975
	Moderate	6	28.6	15	71.4	
	Severe	1	33.3	2	66.7	
Azathioprine treatment	No	8	28.6	20	71.4	0.953
	Yes	5	27.8	13	72.2	
EGFR 497		AA	AA	GG+ AG	GG+ AG	p
		N	%	N	%	
Localization	Proctitis	0	0.0	14	100.0	0.554
	Left-sided	0	0.0	11	100.0	
	Extensive	1	4.8	20	95.2	
Disease Activity (TW)	Mild	0	0.0	22	100.0	0.544
	Moderate	1	4.8	20	95.2	
	Severe	0	0.0	3	100.0	
Azathioprine treatment	No	1	3.6	27	96.4	0.609
	Yes	0	0.0	18	100.0	

UC: ulcerative colitis, EGF: epidermal growth factor, EGFR: epidermal growth factor receptor, TW: Truelove-Witts activity index

In this study, we investigated the presence of EGF +61A/G and EGFR R497 polymorphisms in patients with IBD and the association of these polymorphisms with the clinical features of patients with CD and UC. In our study, the EGFR 497 AA genotype and A allele were significantly decreased in patients with UC compared with controls and patients with CD. However, there was no statistically significant difference between the three groups in EGF +61 genotype frequencies. Geng et al. [22] suggested as a result of their animal studies that EGF helped to recover damage resulting from intestinal ischemia and the reperfusion process. Even though IBD has unknown and unclear etiology to understand the disease, it has multifactorial mechanism including genetic, environmental and immunological mechanisms [23, 24]. In addition, Menard et al. [25] have worked with human fetal intestine culture and they have found the EGF regulates the genes which are related with inflammation process. Bedford et al. [26] have pointed out EGF therapy has the ability to increase the expression of interleukin 13 as an anti-inflammatory cytokine. Therapeutic effects in experimental colitis models and the positive effects of necrotizing enterocolitis treatment have led to the use of EGF in the treatment of IBD.[27] EGF enema treatment was also found effective on the left colon and distal type UC[11]. The data coming from studies on the EGF +61A/G polymorphism in CRC showed that the G + allele and G/G genotype were related with the presence of CRC and more advanced disease [11]. In addition, Shahbazi et al. [10] demonstrated that cells of individuals with the EGF +61 AA genotype produced less EGF compared with individuals who had EGF +61 AG and GG genotypes. Shahbazi et al. [10] also found that position on EGF +61, G allele carriers express significantly more than A allele carriers.

In our study, the results indicate that the EGF +61 A allele is related with particularly active CD. In patients with CD with EGF +61 A alleles, there is a greater risk of increased disease activity index. The risk of using anti-TNF agents was also found to be increased. It was also found that patients with EGF +61AG polymorphism increased the risk of penetrating disease. In patients with UC, there was an increase in the risk of moderate and severe disease. This may be due to the low expression of EGF in patients with alleles of EGF +61 A and consequent deterioration of the mucosal barrier and healing process. In this regard, there is a need for further studies.

EGFR plays an important role in the homeostasis of the colon epithelium, cell proliferation, barrier functions, and ion transport. In a recent study, it was found that microbial products such as lipopolysaccharide caused EGFR activation in macrophages, resulting in decreased anti-inflammatory cytokines such as interleukin (IL)-10 [28]. It has been found that colitis is exacerbated and healing is impaired. In addition to the present study, selective EGFR-depleted macrophages have been shown to increase IL-10 release resulting in the recovery of intestinal inflammation due to proinflammatory cytokine depletion [28].

EGFR R497K polymorphism leads to decreased intracellular signaling pathways by changing some processes such as cell growth factor and ligand binding, and decreased tyrosine kinase activation [17, 22, 28]. In our study, the EGFR497 AA genotype was significantly decreased in patients with UC compared with controls and patients with CD. The EGFR497 AA genotype has more attenuated functions than the GG polymorphism in terms of ligand binding, growth stimulation, and tyrosine kinase activation [28, 29].

In conclusion, this study was a preliminary study that EGF +61 and EGFR497 gene variants in patients with UC and CD. The EGFR 497 AA genotype was significantly decreased in patients with UC compared with controls and those with CD. Further studies with larger sample groups are needed to clarify the role of the EGF +61 and EGFR 497 polymorphisms, and the development of the etiology and pathogenesis of IBD.

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Relationship of hematological and biochemical parameters with WOMAC index to severity of osteoarthritis: A retrospective study

Hematolojik ve biyokimyasal parametreler ile WOMAC indeksinin osteoartrit şiddeti ile olan ilişkisi: Retrospektif bir çalışma

Kenan Özler [1]

Abstract

Aim: Our aim was to investigate whether any hematologic changes that could be detected easily in whole blood counts together with the Western Ontario and McMaster Universities Osteoarthritis score (WOMAC) had diagnostic value for predicting knee osteoarthritis severity.

Methods: A retrospective study including a total of 208 knee osteoarthritis patients (112 patients early and 106 patients late osteoarthritis) was carried out. Cut-off values for age, C-reactive protein, neutrophil leukocyte ratio and WOMAC index for osteoarthritis were calculated. A multivariate logistic regression model was used to identify the independent factors of late osteoarthritis.

Results: Compared with late osteoarthritis with early osteoarthritis, late osteoarthritis had significantly higher C-reactive protein, neutrophil leukocyte ratio and WOMAC index (p=0.019, p=0.028 and p=0.001, respectively). Area Under Curve was found to be 0.922, 0.533, 0.558 and 0.824 for age, C-reactive protein, neutrophil leukocyte ratio and WOMAC index, respectively. Multilogistic regression analysis was performed with C-reactive protein, neutrophil leukocyte ratio and WOMAC index to determine independent risk factors associated with late osteoarthritis. Odds ratios for neutrophil lymphocyte ratio, C-reactive protein and WOMAC index were found to be 1.317 (95% CI = 1.030-1.682, p = 0.034), 1.055 (95% CI = 1.004-1.108, p = 0.028) and 1.078 (95% CI = 1.056-1.100, p=0.001), respectively. Age, neutrophil leukocyte ratio, C-reactive protein and WOMAC index were statistically significant in predicting late osteoarthritis.

Conclusions: Our study suggests that increased neutrophil leukocyte ratio, C-reactive protein and WOMAC index are associated with independent risk factors for late osteoarthritis.

Key words: Neutrophil-lymphocyte ratio, C-reactive protein, WOMAC index, knee, osteoarthritis

Öz

Amaç: Amacımız, Western Ontario ve McMaster Üniversiteleri Osteoartrit skoru (WOMAC) ile birlikte kolayca saptanabilecek tam kanda herhangi bir hematolojik değişikliğin diz osteoartriti şiddetini öngörmede tanısal değere sahip olup olmadığını araştırmaktır.

Yöntemler: 208 diz osteoartrit hastasını (112 hasta erken ve 106 hasta geç osteoartrit) içeren retrospektif bir çalışma planlandı. Yaş, CRP, nötrofil lökosit oranı ve WOMAC index için cut-off değerleri hesaplandı. Geç osteoartrit için bağımsız faktörlerini tanımlamak için çok değişkenli lojistik regresyon modeli kullanıldı.

Bulgular: Erken ve geç osteoartrit karşılaştırıldığında, C-reaktif protein, nötrofil lökost oranı ve WOMAC indeksi anlamlı olarak geç osteoartrit olan grupta daha yüksekti (sırası ile; p=0,019, p=0,028 ve p=0,001). Yaş, C-reaktif protein, nötrofil lökosit oranı ve WOMAC index Area Under Curve değerleri sırasıyla 0,922, 0,533, 0,558 ve 0,824 olarak bulundu. Geç osteoartrit ile ilişkili bağımsız risk faktörlerini belirlemek amacı ile yapılan regresyon analizinde, nötrofil lökosit oranı için odds oranı 1.317 (95% CI = 1.030-1.682, p=0.034), C-reaktif protein için odds oranı 1.055 (95% CI = 1.004-1.108, p= 0.028) ve WOMAC index için odds oranı 1.078 (95% CI = 1.056-1.100, p=0.001) idi. Geç osteoartrit öngörüsünde yaş, nötrofil lökosit oranı, C-reaktif protein and WOMAC index istatistiksel olarak anlamlı idi.

Sonuç: Nötrofil lökosit oranı, C-reaktif protein düzeyleri ve WOMAC indeksinin, geç osteoartrit için bağımsız risk faktörleri ile ilişkili olduğu düşünülmektedir.

Anahtar Kelimeler: Nötrofil lenfosit Oranı, C-Reaktif Protein, WOMAC indeks, diz, osteoartrit

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Introduction

Osteoarthritis (OA) is a progressive degenerative joint disease associated with cartilage destruction, subchondral bone remodeling and synovium inflammation. OA is the leading cause of the lower extremity insufficiency especially in the elderly group. The incidence of OA is now increasing due to the aging population and increasing obesity [1]. OA is characterized with joint pain, pain in movements, short stiffness and crepitation in joints [2].

Although pathophysiology of OA has been proposed for many reasons, recent studies have also shown that inflammatory and anti-inflammatory mediators such as IL-1b, TNF-alpha, leukocyte inhibitory factor, IL- 1 receptor antagonist, matrix metalloproteinases, proteases, chemokines, nitric oxide, and prostaglandins and leukotrienes have been clearly understood to role in the development and progression of the symptoms of OA [3, 4]. Proinflammatory cytokines are altered together with some peripheral blood markers such as leukocytes, lymphocytes and neutrophils in inflammatory responses. Increased lymphocytes levels have been shown to be important in the prognosis of diseases such as over cancer [5], sepsis [6], pneumonia [7] and differentiation of benign and malignant ovarian masses [8]. Neutrophil lymphocyte ratio (NLR) and monocyte-lymphocyte ratio (MLR) were positively correlated with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in rheumatoid arthritis, ankylosing spondylitis, and OA [9]. CRP is a pentameric protein with acute phase reactivity, elevated in serum in cases of inflammation, infection, and tissue damage. CRP can increase inflammation by accelerating leukocyte uptake and proinflammatory cytokine synthesis [10]. Studies have shown that serum CRP levels in OA patients are significantly increased compared to control groups [11, 12]. In clinical practice, the evaluation of knee OA is mainly based on clinical manifestation and radiographic changes. The Kellgren-Lawrence (KL) grading scale was traditionally used to grade the severity of knee OA on radiographs [13].

We aimed to determine levels of inflammatory markers levels such as NLR and CRP in OA patients and to investigate the predictive value of NLR and CRP levels in association with The Western Ontario and McMaster Universities Osteoarthritis score (WOMAC index) index used for severity of knee OA.

Materials and methods

A retrospective study using a prospectively held database was carried out between December 2016 and January 2018. Two hundred and eight patients diagnosed as OA were recruited consecutively from orthopedics outpatient clinics. The study protocol was performed according to the principles of the Declaration of Helsinki and approved by the local Ethical Committee of our hospital.

The diagnosis of knee OA determined by radiographic features, the KL scale was chosen by the World Health Organization as the accepted reference standard. The KL grading was used for classifying OA according to radiographic signs (joint space narrowing, subchondral sclerosis, osteophytes and subchondral cysts) and radiographically are graded from 1 to 4 [13]. Body mass index (BMI) was homogenized in patients with knee OA and BMI <30 kg/m^2 were included in the study.

Patients were excluded if any of the following disorders were present: septic arthritis, patients undergoing surgery with a diagnosis of OA, patients receiving local medication or systemic antibiotic therapy, malignant patients, patients receiving chemotherapy, radiotherapy or immunosuppression, patients with systemic acute infection, patients with chronic inflammatory disease, patients with acute surgery.

All participants included in the study were evaluated at the initial admission. Clinical examination was performed, X-ray images of the knee and anthropometric measurements as well as the previous surgery and medical history were recorded. KL grading of the mostly affected knee was performed for each patient through the evaluation of X-ray images. Blood samples were obtained at the same time with the X-ray images by venipuncture for complete blood count (white blood cell count [/mm^3], lymphocyte count, platelet count [/mm3], platelet lymphocyte ratio (PLR) and mean platelet volume (MPV) [femptolitre-fL]), C-reaktif protein (CRP) [mg/dl] and erythrocyte sedimentation rate (ESR) [mm/hour] measurements.

Patients were then divided into two groups as the patients with KL grades 1–2 (mild-moderate) knee OA and the patients with KL grades 3–4 (severe) knee OA. So, 112 patients were early stage (stage 1 and stage 2) knee osteoarthritis (EOA) and 106 patients were late stage (stage 3 and stage 4) knee osteoarthritis (LOA).

Knee functions were assessed by WOMAC index that is consisting of 24 parameters that include pain (score range: 0–20), stiffness (score range: 0–8), and functional impairment (score range: 0–68) [14].

All data with regard to demographic and clinical features including WOMAC index, laboratory findings and imaging features graded by X-ray images were recorded into the prospectively held database.

Statistical analysis

Data analysis was performed by using SPSS for Windows, version 22 (SPSS Inc., Chicago, IL, United States). Data were shown as mean with 95% Confidence Interval (CI) or number of cases and percentage, where applicable. Continuous variables were tested for normality by the Kolmogorov– Smirnov test. Normally distributed data are presented as mean ± standard error. We used the independent samples t -test for parametric groups. Receiver operating curve (ROC) analysis was performed for age, CRP, NLR and WOMAC index and the correspondent AUC values with 95% CI was calculated in OA. Multivariate logistic regression analysis was used to determine the relationship of WOMAC index, CRP and complete blood count parameters with LOA. A p value less than 0.05 was considered statistically significant.

Results

A total of 218 participants were enrolled in the study. 112 were EOA and 106 were LOA. The baseline anthropometric and biochemical characteristics of EOA and LOA patients are given in Table 1. The patients in the LOA group were older than the EOA group (p=0.001). CRP and NLR levels were 3.65 ±

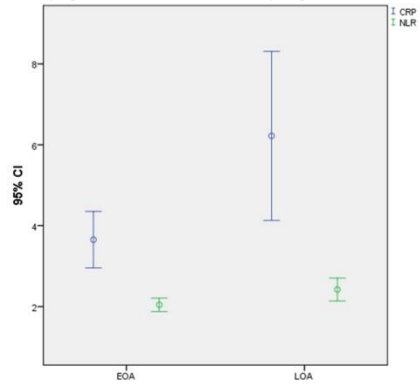
0.35 mg/dl and 2.04 ± 0.08 in the EOA group and 6.22 ± 1.05 mg/dl and 2.40 ± 0.14 in the LOA group, respectively. CRP and NLR were significantly higher in the LOA group than in the EOA group (p=0.019 and p=0.028) (Table 1, Figure1). The WOMAC index was 44.86 ± 1.28 in the EOA group and 64.08 ± 1.60 in the LOA group. The WOMAC index was significantly higher in the LOA group than in the EOA group (p=0.001) (Table 1).

Table 1: Baseline characteristics, clinic and laboratory parameters of EOA and LOA patients.

	EOA (n=112)	LOA (n=106)	p
Age (year)	52.19 ±7.12	67.33 ± 7.99	0.001
CRP (mg/dl)	3.65 ± 0.35	6.22 ± 1.05	0.019
ESR (mm/hour)	12.52 ± 2.60	16.48 ± 1.51	0.198
WBC (/mm^3)	7.53 ± 0.16	7.37 ± 0.22	0.556
Platelet counts (/mm^3)	247.56 ± 5.62	231.30 ± 7.68	0.086
Neutrophil counts	4.44± 0.129	4.69 ± 0.163	0.232
Lymphocyte counts	2.39 ± 0.074	2.27 ± 0.090	0.299
NLR	2.04 ± 0.08	2.40 ± 0.14	0.028
PLR	115.16 ±4.79	117.58 ± 6.34	0.759
MPV (femptolitre-fL)	10.09 ±0.96	11.05 ± 0.81	0.230
WOMAC index	44.86 ± 1.28	64.08 ± 1.60	0.001

Independent simple t test, mean ± standart error mean. CRP; C-reaktif protein, WBC; white blood cell, NLR; neutropil/lymphocyte ratio, PLR; platelet lymphocyte ratio MPV; mean platelet volume, ESR; Erythrocyte sedimentation rate, WOMAC index; Western Ontario McMasters Osteoartritis index.

Figure 1. CRP and NLR graphic from EOA and LOA groups



Counts for white blood cell, lymphocyte and platelet, levels of PLR and MPV, and ESR were not statistically different between EOA and LOA groups (Table 1).

We determined the cut-off level of 45 for age; this cut-off specificity was 83%, sensitivity 78% and AUC 0.897 (0.853-0.940) . The cut-off value for CRP was 5 mg/dL with specificity of 52%, sensitivity of 48% and AUC of 0.467 (0.390-0.544). For NLR, the cut-off level was 4.13 with specificity 48%, sensitivity48 % and AUC 0.558 (0.482-0.635). The cut-off level of WOMAC index was 54; specificity, sensitivity and AUC were 80%, 69% and 0.824 (0.771-0.877), respectively (Table 2, Figure 2).

All parameters were further evaluated with multivariate regression analysis to determine the independent risk factors in LOA (Table 3). Age, CRP, NLR and WOMAC index were found to be significantly associated with LOA (p=0.001, p=0.034, p=0.028 and p=0.001, respectively) (Table 3).

Table 2: The cut-off value, sensitivity, specificity and AUC (95% Cl) of CRP, NLR and WOMAC index in OA.

	Cut off value	Specificity	Sensitivity	AUC (95 % Cl)	p
Age (year)	45	83%	78%	0.922 (0.886-0.957)	0.001
CRP (mg/dl)	5	52 %	48 %	0.533 (0.456-0.610)	0.406
NLR	4.13	48 %	48 %	0.558 (0.482-0.635)	0.137
WOMAC index	54	80 %	69 %	0.824 (0.771-0.877)	0.001

CRP: C-reactive protein, NLR: neutrophil/lymphocyte ratio, WOMAC index: Western Ontario McMasters Osteoartritis index.

Figure 2. Age, CRP, NLR and WOMAC index ROC curve in OA

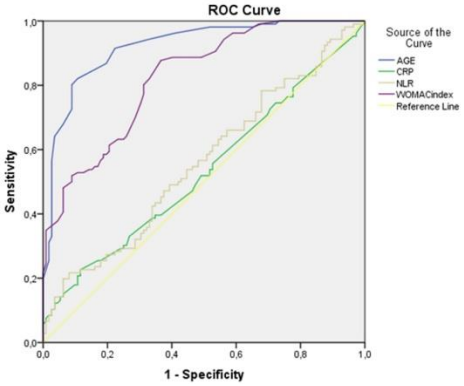


Table 3: Multivariate logistic regression analysis for prediction of LOA.

	Multivariable analysis	
	OR (95 % Cl)	p
Age (year)	1.300 (1.216-1.391)	0.001
CRP (mg/dl)	1.055 (1.004-1.108)	0.034
ESR (mm/hour)	1.010 (0.994-1.025)	0.235
WBC (/mm^3)	0.961 (0.842-1.096)	0.554
Platelet counts (/mm^3)	0.997 (0.993-1.001)	0.089
Neutrophil counts	1.113 (0.934-1.327)	0.232
Lymphocyte counts	0.846 (0.618-1.160)	0.299
NLR	1.317 (1.030-1.682)	0.028
PLR	1.001 (0.996-1.006)	0.758
MPV (femptolitre-fL)	1.153 (0.887-1.498)	0.288
WOMAC index	1.078 (1.056-1.100)	0.001

CRP: C-reactive protein, WBC: white blood cell, NLR: neutropil/lymphocyte ratio, PLR: platelet lymphocyte ratio, MPV: mean platelet volume, ESR: Erythrocyte sedimentation rate, WOMAC index: Western Ontario McMasters Osteoartritis index.

Discussion

In the present retrospective case-control study of knee OA, increased levels of NLR, CRP and WOMAC index were found to be associated with LOA. Knee OA is a chronic disease characterized by progressive chondrocyte degeneration that plays a role in proinflammatory processes. Studies have also shown that mononuclear cell infiltration is increased in synovial fluid of early and late stage OA patients [15]. Tascioglu et al. [16] showed that age, neutrophil, lymphocyte and platelet counts, MPV, PLR, and ESR were significantly higher in the late OA group than in the early OA group. Gundogdu et al. [17] determined that serum white blood cell count, CRP and NLR levels were not different between OA and healthy controls, but NLR was higher in stage 4 knee OA cases [17].

In the present study we found that age, NLR and CRP levels were significantly higher in EOA compared to LOA. Many studies have shown the relationship between serum CRP levels and OA [18]. At the same time, CRP is one of the

systemic markers showing synovitis [18]. BMI homogenized studies have also shown that CRP is an independent risk factor for OA [11]. Hanata et al. [19] determined that ESR increased in OA patients and was also significantly higher in grade 3-4 OA patients than in grade 1 OA patients. ESR and high-sensitivity CRP concentration were higher in knee OA and related to clinical features [19, 20].

Benito et al. [21] reported that the infiltration of CD4 and CD68 cells were increased in the synovial fluid and that TNF alpha and IL-1 beta levels in these cells were significantly higher in the early OA group than in the LOA group.

Radiography is used first to determine structural changes in OA [22]. However, the diagnostic value of radiographic imaging is limited to development of EOA and progression of OA. However, non-invasive methods such as magnetic resonance imaging and 3D ultrasonography are used to determine the progression of the OA disease by looking at joint morphology, but it is known that these tests show a low rate of progression in a large population [23]. In some studies, serum CD14 and CD163 macrophage markers have been shown to be associated with joint symptoms, severity and progression of radiological osteoarthritis [24

The limit of our study is patient count is low and proinflammatory markers are not working. The other limitation is that the four osteoarthritis stages are not evaluated separately.

In conclusion, we found that age, NLR and CRP levels were significantly higher in EOA compared to LOA. Also age, CRP, NLR and WOMAC index were found to be significantly associated with LOA in our study. We think that the progression of loss of cartilages can be independent risk factors by using clinical features (WOMAC index), inflammatory markers (NLR, CRP) and imaging features and these factors can be used in the detection of high-risk population for progression.

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Effects of postoperative intravenous infusion of tramadol and addition of dexmedetomidine to tramadol on analgesia and hemodynamic parameters in gynecologic surgery: a prospective (double blind) randomised controlled trial

Jinekolojik cerrahide postoperatif uygulanan intravenöz tramadolün ve tramadole deksmedetomidin ilavesinin analjezi ve hemodinamik parametreler üzerine etkileri: Prospektif (çift kör) randomize kontrollü çalışma

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Abstract

Aim: We designed this double-blind study to test and compare the effects of intravenous tramadol and intravenous tramadol plus dexmedetomidine on analgesia and hemodynamic parameters for treatment of postoperative pain in gynecologic surgeries with Pfannenstiel incision.

Methods: Sixty patients undergoing total abdominal hysterectomy with Pfannenstiel incision under general anesthesia were randomly allocated into two groups. Group C (Tramadol) and Group D (Tramadol + Dexmedetomidin). The anesthetic technique was standardized. Postoperatively, the patients in both groups received patient controlled analgesia during 24 hours after surgery (tramadol 20 mg bolus for Group C, tramadol 20 mg+dexmedetomidine 10 mg first four hours, then tramadol 20 mg for Group D with a lock-out time of 15 minutes). Postoperative assessment included verbal pain score, sedation score, nausea and vomiting score, consumption of tramadol, hemodynamic parameters and patient's satisfaction.

Results: Postoperative pain scores were significantly lower in Group D compared with Group C and patient-controlled analgesia tramadol use was significantly reduced in Group D. Total PCA tramadol use was decreased by 27% in Group D compared with Group C (p=0.001). Patient satisfaction with pain treatment was significantly improved in Group D compared with Group C (p=0.001). A significant increase in sedation scores at the 1st, 2nd and 4th hours were observed in Group D. Heart rate was lower in Group D at the 1st, 2nd and 4th hours postoperatively (p=0.001, p=0.001 and p=0.01, respectively). Nausea and vomiting score was lower in Group D (p<0.05 for all).

Conclusion: The addition of dexmedetomidine to tramadol by patient controlled analgesia method significantly reduces tramadol consumption and increases analgesia level and patient satisfaction in gynecological operations.

Keywords: Dexmedetomidine, gynecological operations, patient controlled analgesia, postoperative pain, tramadol

Öz

Amaç: Bu çalışmada Pfannenstiel kesisi yapılan jinekolojik prosedürlerde postoperatif ağrı tedavisinde intravenöz tramadol ile intravenöz tramadole ilave deksmedetomidinin analjezi ve hemodinamik parametreler üzerine etkilerinin karşılaştırılması amaçlanmıştır.

Yöntemler: Genel anestezi altında elektif Pfannenstiel kesisi uygulanarak jinekolojik operasyon planlanan ASA I-II grubuna dahil 60 hasta randomize olarak iki gruba ayrıldı (Grup C (Tramadol grubu) ve Grup D Tramadol + Deksmedetomidin). Operasyon sonrası derlenme odasına alınan her iki gruptaki hastalara ameliyat sonrası 24 saat boyunca hasta kontrollu analjezi (HKA) uygulandı (Grup C için 20 dk kilitli kalma süresi ile 20 mg tramadol bolus doz, Grup D için ilk 4 saat 20 mg tramadol+10mcg deksmedetomidin bolus doz, daha sonra 20 mg tramadol bolus doz). Postoperatif değerlendirmede, sözel ağrı skoru, sedasyon skoru, bulantı ve kusma skoru, tramadol kullanımı ile hemodinamik parametreler ve hasta memnuniyeti kaydedildi.

Bulgular: Postoperatif ağrı skorları Grup D'de, Grup C'ye göre anlamlı olarak düşüktü ve hasta kontrollü analjezi tramadol kullanımı Grup D'de anlamlı olarak azaldı. Toplam PCA tramadol kullanımı Grup D'de Grup C ile karşılaştırıldığında % 27 azaldı (p=0,001). Ağrı tedavisi ile hasta memnuniyeti Grup D'de Grup C'ye göre anlamlı olarak yükseldi (p=0,001). Grup D'de 1, 2 ve 4 saatte sedasyon skorlarında anlamlı bir artış gözlendi. Kalp hızı, Grup D'de postoperatif 1, 2 ve 4 saatte daha düşüktü (sırası ile p=0,001, p=0,001 and p=0,01, respectively). Bulantı ve kusma skoru Grup D'de daha düşüktü (hepsi için p<0,05).

Sonuç: Deksmedetomidinin PCA yöntemiyle tramadole eklenmesi, tramadol tüketimini önemli ölçüde azaltmakta ve jinekolojik operasyonlarda analjezi düzeyini ve hasta memnuniyetini artırmaktadır.

Anahtar kelimeler: Deksmedetomidin, jinekolojik ameliyatlar, hasta kontrollü analjezi, postoperative ağrı, tramadol

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Introduction

Objectives of the postoperative pain treatment include minimizing or eliminating pain of the patient, facilitating recovery, preventing complications that may occur due to pain and ensuring a cost-effective treatment [1]. An additive, even synergistic analgesic effect may be obtained with the combination of two agents that provide analgesic effect by different mechanisms. Recently, multimodal approaches are studied using the different types of analgesics. Dexmedetomidine is a potent and highly selective α2 receptor agonist. It creates a state of deep sedation at therapeutic doses but does not cause respiratory depression [2]. Dexmedetomidine, when used as premedication, is known to reduce the analgesic requirement during and after surgery. Analgesic requirement is also reduced in patients given sedation with dexmedetomidine at intensive care unit [3].

In our study, we aimed to investigate and compare the effects of intravenous (IV) tramadol and addition of IV dexmedetomidine to tramadol by patient-controlled analgesia (PCA) method on postoperative analgesia, postoperative tramadol consumption, pain score, sedation score, nausea and vomiting, hemodynamic and respiratory parameters and patient satisfaction during early postoperative period in gynecologic procedures.

Materials and methods

The study was designed as a prospective, randomized controlled trial to be conducted at a public hospital, Department of Anesthesiology and Reanimation, between December 2009 and June 2010. After obtaining ethics approval, 60 patients were included in the study who was aged 18-65 years, categorized in American Society of Anesthesiologists Classification (ASA) risk group I-II, undergoing total abdominal hysterectomy with general anesthesia. The statistical power of a study was 100% when the average of the 24th hour Visual Analog Scale (VAS) was taken 1.60 ± 1.0 for Group C, 0.17 ± 0.37 for Group D with 5% alpha error, also the statistical power of the study was 98.6% when an average of tramadol was taken 432.00 ± 146.27 for Group C and 316.00 ± 44.06 for Group D. At the end of the study, it was found that the effect size for the Visual Analog Scale (VAS) in each group with a sample of 30 people was 1.55 and that power was 0.99.

This trial was approved by the Ministry of Health of Turkey, General Directorate of Pharmaceuticals and Pharmacy, Drug Clinical Research Ethics Advisory Committee-II with a date of 31.05.2010 and decision number of 16. Written informed consent was obtained from all participants. The study was performed according to the Helsinki Declaration.

Exclusion criteria were age below 18 years and above 65 years, advanced heart disorder, kidney disorder, history of epilepsy and convulsion, use of antidepressants, presence of liver disorder, neuropsychiatric disorders, use of antidepressants and beta-adrenoceptor blocking agents, history of allergy to the agents to be used, history of chronic analgesic use, patients who will not be able to comply with patient controlled analgesia (PCA) use, who do not agree to participate in study and who are not cooperative.

60 ASA I-II subjects included in the study were divided into 2 groups according to computerized randomization table during the study as Group C (Control - Tramadol group) (n=30) and Group D (Tramadol + Dexmedetomidine group) (n=30). Both the patients and the observers were blinded with respect to the group allocation. Double-blinding was obtained by labeling the PCA reservoir bags with a specific identification number only. The blinding code retained by the pharmacy was opened after completion of the study. For reasons of patient safety, a sealed envelope containing the treatment assignment was kept with the patient in the post anesthesia care unit (PACU) and general ward. Unblinding would be carried out when an adverse event occurred and this knowledge was required for emergency treatment. Patients developing any complication during and after surgery were planned to be excluded from study. Patients were given detailed information on whole anesthesia procedure, surgical preparations, premedication, transfer to operating room and operations thereof and written consents were obtained. Patients were instructed on use of PCA device (Abbott Pain Manager, Abbott Laboratories, Chicago, IL, USA) and verbal rating scale (VRS), which we used in evaluation of pain.

No premedication was administered to the patients before the surgery. Standard monitoring including systolic, diastolic and mean blood pressures (SBP, DBP, MBP), heart rate (HR) and peripheral oxygen saturation (SpO2) by pulse oximetry was applied to the patients transferred to operating room. 20 G intravenous catheter was inserted through a suitable vein at antecubital region and infusion of 0.9% NaCl was initiated for the patients.

Induction was started by 2 mg/kg propofol (Propofol 1 %, Fresenius Kabi, Istanbul, Turkey), fentanyl 2 mcg/kg (Fentanyl 0,05 mg/ml, Johnson and Johnson, Istanbul, Turkey) and 0.1 mg/kg vecuronium (Norcuron, Merck Sharp & Dohme, Istanbul, Turkey) followed by intubation of the patients and anesthesia was maintained by 1-2% sevoflurane (Sevorane, Abbott, Istanbul, Turkey) in a 50/50% mixture of O2/N2O with a flow of 6 L/min. An additional vecuronium bromide of 0.01 mg/kg was administered as needed for neuromuscular block. All patients were applied subcutaneous suture and given 1 mg/kg tramadol HCl (Contramal, Abdi Ibrahim, Istanbul, Turkey) by intravenous route. At the end of the surgery, residual neuromuscular block was antagonised by 0.06 mg/kg neostigmine methylsulphate (Neostigmine, Adeka, Samsun, Turkey) and 0.02 mg/kg atropine sulphate (Atropine Sulphate, Biofarma, Istanbul, Turkey). Patients were extubated according to extubation criteria.

Patients were awakened at the end of surgery and taken into the recovery room where they were given oxygen at a rate of 3-5 L/min by a face mask. Patients in Group C (Tramadol group) were given 2 mg/ml tramadol HCl (Contramal, Abdi Ibrahim, Istanbul, Turkey) in 100 mL 0.9% NaCl by PCA device for 24 hours with a bolus dose of 20 mg, lockout time of 15 minutes and a 4-hour limit dose of 200 mg and no basal infusion was administered.

Patients in Group D were given 2 mg/mL tramadol HCl (Contramal, Abdi Ibrahim, Istanbul, Turkey) in 100 mL 0.9% NaCl and 1 mcg/mL dexmedetomidine (Precedex, Abbott, Istanbul, Turkey) by PCA pump at the recovery room for the first

4 hours postoperatively with a lockout time of 15 minutes and a bolus dose of 20 mg tramadol HCl + 10 mcg dexmedetomidine and no basal infusion was administered. Afterwards, treatment of patients was continued with 2 mg/ml tramadol HCl (Contramal, Abdi Ibrahim, Istanbul, Turkey) in 100 mL 0.9% NaCl by PCA pump with a bolus dose of 20 mg, lockout time of 15 minutes and a 4-hour limit dose of 200 mg until 24 hours postoperatively. During follow-up, a VRS score of >4 was considered to be insufficient analgesia and; thus, 0.5 mg/kg intramuscular meperidine (Aldolan 100 mg, Liba, Istanbul, Turkey) was administered as rescue analgesia and the time of administration was recorded.

Patients were visited at the 1st, 2nd, 4th, 8th, 12th, 16th, 20th and 24th hours postoperatively and monitored for HR, SBP, DBP, MBP, SpO2, respiratory rate, VRS (pain score at rest and with coughing), sedation score, total amount of dexmedetomidine intake, additional analgesic need, demanded vs. total consumed tramadol amount and side effects (nausea, vomiting, itching, sedation, hypotension, bradycardia, respiratory depression, dizziness, headache) and the results were recorded. There was no lost data because all data is recorded by researchers.

Patients' satisfaction with their postoperative pain management was assessed using a 10-point VRS, with 1=highly dissatisfied to 10=completely satisfied. Assessment of post-discharge pain was performed using a 10-point VRS, with 0=no pain and 10=worst pain imaginable. All measurements were recorded by a research assistant who was blinded to the study medication. Sedation score was evaluated by a 4-point scale (0=awake; 1= sleepy; 2=arousable; 3=deep sleep). Nausea and vomiting was evaluated by a 3-point scale (0= no nausea; 1=only nausea, no vomiting; 2=nausea with vomiting).

A HR below 50 beat/min was considered as bradycardia and a respiratory rate of ≤ 8 and SpO2 below 90% were considered as respiratory depression. It was planned to administer 0.5 mg IV atropine (Atropine Sulphate, Biofarma, Istanbul, Turkey) for bradycardia and respiratory and oxygen support for respiratory depression which was to be followed by naloxone (Nalokson HCI, Abbott, Istanbul, Turkey) (0.1 mg every 2-3 minutes until the response is achieved) in case of absence of response. A reduction of > 30% in MBP from baseline or a SBP below 90 mmHg was considered as hypotension and it was planned to administer a rapid infusion of 500 mL crystalloid followed by 5 mg IV ephedrine (Ephedrine, Osel, Istanbul, Turkey) in case of absence of response. 4 mg IV ondansetron (Zofran, Glaxo Smith Kline, Istanbul, Turkey) was planned to be administered to subjects with a nausea-vomiting score of 2. 1 mg IV pheniramine maleate (Avil, Sandoz, Istanbul, Turkey) was planned to be administered in case of itching.

Statistical Analysis

Data were collected after that transferred into the computer. Statistical Package for Social Sciences (SPSS) for Windows 15.0 program was used for statistical analyses when evaluating the study findings. The descriptive statistics for categorical variables are presented as counts and percentages and for continuous variables they are presented as averages, standard deviations, medians, 25 and 75 percentiles with minimum and maximum. For continuous variables Kolmogorov-Smirnov test is used for testing differences between groups when the assumption of normality is not satisfied. Independent samples t-test was used to compare continuous data in two independent groups that fit normal distribution, while Mann Whitney U-test was used in non-parametric tests in non-normal distributions. Fischer's Exact test was used in comparison of discrete data. A p value of < 0.05 was considered to be statistically significant.

Results

No statistically significant difference was detected between the study groups with respect to age, body weight, height, ASA and duration of anesthesia (Table 1). Comparison of mean arterial pressures between the study groups showed no statistically significant difference ($p>0.05$ for all). Heart rates were statistically significantly lower in Group D compared to Group C at 1st, 2nd and 4th hours ($p=0.001$, $p=0.001$ and $p=0.01$, respectively) (Table 2).

Table 1: Demographic characteristics of the patients and duration of anesthesia

	Group C (n=30) Mean ± SD	Group D (n=30) Mean ± SD	p*
Age (years)	45.93 ± 9.01	47.20 ± 6.20	0.53
Body weight (kg)	69.73 ± 11.70	67.40 ± 12.17	0.45
Height (cm)	163.10 ± 4.26	162.96 ± 4.82	0.91
Duration of anesthesia (min)	75.13 ± 18.02	69.86 ± 20.57	0.29
ASA (I/II)	30/9	30/4	0.52

ASA: American Society of Anesthesiologists Classification

Table 2: Postoperative hemodynamic parameters of groups (MBP, HR).

	Group C (n =30)	Group D (n =30)	p
MBP (1 h)	89.33 ± 12.51	86.603 ± 10.72	0.36
MBP (2 h)	87.77 ± 7.80	86.03 ± 11.05	0.48
MBP (4 h)	84.87 ± 19.73	84.50 ± 7.45	0.92
MBP (8 h)	85.20 ± 8.40	88.70 ± 3.23	0.06
MBP (12 h)	84.13 ± 9.40	81.97 ± 5.73	0.28
MBP (16 h)	82.67 ± 9.25	84.90 ± 10.78	0.39
MBP (20 h)	84.37 ± 10.41	83.63 ± 8.39	0.76
MBP (24 h)	83.30 ± 10.31	82.37 ± 7.50	0.69
HR (1 h)	77.53 ± 10.47	66.53 ± 11.05	<0.001
HR (2 h)	77.17 ± 8.28	66.80 ± 11.32	<0.001
HR (4 h)	78.73 ± 10.78	67.43 ± 14.18	0.01
HR (8 h)	74.33 ± 5.92	70.70 ± 11.09	0.12
HR (12 h)	73.90 ± 6.70	71.97 ± 10.74	0.41
HR (16 h)	73.57 ± 7.89	69.87 ± 9.63	0.10
HR (20 h)	72.20 ± 6.47	68.97 ± 6.42	0.06
HR (24 h)	71.27 ± 5.42	68.97 ± 5.46	0.11

MBP: Mean Blood Pressure, HR: Heart Rate

Scores for pain at rest (VRSr) were statistically significantly lower in Group D compared to Group C at all postoperative time points ($p=0.001$) (Table 3). Scores for pain with coughing (VRSc) were statistically significantly lower in Group D compared to Group C at all postoperative time points ($p=0.001$) (Table 3). Postoperative hourly tramadol consumption of the patients by PCA device were statistically significantly lower in Group D compared to Group C at 12th, 16th, 20th and 24th hours postoperatively ($p=0.001$ for all) (Table 4). Total tramadol consumption was also lower in Group D compared to Group C ($p=0.001$) (Table 4). The hourly and total dexmedetomidine consumption used by Group D was also calculated. Total dexmedetomidine consumption was 79.7 ±11.3 mcg in first 4 hours (Table 5).

Table 3: VRSr values of the groups (at the rest and with coughing).

VRSr	Rest			With coughing		
	Group C (n =30)	Group D (n =30)	p	Group C (n =30)	Group D (n =30)	p
1 h	4.43 ± 2.70	2.60 ± 1.13	<0.001	6.67 ± 2.29	4.23 ± 0.97	<0.001
2 h	4.33 ± 1.95	2.07 ± 0.78	<0.001	6.40 ± 1.94	3.50 ± 0.73	<0.001
4 h	4.47 ± 5.56	1.40 ± 1.03	<0.001	5.63 ± 1.67	2.77 ± 1.35	<0.001
8 h	2.93 ± 1.25	1.37 ± 1.06	<0.001	5.03 ± 1.84	3.27 ± 1.63	<0.001
12 h	2.50 ± 1.07	0.90 ± 1.06	<0.001	4.37 ± 1.77	2.77 ± 0.97	<0.001
16 h	2.20 ± 1.32	0.63 ± 0.61	<0.001	3.80 ± 1.60	2.20 ± 0.96	<0.001
20 h	2.13 ± 1.16	0.50 ± 0.63	<0.001	3.40 ± 1.47	1.83 ± 0.98	<0.001
24 h	1.60 ± 1.03	0.17 ± 0.37	<0.001	2.77 ± 1.35	1.30 ± 1.11	<0.001

VRS: verbal rating scale

Number of postoperative analgesic demands of the patients by PCA device were statistically significantly lower in Group D compared to Group C at all follow-up time points ($p<0.05$ for all). Comparison of the study groups showed that the number of patients with an additional analgesic need postoperatively was statistically lower in Group D with six patients (20%) compared to Group C with 14 patients (46.7%), and the patient satisfaction was significantly higher in Group D (9.23±0.72) compared to Group C (8.20±0.84) ($p=0.04$ and $p=0.001$, respectively).

Table 4: Comparision of hourly and 24 hours total tramadol consumption of groups (mg).

Hourly Tramadol consumption (mg)	Group C (n =30)	Group D (n =30)	p
1 h	56.00 ± 19.93	60.66 ± 16.17	0.32
2 h	50.00 ± 23.34	42.66 ± 11.42	0.12
4 h	60.66 ± 19.98	56.00 ± 15.22	0.31
8 h	67.33 ± 37.31	52.66 ± 23.77	0.07
12 h	70.00 ± 35.13	42.66 ± 20.16	<0.001
16 h	52.66 ±30.39	28.66 ± 18.70	<0.001
20 h	44.66 ± 35.88	20.66 ± 12.29	<0.001
24 h	30.66 ± 23.91	12.00± 9.96	<0.001
24 hours total	432.00±146.27	316.00±44.06	<0.001

Table 5: Hourly Dexmedetomidin consumption by PCA device (mcg).

Hourly Dexmedetomidine consumption (mcg)	Mean±SD	Range
1 h	30.33 ± 8.08	0-40
2 h	21.33 ± 5.71	10-30
4 h	28.00 ± 7.61	10-40
Total	79.66±11.29	40-100

Comparison of side effects revealed no instances of bradycardia, hypotension, dry mouth, itching and respiratory depression in the patients. Comparison of nausea and vomiting scores of groups showed statistically significantly lower scores for Group D compared to Group C ($p<0.05$ for all) (Table 6). Sedation score was found to be statistically significantly high at 1st, 2nd and 4th hours in Group D ($p<0.05$ for all).

Table 6: Nausea-vomiting scores of the groups.

Nausea Vomiting	Group C (n=30) n (%)	Group D (n=30) n (%)	p
0	10 (33.3)	20 (66.7)	0.03
1	17 (56.7)	9 (30)	0.03
2	3 (10)	1 (3.3)	0.01

Discussion

Our study demonstrated that the combination of dexmedetomidine and tramadol administered by PCA for the first 4 hours postoperatively minimized the analgesic consumption for the first 24 hours postoperatively, reduced opioid-related nausea-vomiting and increased the patient satisfaction in gynecologic procedures with Pfannenstiel incision. In addition, no cases of severe bradycardia, oversedation and respiratory depression were observed.

Many studies conducted during the postoperative period reported that tramadol induces less respiratory depression, less sedation and fewer effects on intestinal motility than potent opioids [4]. Dexmedetomidine is a potent selective alpha-2 - agonist that has sedative, analgesic and anxiolytic properties [5]. Alpha-2 agonists and especially dexmedetomidine have come into prominence for postoperative pain management in many reports published in recent years [6, 7], and become an attractive treatment option in multimodal pain management [8, 9]. Dexmedetomidine was observed to have a widespread coverage in anesthesia literatures because of its desired properties in perioperative and postoperative periods [7, 10, 11].

Hemodynamic changes developed following the administration of dexmedetomidine are complex. Following the loading dose, a transient hypertension develops with subsequent hypotension and bradycardia because of its direct vasoconstrictive effect [7, 12]. Use of an agent with such direct cardiovascular effects as part of the postoperative analgesia regimen may give rise to concerns about the occurrence of potentially harmful hemodynamic effects. Icrkering et al. [13] have demonstrated that the infusion without a loading dose leads to a reduction in undesirable hemodynamic effects. Therefore, we preferred to use PCA device only for postoperative pain management in our study. Omission of intraoperative loading dose of dexmedetomidine reduced the suspicions about the potential negative chronotropic effects. A meta-analysis by Wang Guoqi et al. [14] reported that dexmedetomidine reduces the arterial blood pressure and heart rate. Likewise, Cormack et al. [15] emphasized that dexmedetomidine has complications such as hypotension and bradycardia but these are dependent on the dose and can easily be treated. We found no statistically significant difference in MBP in comparison of our study groups. Heart rate values were found to be statistically lower in dexmedetomidine + tramadol HCL group at the 1st, 2nd and 4th hours. We believe that this result is related to the effect of dexmedetomidine, in consistent with the results of other studies. No bradycardia case was observed clinically in our patients. We attributed this to the use of low dose dexmedetomidine.

Cortinez et al. [16] have demonstrated the analgesic efficacy of dexmedetomidine in humans by target controlled infusion of intravenous dexmedetomidine (equal to 0.5 mcg/kg concentration) which results in a blood concentration of 0.6 ng/mL. Recent studies showed that intraoperative dexmedetomidine use (bolus dose of 0.5–1 μg/kg, with or without continuous infusion of 0.5–2 μg/kg per hour) leads to an important reduction in intraoperative and postoperative analgesic need. [17, 18]. In one study, authors reported that intraoperative

dexmedetomidine use does not only reduce the postoperative analgesic requirements but also intraoperative anesthetic need [19].

Cold compression test was performed in subjects following the administration of dexmedetomidine or clonidine in several experimental studies conducted with volunteers. These studies showed that the VRS pain scores are reduced by 20 to 30% in individuals in state of moderate to deep sedation depending on the various doses of these agents [20, 21]. Improved analgesia by dexmedetomidine might come from the synergistic analgesic interactions with opioids, reduction of stress, and attenuation on the affective–motivational component (unpleasantness) of pain. Also in our study, postoperative VRS pain scores and sedation evaluations between groups demonstrated that the VRS pain scores were significantly lower in dexmedetomidine group at all time-points. Sedation score was found to be statistically significantly high at the 1st, 2nd and 4th hours. Because the mean VRS pain scores were below 5 at all time-points in dexmedetomidine group, we concluded that the addition of dexmedetomidine leads to a more rapid and effective analgesia. In addition, based on the mean sedation scores of 0-1, we believe that the patients can be more cooperative and relaxed during the postoperative care. We also believe that the sedative efficacy obtained at the recovery room and after surgery by the addition of dexmedetomidine to tramadol may contribute to the low levels of pain in patients. Furthermore, because of the sedated state of patients, tramadol HCL use by PCA device, which is based on the patient's direct participation to the therapy, may have been reduced.

Arain et al. [22] demonstrated that the administration of 1 mcg/kg dexmedetomidine injection within 10 minutes before termination of surgery followed by 0.4 mcg/kg/hour dexmedetomidine infusion for 4 hours better reduced the postoperative morphine use when compared to 0.08 mg/kg morphine injection. Likewise, Lin et al. [23] compared morphine only and dexmedetomidine + morphine groups using PCA for postoperative analgesia in total hysterectomy procedures and found a significantly lower analgesic need in dexmedetomidine + morphine group. In addition, single dose of dexmedetomidine given prior to induction reduced the postoperative morphine use by PCA device [24]. Our study found that tramadol dose used postoperatively was lower in the group given combination of dexmedetomidine-tramadol when compared to group given tramadol only for 24 hours. Tramadol need was 27% lower in the group given dexmedetomidine. Number of analgesic demands by PCA device was also significantly lower in dexmedetomidine-tramadol group.

Venn et al. [25] investigated the effects of dexmedetomidine in postoperative setting in a study conducted in 119 cardiac surgery and general surgery patients who were in need of mechanic ventilation intensive care and sedation. They found that dexmedetomidine reduced the need for emergency sedation and exhibited a depot analgesic effect. Elimination half-life of dexmedetomidine is approximately 2-3 hours and the authors suggest that its depot analgesic effect is prolonged up to 24 hours. In support of these results, we also observed that the VRS pain scores in first 24 hours postoperatively were lower than those of control group at all time-points with a significant reduction in tramadol requirement and a significant reduction in additional analgesic need in dexmedetomidine group. This prolonged postoperative analgesic effect of dexmedetomidine can be explained by the effects of alpha-2 agonists on emotional component of the postoperative pain owing to their anxiolytic and thymoanaleptic effects [26].

No patient developed respiratory depression (respiratory rate < 10) or desaturation episode (SpO_2 < 90) during the postoperative follow-up. Previous studies have demonstrated that dexmedetomidine does not cause respiratory depression despite the deep sedation levels achieved with it. It was determined that alpha-2 adrenoceptors do not play an active role in respiratory center [27].

Dexmedetomidine reduces the noradrenergic activity by its effect on presynaptic alpha-2 receptors, and this may be responsible for its antiemetic effect [28]. Sedative effect of dexmedetomidine on locus coeruleus exerted through adrenoceptors may also contribute to its antiemetic effect. In our study, addition of dexmedetomidine to tramadol resulted in a lower incidence of nausea and vomiting and reduced metoclopramide need at recovery room. This may be associated with the reduced use of tramadol, which causes nausea, ensured by dexmedetomidine as well as the alpha-2 agonist effect of dexmedetomidine that relieve nausea [29, 30]. Dexmedetomidine use by PCA device can be a reasonable strategy in coping with postoperative nausea and vomiting especially in patients with a history of treatment-resistant nausea [27]. Based on these, patient satisfaction was found to be higher in dexmedetomidine group in our study.

Limitations of the study are the number of patient groups in the study. Also patients' postoperative analgesic needs, patient comfort and satisfaction could be assessed longer time and postoperative Tramadol + Dexmedetomidine administration could be longer than 24 hours.

In conclusion, the combination of tramadol-dexmedetomidine reduces the postoperative analgesic use in patient-controlled analgesia when compared to tramadol alone. In addition, combination of tramadol-dexmedetomidine leads to a reduction in frequency of nausea and vomiting as well as antiemetic use and does not impact respiratory parameters. Postoperative use of dexmedetomidine might create hesitation due to sedation side effects, but we did not find such an effect in our work. We thought that the most important reason was the use of PCA set at the appropriate dose.

Based on these findings, we believe that the addition of dexmedetomidine, which exerts sedative, analgesic and anxiolytic effects, to tramadol by intravenous route will provide an effective analgesia and a more comfortable postoperative care for the patients.

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DOI: 10.25000/acem.409592 Olgu Sunumu / Case Report

Vandetanib-induced photoallergic dermatitis: A case report

Vandetanib'e bağlı gelişen fotoallerjik dermatit: Bir olgu sunumu

Gurbet Acar Yüce [1], İsa An [2], Mustafa Esen [2], Nadiye Akdeniz [3]

Abstract

Vandetanib is a multi-kinase inhibitor of epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGFR). Most common dermatological side effects induced by vandetanib include papulopustular eruption, hand-foot syndrome, and hyperpigmentation.

In this report, we present a case with metastatic medullar thyroid carcinoma who developed vandetanib-induced photoallergic dermatitis.

Keywords: Dermatitis, photoallergic, vandetanib

Öz

Vandetanib, epidermal büyüme faktörü reseptörü ve vasküler endotelyal büyüme faktörünü inhibe eden bir multi-kinaz inhibitörüdür. Vandetanib kaynaklı en sık görülen dermatolojik yan etkiler papülopüstüler erüpsiyon, el - ayak sendromu ve hiperpigmentasyondur.

Burada, vandetanib ile ilişkili fotoalerjik dermatit gelişen metastatik medüller tiroid karsinomlu bir hastayı sunduk.

Anahtar sözcükler: Dermatit, fotoallerjik, vandetanib

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Introduction

Vandetanib is a multi-kinase inhibitor of epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGFR) [1, 2]. Vandetanib has been approved by the Food and Drug Administration for the treatment of advanced or metastatic thyroid medullar carcinoma. In the literature, there are few cases of photoonycholysis, lichenoid photodermatitis and photoallergic dermatitis due to vandetanib treatment [1-3].

In this paper, we aim to report vandetanib-induced photoallergic dermatitis due its rarity.

Case report

A 49-year-old male patient presented to our clinic with erythematous and squamous lesions distributed in the face, the "V" area of the neck, and both forearms. The patient had been diagnosed with thyroid medullar carcinoma 8 years earlier and a metastasis was detected 1 year earlier. Since the patient showed no response to chemotherapy, the patient had been started on vandetanib therapy (300 mg/day) (Caprelsa, AstraZeneca, Turkey). At the second week of the vandetanib therapy, multiple itchy erythematous and squamous lesions occurred in the face, "V" area of the neck, and the sun-exposed areas of the forearms (Figures 1 and 2). Laboratory tests including complete blood count and liver function tests were normal. No biopsy samples were taken since the patient refused biopsy. The patient was diagnosed as having vandetanib-induced photoallergic dermatitis since the lesions only occurred in the sun-exposed areas and the patient had received no drugs other than vandetanib that could cause photoallergic dermatitis. The lesions resolved significantly after the termination of the vandetanib therapy followed by the administration of systemic methyl prednisolone and continuous protection from sunlight.

Written consent was taken from the patient.

Figure 1: Itchy erythematous and squamous lesions at "V" area of the neck covering the face.

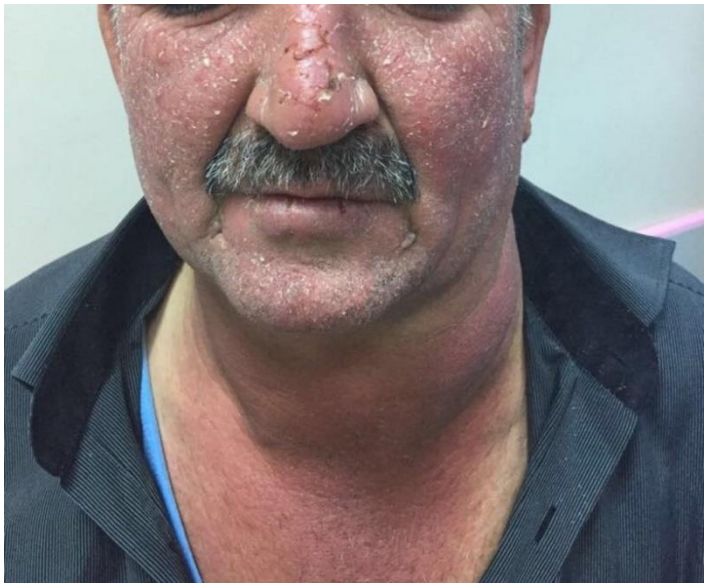
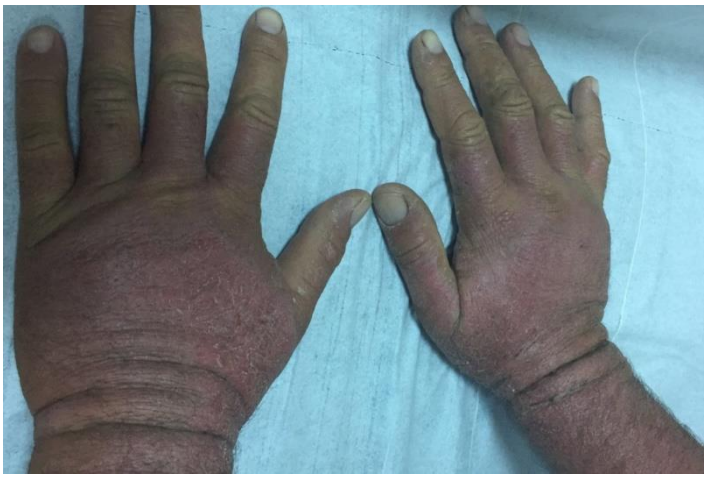


Figure 2: Itchy erythematous and squamous lesions at the sun-exposed areas of the forearms.



Discussion

The epidermal growth factor receptor tyrosine kinase (EGFR-TK) inhibitors cause less side effects compared to standard chemotherapeutics [4]. As the EGFRs are intensely expressed in the epidermis, the hair follicles and the sebaceous glands, these inhibitors mostly lead to dermatological side effects in 50%-100% of the cases [5]. Most common dermatological side effects induced by vandetanib include papulopustular eruption, hand-foot syndrome, hyperpigmentation, mucosal changes, dry skin, hair changes, paronychia, and pyogenic granuloma [1, 2, 5].

Photosensitivity caused by vandetanib is rarely reported. A previous study reported that vandetanib resulted in dermatologic side effects in 37% of the patients, causing sunburn-like erythema in the sun-exposed areas in most of the patients [3]. On the other hand, it has also been reported that vandetanib may lead to a sense of burning, edema, and bulla formation within several days or weeks after the initiation of the therapy [1].

Chemicals causing photosensitivity have a low molecular weight, which often have a plain, tricyclic or polycyclic structure and include a heteroatom. Moreover, these chemicals absorb UV radiation, which is a photosensitizer [2]. Vandetanib also has a low molecular weight [1, 2].

UV radiation and EGFR inhibition increase the oxidative stress in the keratinocytes, causing inflammatory burn on the skin which may lead to skin rash [4]. Photosensitive reactions may be phototoxic or photoallergic and are formed by the compounds that are activated with the radiation harming cell membrane and DNA. The immune response developed against these activated compounds is responsible for photoallergic reactions. In most patients, phototoxic reactions develop within a few days in the presence of adequate sunlight and as a result of drug administration. Moreover, these photoallergic reactions may develop several days or even weeks after the development of the immune response. During the vandetanib therapy, phototoxic reactions occur more frequently than photoallergic reactions [2]. Literature reviews indicate that there have been very few cases of vandetanib-induced photoallergic dermatitis in the literature [2, 6].

In our patient, the fact that the lesions occurred 2 weeks after the initiation of the vandetanib therapy and the lesions were itchy and only occurred in the sun-exposed areas made us consider photoallergic dermatitis rather than a phototoxic reaction. Moreover, our patient had received no drugs or herbals other than vandetanib that could cause photoallergic dermatitis.

Definitive diagnosis of photoallergic dermatitis includes irritant contact dermatitis and allergic contact dermatitis [7, 8]. In our patient, photoallergic dermatitis was diagnosed since the lesions occurred in the sun-exposed areas.

Literature also indicates that there is no certain evidence suggesting that restarting vandetanib treatment is safe in severely photosensitive patients [2]. These reactions mostly recover through protection from sunlight and by avoiding sunscreens [2, 4]. In our patient, the lesions resolved significantly after the termination of the vandetanib therapy followed by the administration of systemic methyl prednisolone and continuous protection from sunlight.

In conclusion, photosensitive reactions and photoallergic dermatitis may be induced by vandetanib and similar drugs. Therefore, in the presence of dermatological side effects caused by these drugs, the drug therapy can be gradually diminished or even discontinued. During the vandetanib therapy, clinicians should warn the patients to protect themselves from sunlight.

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Conjunctivitis secondary to chickenpox: A case report

Suçiçeği nedeniyle gelişen konjonktivit : Bir olgu sunumu

Gurbet Acar Yüce [1], İsa An [2], İsmail Alpfidan [3]

Abstract

Chickenpox is a common benign disease that is typically characterized by vesicular rashes. The disease is more common in children. Ocular complications of the chickenpox are rare. Vesicular eyelid lesions, conjunctivitis and corneal lesions are seen in almost 4% of chickenpox cases.

Here, we report on a rare case of conjunctivitis secondary to chickenpox.

Keywords: Conjunctivitis, chickenpox, vesicular

Öz

Suçiçeği, yaygın veziküler döküntüler ile karakterize, benign bir hastalıktır. Hastalık çocuklarda daha sık görülür. Suçiçeğine bağlı gelişen oküler komplikasyonlar nadirdir. Suçiçeği olgularının yaklaşık %4'ünde veziküler göz kapağı lezyonları, konjonktivit ve korneal lezyonlar görülür.

Bu yazıda suçiçeğine ikincil nadir görülen bir konjonktivit olgusunu sunuyoruz.

Anahtar sözcükler: Suçiçeği, konjonktivit, veziküler

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Informed Consent: The written consent was received from the patient who was presented in this study.
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Introduction

Primary varicella infection, also referred to as chickenpox, is a common benign disease that is typically characterized by fever and exanthamatous vesicular rashes. Although the disease is more common in children, it can also be diagnosed in healthy or immunocompromised adults. Ocular complications of the chickenpox are rare [1-4]. Anterior uveitis is one of the most frequently reported ocular manifestations of chickenpox in childhood. However, conjunctivitis is rarely seen in chickenpox cases [1, 5].

Here, we report on a rare case of conjunctivitis secondary to chickenpox.

Case report

A nine-year-old male child presented to our clinic with erythematous papules and pustules on his face and trunk that developed 1 week ago. Dermatological examination was notable for numerous erythematous papules and pustules on the face (Figure 1 and Figure 2) and the neck. The patient was diagnosed as chickenpox based on existing clinical signs and symptoms. The patient was referred to ophthalmology clinic due to complaints of redness, irritation, watering and gums in the eyes, more remarkably in the right eye (Figure 3). A complete ophthalmological examination was done. In the examination, visual accuracy was absolute in bilateral eyes. Non-contact tonometer showed normal intraocular pressures in bilateral eyes. In biomicroscopic examination, a localized hyperemic lesion was identified that was located at 8 o'clock radius in the conjunctiva of the right eye, not reaching to the limbus. There was no involvement of the sclera with an intact area in the limbus. However, minimal diffuse hyperemia in bilateral conjunctiva was also seen. No pseudo-membrane or membrane formation was observed in the palpebral conjunctiva. Eye movements and light reflexes were normal in bilateral eyes. Bilateral cornea and the anterior chamber were intact, while other findings of the anterior and posterior segments were normal. Conjunctivitis secondary to chickenpox was diagnosed based on current signs and symptoms. The patient was started on topical acyclovir 3% ointment (Zovirax 3% eye ointment, Glaxo, UK) 5X a day and prophylactic topical netilmicin 0.3% drop (netira drop, Teka, Turkey) q.6hr for conjunctivitis. In the follow-up, potential involvement of the anterior and posterior segments was not observed, while the conjunctival lesion and conjunctivitis improved.

Written consent was taken from the parents of the patient.

Figure 1: Numerous erythematous papules and pustules are seen on the face.

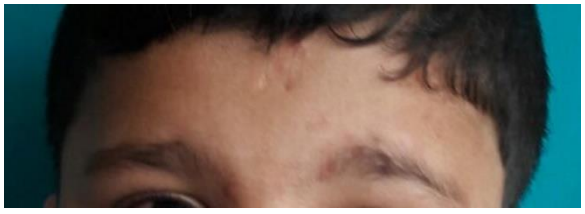

Figure 2: Numerous erythematous papules and pustules are seen on the neck.

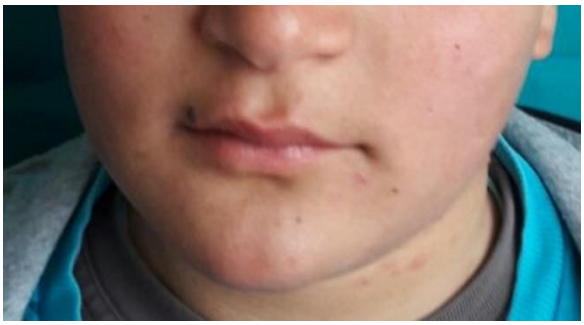

Figure 3: Diffuse, but mild hyperemia exists in bilateral conjunctiva of the patient, more remarkably in the right conjunctiva.

Discussion

Varicella zoster virus may re-activate and cause Herpes Zoster and many neurological conditions following a long incubation period in sensorial nervous ganglion [6]. Although ocular involvement is well known in Herpes Zoster, ocular complications of the chickenpox are rare. Vesicular eyelid lesions, conjunctivitis and corneal lesions are seen in almost 4% of chickenpox cases. Other ocular complications such as canalicular obstruction, anterior uveitis, cataract, optic neuritis, pigmented optic disc and extraocular muscle paralysis as well as internal ophthalmoplegia may be seen in relation with chickenpox, while central nervous system involvements are usually manifested by aseptic meningitidis and fulminant encephalitis [2, 7].

Mild catarrhal conjunctivitis is identified in the chickenpox; discrete lesions in the conjunctiva, excluding the limbus, are very rare. Limbal lesions mimic phlyctenule and may improve without development of ulcers. However, it usually transforms into vesicular form followed by pustules and ulceration [8].

Jordan et al. [5] identified chickenpox-related conjunctival vesicles in 8 of 24 children with active chickenpox and ocular involvement and conjunctivitis in only one patient. These lesions developed in day 1 to day 5 of the onset in all patients and they disappeared within 2 weeks without any complication. Those patients with conjunctival involvement were followed up without a treatment; all lesions healed without development of squeal. Our patient was started on topical acyclovir and topical netilmicin and the patient recovered within 2 weeks without any sequeal.

To our best knowledge, the literature reports very scarce cases with conjunctivitis secondary to chickenpox. Clinicians should recognize this rare complication of the chickenpox infection that is commonly faced in the clinical practice.

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DOI: 10.25000/acem.398477 Olgu Sunumu / Case Report

Hyponatremia induced by stable high dose risperidone in bipolar disorder: A case report

Bipolar bozuklukta stabil yüksek doz risperidon sonrası oluşan hiponatremi: Bir olgu sunumu

N.A. Uvais [1], T.P. Mohammed [2]

Abstract

Risperidone is a commonly prescribed atypical antipsychotic. Hyponatremia has been reported rarely as an adverse effect of risperidone. We report a case of a patient with bipolar affective disorder, who developed the syndrome of inappropriate antidiuretic hormone secretion, probably induced by high dose risperidone. A 60-year-old male with bipolar affective disorder, who was on risperidone 6 mg per day and sodium valproate 1200 mg per day, developed lethargy, unsteady gait, disorientation for the past 4 days followed by fever and productive cough with yellow sputum. Laboratory screening revealed that the serum sodium level was 117 mol/L, the urine sodium concentration was 106 mmol/L and plasma osmolarity was 260.57 mmol/Kg. A diagnosis of the syndrome of inappropriate antidiuretic hormone secretion was made. Risperidone was thought of as a precipitating agent and changed over to olanzapine resulting in improvement in hyponatremia. In this patient, high-dose risperidone treatment was the most probable cause, and the mechanisms may be related to risperidone's high affinity for the 5-hydroxytryptamine 2A and dopamine 2 receptors.

Keywords: risperidone, high-dose, syndrome of inappropriate antidiuretic hormone secretion, bipolar affective disorder

Öz

Risperidon genellikle kullanılan bir atipik antipsikotiktir. Hiponatremi nadiren risperidonun bir yan etkisi olarak bildirilmiştir. Bipolar affektif bozukluğu olan, uygunsuz antidiüretik hormon salınımı sendromu gelişen, muhtemelen yüksek doz risperidonun neden olduğu bir hastayı sunuyoruz. Bipolar duygulanım bozukluğu olan ve günde 6 mg risperidon ve günde 1200 mg sodyum valproat kullanan 60 yaşındaki bir erkek hastada letarji, dengesiz yürüme, son 4 gün boyunca yönelim bozukluğu, ardından ateş ve sarı balgamla karakterize öksürük gelişti. Laboratuvar taraması sonucunda serum sodyum seviyesi 117 mmol/L, idrar sodyum konsantrasyonu 106 mmol/L idi ve plazma ozmolaritesi 260.57 mmol/Kg olarak hesaplandı. Uygunsuz antidiüretik hormon salınımı sendromu olarak değerlendirildi. Risperidonun çökeltici bir madde olduğu düşünülmüş ve tedavisi olanzapine değiştirilerek hiponatremisi düzeltilmiştir. Bu hastada yüksek doz risperidon tedavisi en muhtemel neden olup, oluşum mekanizması risperidonun 5-hidroksitriptamin 2A ve dopamin 2 reseptörlerine yüksek afinitesi ile ilişkili olabilir.

Anahtar kelimeler: risperidon, yüksek doz, uygunsuz antidiüretik hormon salınımı sendromu, bipolar affektif bozukluk

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Introduction

Risperidone is a commonly prescribed atypical antipsychotic, with high affinity for the 5-hydroxytryptamine 2A (5-HT2A) and dopamine 2 (D2) receptors [1]. Common adverse effects of the drug are dizziness, akathisia, extrapyramidal symptoms, weight gain, and other autonomic adverse effects [2]. Hyponatraemia has been reported more with typical than with atypical antipsychotic agents, more often in schizophrenia than in other psychosis [3]. A literature search revealed two reports of risperidone-induced hyponatremia, and nine such cases have been reported at a Dutch pharmacovigilance centre [4-6]. Here, we report a case of hyponatremia induced by high stable dose of risperidone in a male with bipolar affective disorder.

Case report

A 60-year-old male with a diagnosis of bipolar affective disorder was brought by his family to medical emergency room. According to his family, the patient developed lethargy, unsteady gait, disorientation for the past 4 days followed by fever and productive cough with yellow sputum, and the patient was admitted. The patient's medication at the time of admission included risperidone 6 mg per day and sodium valproate 1200 mg per day. He had been in remission for the last two years on the current medications.

His physical examination revealed fever (101° F), tachycardia (108 beats/min), high blood pressure (150/100 mmHg), moderate dehydration as shown by dry skin and disorientation of time, place and person. Respiratory system examination showed crepitations in the right lower zone.

His blood investigations revealed serum sodium was 117 mmol/L (normal range 136-145 mmol/L), serum potassium was 4.68 mmol/L (normal range 3.6-5.2 mmol/L), urine sodium was 106 mmol/L, plasma osmolarity was 260.57 mmol/Kg, uric acid was 3.6 mg/dl (normal range 3-7 mg/dL) and total leucocyte count was 7800/mm3 (4500-11000/ mm3) with the dominance of the neutrophils as 71%. Hemoglobin, blood sugar, albumin, and liver and renal function tests were normal. Creatine kinase was 513 U/L on the third day. Chest X ray revealed features consistent with aspiration pneumonia. There was no evidence of excessive fluid intake or psychogenic polydipsia. The patient was diagnosed with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) based on his clinical presentation and his blood work. He was treated with parenteral antibiotics (Lactagard 1000 mg/500mg Injection: Cefoperazone and Sulbactam, Ipca Laboratories Ltd, India) and oral fluid restriction. Considering physical condition of the patient, the antipsychotics drugs were reduced to a dose of 1000 mg/day for sodium valproate and 3 mg/day for risperidone. But hyponatremia and delirious symptoms persisted between the day 2 and day 4. Considering worsening of the physical symptoms, the antipsychotics were withheld for a day; they were restarted due to the precipitating manic symptoms. Though physical conditions were improved, manic symptoms and hyponatremia persisted. Risperidone was thought of as a precipitating agent and changed over to olanzapine resulting in improvement in manic symptoms and hyponatremia over the next 2 days. The patient was discharged on sodium valproate 1200 mg/day and olanzapine 7.5 mg/day. On subsequent two follow ups, he was maintaining well and his serum electrolyte estimation was within the normal range.

Written consent was taken from the patient.

Discussion

The patient's SIADH developed when receiving risperidone at high dose and resolved after the drug was discontinued. The causal relationship is also supported by the Naranjo Adverse Drug Reaction Probability Scale with a score of 4 on a 0- to 13-point scale, and it has been reported that high-dose risperidone is the possible cause of the SIADH [7].

The mechanism linking risperidone to SIADH remains unclear. It was postulated that by its antagonistic action at 5-HT2A and 5-HT7 receptors in the medial preoptic area/anterior hypothalamus, it can disinhibit antidiuretic hormone (ADH) secretion resulting in water reabsorption by aquaporins [8]. Long-term blockade of D2 receptors also can result in the hypersensitivity hypothalamic dopaminergic pathways involved in the regulation of water consumption and ADH release [9]. Furthermore, dopamine 2 blockers have been proposed as facilitators of ADH response and high dose treatment with risperidone can enhance this response [10]. As a result, high-dose risperidone might have triggered SIADH in our patient. Contrary to our report, risperidone have also been used in the treatment of psychogenic polydipsia with associated hyponatremia; however, their role is not clear as there are reports of both improving and causing polydipsia [11]. Though we found improvement in hyponatremia and manic symptoms in our case after shifting to olanzapine, there are reports of hyponatremia with olanzapine also. The only antipsychotic consistently found to have a beneficial effect on polydipsic behavior and development of hyponatremia is clozapine, may be due to its lower binding affinity to D2 receptors [12].

In conclusion, we suggest that, in patients with bipolar affective disorder, high doses of risperidone may cause SIADH. Therefore, we recommend that clinicians should regularly evaluate serum electrolyte levels to detect SIADH in suspected patients with bipolar affective disorder, just like they are advised to do in schizophrenia using high-dose risperidone treatment.

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DOI: 10.25000/acem.402632 Olgu Sunumu / Case Report

Tekrarlayan auriküler hematom: Bir olgu sunumu

Recurrent auricular hematoma: A case report

Erdal Tekin [1], Yunus Ağar [2], Fatma Kesmez Can [3]

Öz

Otohematom (güreşçi kulağı), genellikle güreş ve boks gibi sporlar esnasında künt travma sonucu meydana gelir. Perikondriumun kıkırdaktan ayrılması nedeniyle perikondrium ve kıkırdak arasında bulunan subperikondriyal boşlukta kan birikmesi ile ortaya çıkar. Aurikular kıkırdakta vasküler yapı olmadığı için perikondrial beslenme bozulur. Otohematomlu hastalarda, kulakta kızarıklık, ekimoz ve ağrılı ödem oluşur. Tedavide geç kalınması durumunda kulakta deformiteye ve bazen de nekroza neden olabilir. Bu çalışmada güreşçi olduğu öğrenilen hastanın sağ kulağına tekrarlayan darbeler alması sonucu gelişen otohematom vakası sunulmuştur.

Anahtar Kelimeler: Otohematom, güreşçi kulağı, enfeksiyon, künt travma

Abstract

Otohematoma (wrestler's ear) usually occur as a result of blunt trauma during sports such as wrestling and boxing. The perichondrium is separated from the cartilage by blood accumulation in the subperichondrial space between the pericondrium and the cartilage. Pericondrial nutrition is impaired as the auricular cartilage is not a vascular structure. Patients with otohematomas have redness, ecchymosis, and painful edema in the ear. In case of delayed treatment, it causes deformities and necrosis in the ear. In this study, an otohematoma case was presented which resulted in recurrent blows on the right ear of a patient who was learned to be a wrestler.

Keywords: Otohematoma, Wrestler’s ear, infection, blunt trauma

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Giriş

Aurikula düzensiz girinti ve çıkıntılardan oluşmaktadır. Aurikula kulağa şeklini veren kıkırdak ve kıkırdağın üzerini örten perikondriumdan oluşur. Perikondrium avasküler olması nedeniyle kıkırdak yapı subperikondrial alandan difüzyon yoluyla beslenmektedir [1,2]. Deri kıkırdağa sıkıca bağlıdır ve genellikle tekrarlayan travmalar sonucu kıkırdakla perikondrium arasında ölü boşluklar oluşmaktadır. Zamanla bu ölü boşluklara sızan kan ve kan ürünleri hematom oluşturarak granülasyon dokusu meydana getirir. Zamanında tedavi edilmezse bu granülasyon dokusu yerini fibrotik dokuya bırakarak deformiteye (karnıbahar deformitesi) neden olur. Tekrarlayan travmalar sonucu bu bölgede apse ve nekrozda oluşabilmektedir [1, 3].

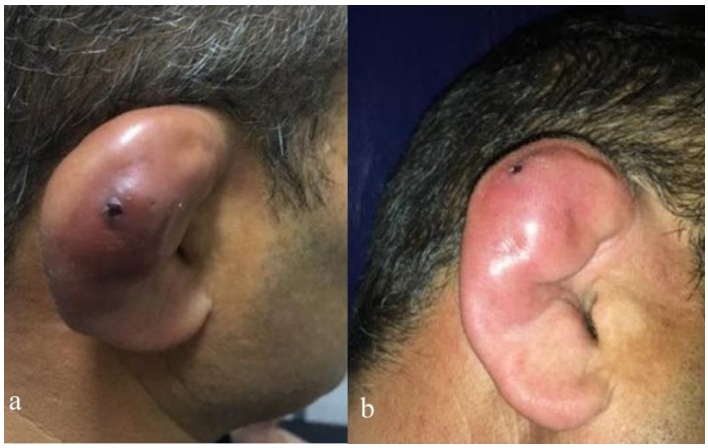
Bu çalışmada kulağına tekrarlayan künt travmalar sonucunda daha önceden çok kereler auriküler hematom gelişen ve bu gelişen hematomlarına rağmen tedaviyi kabul etmemesi sonucu hematomu apseleşip fistülize hale gelen bir olguyu sunmayı amaçladık.

Olgu Sunumu

40 yaşında bir erkek hasta sağ kulağında şişlik, kızarıklık, ağrı ve akıntı oluşması nedeniyle acil servise müracaat etti. Öyküsünde güreşçi olduğu öğrenilen hastanın bilinen başka bir ek hastalığı bulunmayıp, diğer sistem muayeneleri normaldi. Daha önceden de birkaç defa aynı kulağında şişlik, kızarıklık ve ağrı oluştuğu, hastaneye başvurduğunda hematomun drene edilmesi gerektiği belirtilmesine rağmen hastanın tedaviyi kabul etmediği öğrenildi. Yapılan laboratuvar tetkiklerinde lökosit 10200/mm3, C-reaktif protein 6 IU/ml ve eritrosit sedimantasyon hızı 25 mm/saat olarak tespit edildi. Hastanın fizik muayenesinde vücut sıcaklığı normal olup, sağ kulak aurikulada hematom, ekimoz ve fistülize olmuş nekrotik doku mevcuttu (Resim 1 a-b). Hasta kulak burun boğaz kliniği ile konsülte edildi ve aurikular bölgedeki apseleşmiş hematoma insizyon yapılarak hematom boşaltıldı. Hastanın subperikondrial alanının yer yer yoğun fibrotik dokular içerdiği ve oldukça sertleşmiş olduğu izlendi. Boşaltılan sıvıdan kültür gönderildi. Hematomun yeniden oluşmaması için aurikula sıkı bandajla sarıldı. Enfeksiyon hastalıklarına danışılarak parenteral uygun antibiyoterapi (ampisilin-sulbaktam, 1gr flakon, intravenöz, Sulcid 1 gr, İbrahim Etem Ulagay İlaç Sanayi Türk A.Ş. İstanbul/Türkiye) ve analjezik tedavisi başlandı. Sıvıdan alınan kültürde üreme olmadı.10 gün sonra yapılan kontrolde hematomun tekrarlamadığı ve kan tetkiklerinin normal olduğu görüldü.

Hastadan, olgu sunumu ile ilişkili yazılı onam alındı.

Resim 1a-b: Otohematom.



Tartışma

Auriküler hematom özellikle boks ve güreş gibi kulağa tekrarlayan künt travmaların yaşandığı sporlar sonrası görülmektedir [4]. Kulak kepçesinin ön tarafındaki deri arkaya göre daha incedir ve perikondriumla direkt bağlantılıdır [5]. Bu yüzden kulağa ön taraftan uygulanan künt travmalarda deri ve perikondrium kıkırdak yapıdan kolayca ayrılır. Kıkırdakla perikondrium arasında ölü boşluk oluşması kan ve kan elemanlarının birikerek hematom oluşmasına sebep olur. Otohematom vakalarında ölü boşluğun giderilmesi için pek çok yöntem tarif edilmiştir [6]. Klasik tedavide; erken evrede insizyon ile hematom boşaltılması ve ölü boşlukta tekrar hematom oluşmasını engellemek için 7-10 gün boyunca baskılı pansuman uygulanır. Burada önemli olan drenaj sonrası mutlaka baskılı pansuman yapılmasıdır [4]. Yine de sunulan bazı vakalarda drenaj ve baskılı sargı sonrası da nüks görüldüğü bildirilmiştir [3].

Zamanında tedavi edilmememiş veya sık nüks eden hematomlar kıkırdak yapısındaki beslenme bozukluğuna bağlı olarak o bölgede enfeksiyon oluşturmaktadır. Enfeksiyonun ilerlemesiyle apse ve nekroz görülebilmektedir. İlerleyen aşamalarda otohematom aurikular yapıda fibrozis ve kalıcı kulak deformitelerine sebep olmaktadır. Bu noktadan sonra otohematomun tedavisi daha zordur ve nüksler daha sık görülmektedir [7, 8]. Bizim vakamızda hasta tekrarlayan aurikular hematom nedeniyle gelişlerinde tedaviyi reddetmesinden dolayı sağ kulağında apse formasyonu oluşup, fistül gelişimi izlenmiştir.

Geç dönemde fibrotik hale gelmiş olan kartilaj yapının debritmanı ve hematomun aspirasyonu sonucu oluşan ölü boşluğun giderilmesi için çeşitli baskılı tamponlar ve çeşitli sütürasyon teknikleri kullanılmaktadır. Ayrıca geç müdahalede bazen kıkırdak yapının plastik cerrahi tarafından yeniden yapılandırılması gerekebilmektedir [2, 9, 10].

Sonuç olarak otohematom uygun ve erken cerrahi müdahale ile aurikular bölgede deformite olmasına izin verilmeden tedavi edilebilir. Geç kalınan olguların tedavisinde insizyon ile hematomun boşaltılır. Fibrozis gelişmiş olan dokunun debride edilmesi nedeniyle oluşan ölü boşluğun sutürasyon tekniği, eksternal baskılı tampon veya çeşitli dolgu materyalleri doldurulması ile tedavisi sağlanır. Bu şekilde auriküler deformite en aza indirilmiş ve enfeksiyon oluşumunun önüne geçilmiş olunur.

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DOI: 10.25000/acem.403140 Olgu Sunumu / Case Report

Posttraumatic pulmonary pseudocyst: Report of two cases

Posttravmatik pulmoner psödokist: İki olgu sunumu

Cihan Bedel [1], Muharrem Özkaya [2]

Abstract

Posttraumatic pulmonary pseudocyst is a rare complication of blunt thoracic trauma. It is commonly seen in pediatric and young adult patients. In the literature, traumatic pseudocysts are also defined as pseudocystic hematoma, traumatic lung cavity and traumatic pneumatocele. Traumatic pseudocysts usually have good clinical prognosis, recover spontaneously with supportive treatment and do not require surgery. In this report, we present rare cases of two posttraumatic pulmonary pseudocysts developed after traffic accidents, where conservative treatment contributed excellent outcomes.

Keywords: Chest trauma, traumatic pulmonary pseudocyst, cyst

Öz

Posttravmatik pulmoner psödokist künt toraks travmalarının nadir bir komplikasyonudur. Genellikle pediatrik ve genç erişkin hastalarda görülür. Literatürde travmatik psödokistler hematom, travmatik akciğer kavitesi ve travmatik pnömatosel olarak tanımlanmıştır. Travmatik psödokistler genellikle iyi bir klinik prognoza sahiptir, destek tedavisi ile kendiliğinden iyileşir ve ameliyat gerektirmezler. Bu yazıda, trafik kazasından sonra gelişen ve konservatif tedavinin mükemmel sonuçlarla katkıda bulunduğu iki nadir posttravmatik pulmoner psödokist olgusunu sunuyoruz.

Anahtar kelimeler: Toraks travması, travmatik pulmoner psödokist, kist

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Introduction

Posttraumatic pulmonary pseudocyst (TPP) is a rare pulmonary lesion of the lung that can be seen after blunt or penetrating chest trauma. Young adults and children are most commonly impressed [1]. The clinical presentation is variable and ranges from asymptomatic to acute respiratory distress. Chest pain, dyspnea, cough, and hemoptysis are commonly reported [2]. Differential diagnosis of TPP includes lung abscess, bronchial cyst, post-inflammatory pneumatocele, tuberculosis, mycosis, herniation of the viscera, esophageal rupture, and neoplasm [3]. Chest computed tomography (CT) is important for early diagnosis [4]. Spontaneous remission is the usual outcome, but sometimes they can be complicated and surgical treatment is required [5].

We here report two cases of TPPs, which are rare cases, developed after blunt chest trauma due to traffic accident where conservative treatment contributed excellent outcomes.

Case reports

Case 1

A 26-year-old male was admitted to our hospital after a traffic accident. No characteristic feature was found in the patient's medical history. He was a smoker and often abused alcohol. The patient complained of right shoulder and right chest pain. On physical examination, he was hemodynamically stable and well perfused. Auscultation of the lungs revealed decreased respiratory sounds over the right hemithorax and painful right shoulder motions were noted.

The hemoglobin count was 13.1 g/dL; white blood cell count was 16.5x103/mm3 and there was a mild increase in serum transaminase, creatine phosphokinase and lactic dehydrogenase activity. CT revealed bilateral pneumothorax, which was more prominent on the right side, lung contusion, and bilateral cavitary lesions particularly on the right side (Figure 1 a-b). A chest tube was placed in the right pleural cavity. He was treated with antibiotics (cephazoline sodium, Cefamezin, Eczacıbaşı, Istanbul, Turkey), postural drainage and analgesics. With this treatment, the patient improved with disappearance of pain ant it disappeared completely in two weeks. The drain was removed on the 5th day and the control x-ray of the patient showed no complication. Follow-up radiographs also showed gradual improvement. Radiograph taken after three months of the treatment showed almost complete resolution of the lesions.

Written consent was taken from the patient.

Case 2

A 22-year-old male was admitted to our hospital after a traffic accident. No characteristic feature was found in the patient's medical history. He was mentally alert and physical examination revealed subcutaneous emphysema, tachypnea, and hemoptysis. Respiratory sounds were diminished over the left lung. Other systems were normal with the exception of the left femur fracture.

The hemoglobin count was 11.7 g/dL; white blood cell count was 13.6x103/mm3 and other hematologic and biochemical findings were normal. Chest X-ray (Figure 2) and chest CT scanning (Figure 3a-b) revealed subcutaneous emphysema, multiple bilateral rib fractures, left hemopneumothorax, bilateral contusions and bilateral cavitary lesions particularly on the left side. The patient was treated by catheter aspiration and operation for his femur fracture was performed. He was treated with antibiotics (cephazoline sodium, Cefamezin®, Eczacıbaşı, Istanbul, Turkey and gentamicin sulphate, Genta® 80 mg, I.E. Ulagay, Istanbul, Turkey, postural drainage and analgesics. With this treatment, the patient improved with disappearance of pain and it was disappeared completely in three weeks. Follow-up radiographs also showed gradual improvement. Radiograph taken after four months of the treatment showed almost complete resolution of the lesions.

Written consent was taken from the patient.

Figure 1 a-b: Computed tomography of the thorax revealed bilateral pneumothorax, lung contusion, and bilateral cavitary lesions particularly on the right side (axial and coronal view).

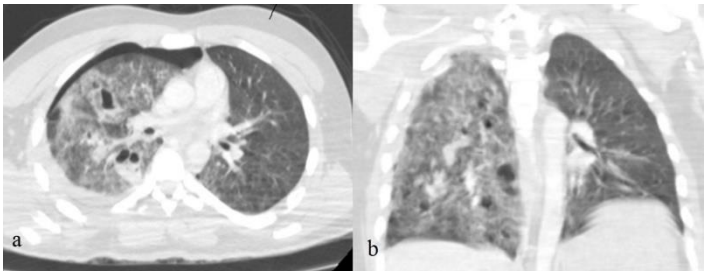


Figure 2: Chest radiograph shows subcutaneous emphysema and consolidation of the left lung.

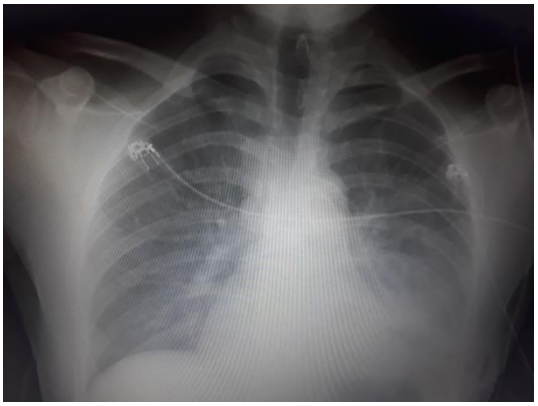
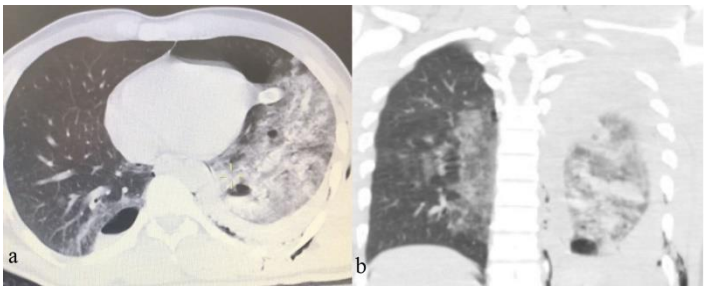


Figure 3 a-b: Computed tomography of the thorax revealed subcutaneous emphysema, multiple rib fractures, left hemopneumothorax, contusions and bilateral cavitary lesions (axial and coronal view).



Discussion

Traumatic pulmonary pseudocyst is a cavitary lesion that can be seen after thoracic trauma. These lesions are usually seen after blunt trauma; however, cases associated with penetrant trauma are rarely reported [6]. TPP constitutes of 2.9% of all parenchymal injuries of the lungs and males younger than 30 years of age enclose the majority of the affected patients [7]. This can be clarified by higher exposure to higher energy trauma like motor vehicle accidents in men or falls from a height.

The lesions result from blunt trauma causing local lacerations of the lung parenchyma. Elastic tapping allows air inlet. TPPs are more often seen in children and young adults because of greater adaptation of the chest wall leads to greater

force transmission to the parenchyma [8]. The current cases were also young male patients, consistent with these reports.

The etiology of TPP is usually associated with blunt thoracic trauma. Motor vehicle accidents and falls have been reported as the most common mechanisms of injury, but little is known about the prevalence of pseudocyst according to mechanism of injury [9]. In our cases, the lesions occurred after traffic accidents consistent with the literature.

Characteristic symptoms of TPPs are hemoptysis, chest pain, dyspnea, cough, and sometimes a small rise in temperature in the early days after the trauma. Mild leucocytosis may be present in blood analyses [8]. In our cases consistent with the literature, the patients presented with a complaint of chest pain and leukocytosis was seen.

Post-traumatic pulmonary pseudocysts may be diagnosed on the chest radiograph, but CT is superior for detecting them. Unlike other cystic and cavitary lesions, the size, shape, and nature of the wall of a post-traumatic pulmonary pseudocyst change relatively quickly, so a series of chest radiographs over several days can help differentiate pseudocyst from other lesions [10].

The differential diagnosis includes postinfectious pneumatocele, tuberculous or mycotic cavity, pulmonary abscess, cavitating carcinoma, cavitating or infected hematoma, and ruptured diaphragm with protrusion of bowel into the chest space. The history of trauma and the CT scan of the chest, usually are enough to confirm the diagnosis of pseudocyst [11].

TPPs are treated conservatively. Resolution of the lesion can be seen after six weeks; however, surgery can be required in certain circumstances. Progressively enlarging and infected lesions, abscessed cysts, and cysts that are associated with hemorrhage or rupture into the pleural cavity can require surgical intervention [12]. The mean time for spontaneous radiologic resolution has been reported within three months in TPPs [7]. In our cases, consistent with the literature, we treated conservatively.

In conclusion, TPP is a rare complication of blunt chest trauma. It usually resolves spontaneously but may require surgery. CT is more valuable than chest radiograph for early diagnosis. Prophylactic antibiotics may be indicated. Clinicians should conduct follow-up radiographs or CT scans until the pseudocyst resolves.

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Asymptomatic giant pneumatization of the middle turbinate: A case report

Orta konkanın asemptomatik dev pnömatizasyonu: Bir olgu sunumu

Süha Ertuğrul [1]

Abstract

Concha bullosa is a pneumatization of the turbinates at several degrees. Pneumatization of the middle turbinate is generally asymptomatic; however, it may become symptomatic depending on its degree of pneumatization. All giant pneumatizations of the middle turbinate reported in the literature are reported to cause nasal obstruction. In this article, we present a case of asymptomatic giant pneumatization of the middle turbinate that was detected incidentally in a patient who presented with acute tonsillitis infection with sore throat and swallowing difficulty. To the best of our knowledge, this is the first asymptomatic giant pneumatization of the middle turbinate in the literature. In this article, we discussed how pneumatization of the middle turbinate could be symptomatic in the context of this case.

Key Words: Asymptomatic, concha bullosa, giant, middle turbinate, pneumatization

Öz

Konka bülloza, konkaların çeşitli derecelerdeki pnömatizasyonudur. Orta konkanın pnömatizasyonu genellikle asemptomatiktir. Ancak pnömatizasyon derecesine bağlı olarak semptomatik olabilir. Literatürde sunulan tüm orta konka dev pnömatizasyonlarının burun tıkanıklığına neden olduğu bildirilmiştir. Bu yazıda boğaz ağrısı ve yutma güçlüğü ile başvuran akut tonsillit hastasında rastlantısal saptanan orta konkanın asemptomatik dev pnömatizasyonu olgusu sunulmuştur. Bildiğimiz kadarıyla bu literatürdeki ilk orta konkanın asemptomatik dev pnömatizasyonudur. Bu yazıda, bu olgu bağlamında orta konka pnömatizasyonunun nasıl semptomatik olabileceğini tartıştık.

Anahtar kelimeler: Asemptomatik, konka bülloza, dev, orta konka, pnömatizasyon.

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Introduction

Concha bullosa is a pneumatization of the turbinates at several degrees and it is one of the most frequently seen variations of the nasal cavity [1]. Approximately 55% of the cases have the anterior and the posterior ethmoid cells that are held responsible for the pneumatization of the middle turbinate (PMT) for about 45% of them [2]. Middle turbinate has functions such as olfaction, humidifying the air and regulating the air flow [3]. PMT is generally asymptomatic; however, it becomes symptomatic depending on its degree of pneumatization and its relation with adjacent structures [4]. The most frequent symptoms include nasal obstruction, headache and olfactory disorder. All giant PMT reported in the literature are reported to cause nasal obstruction [4, 5].

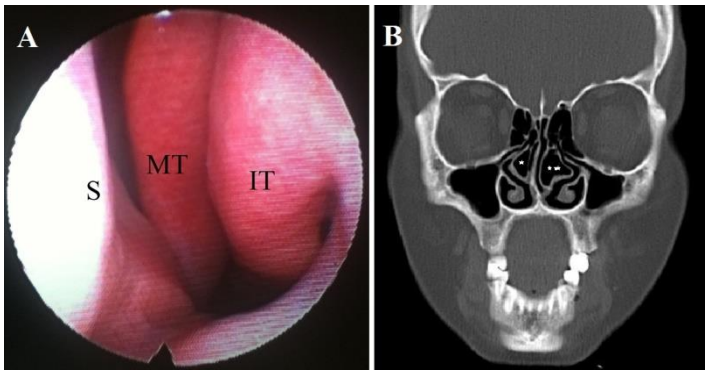
In this article, we presented a case of asymptomatic giant PMT that was detected incidentally in a patient who presented with acute tonsillitis infection with sore throat and swallowing difficulty.

Case report

A 28-year-old female patient presented to our clinic with the symptom of sore throat and swallow difficulty. Acute tonsillitis infection was observed on the oropharyngeal examination and antibiotherapy was started. She did not have a nasal obstruction, headache, postnasal discharge and olfactory disorder. But her anterior rhinoscopic examination showed a mass with mucosal surface blocking the nasal passage in both nasal cavities. When an endoscopic examination was performed, it was seen that the middle turbinates in both nasal cavities were large. Especially in the left nasal cavity, it was observed that the middle turbinate extended down to the nasal base (Figure 1a). The paranasal computerized tomography scan that was taken showed that both middle turbinates were extremely pneumatized with the left side being more pneumatized (Figure 1b). The sinus aeration was normal. As it was asymptomatic, no intervention was planned for PMT.

Written informed consent was obtained from the patient.

Figure 1. A. Endoscopic view of the left nasal cavity (IT: inferior turbinate, MT: middle turbinate, S: septum). B. Coronal computed tomography showing the over pneumatization of the bilateral middle turbinates (single star: right pneumatization of the middle turbinate, double star: left pneumatization of the middle turbinate).



Discussion

The incidence of PMT is in the range of 13%-53% [1, 2, 6]. Bolger et al. [1] classified PMT as lamellar, bullous and extensive depending on the degree of pneumatization and localization. Accordingly, they defined pneumatization on the vertical lamella of the middle turbinate as lamellar type, on the inferior segment of the middle turbinate as bullous type and on the entire middle turbinate as extensive type. Our case had a PMT of the extensive type [1].

Even though the development mechanism of PMT has not been fully elucidated, various theories have been brought forward. According to one theory (ex vacuo), the vacuum formed at the opposite side of deviation after the development of a septum deviation and the air flow pattern of the nasal cavity trigger the development of PMT. Uzun et al. [7] reported that the incidence of PMT was increased in patients with advanced septum deviation in such a way as to support this theory in their study of 140 cases. According to a second theory, it is defended that the development of PMT is not related to septum deviation, but to the aeration of middle turbinate. The study conducted by Uygar et al. [8] actually supports the second theory. The fact that our case had bilateral PMT and not a septal deviation suggests that the second theory is more valid.

PMT is generally asymptomatic; however, it becomes symptomatic depending on the degree of pneumatization or its relation with adjacent structures. All giant PMT's reported in the literature are reported to cause nasal obstruction [4, 5]. In our case, the PMT did not cause nasal obstruction, even though it reached the nasal base. It is not right to associate symptoms with only the degree of pneumatization. Concomitant septum deviation or inferior turbinate hypertrophy can lead to nasal obstruction, sinusitis attacks if ventilation and drainage of the osteomeatal complex are disturbed, or contact headache if contact with surrounding tissues. If there are no such events, they may be asymptomatic even at giant sizes, as in our case. We conclude that the association of PMT with surrounding tissues is more important than the degree of pneumatization in the symptomatic case of PMT.

In conclusion, the middle turbinates may reach gigantic proportions, which sometimes extend to the nasal base, as a result of extreme pneumatization. However, PMT can be asymptomatic even if it reaches giant dimensions.

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Plaque with Asymptomatic Verrucous Surface on the Right Leg: Dermatofibroma

Sağ bacakta asemptomatik verrüköz yüzeyli plak: Dermatofibrom

İsa An [1], Derya Uçmak [1], İbrahim İbiloğlu [2], Murat Öztürk [3]

Abstract

Dermatofibroma is a benign fibrohistiocytic neoplasia. The etiology of dermatofibroma remains uncertain but it is considered to have a traumatic origin such as an insect bite or follicular rupture. Dermatofibroma clinically presents as smooth-surface nodular lesions. We report a patient with a plaque with asymptomatic verrucous surface on the right leg.

Keywords: dermatofibroma, verrucous, leg

Öz

Dermatofibrom sık görülen benign fibrohistiyositik bir neoplazidir. Etiyolojisi halen belirsizliğini korumaktadır fakat böcek ısırması ve follikül rüptürü gibi bir travmadan kaynaklanabileceği kabul edilmektedir. Dermatofibrom klinikte genellikle düzgün yüzeyli nodüler lezyonlar şeklinde görülmektedir. Burada sağ bacakta asemptomatik verrüköz yüzeyli plağı olan bir hastayı sunuyoruz.

Anahtar sözcükler: Dermatofibrom, verrüköz, bacak

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Introduction

Dermatofibroma (DF) is a commonly seen benign fibrohistiocytic neoplasia. Although it is mostly seen in adults and in the lower extremities, it can also affect any part of the body. There is a slight female predominance in DF [1]. DF clinically presents as smooth-surface nodular lesions [1].

We report a patient with plaque with verrucous surface on the leg.

Case report

A thirty-year-old male patient presented to our clinic with a 3-year history of asymptomatic mass on the right leg. The patient had no systemic disease, drug use, and no history of trauma in the lesion site. Physical examination revealed a 3x3 cm immobile, firm plaque with verrucous surface on the extensor surface of the right leg (Figure 1). No lesions were seen on the mucosal surfaces and the nails. Routine laboratory tests including complete blood count and liver function tests were normal. Histopathological evaluation showed a lesion with acanthosis on the epidermis, increased basal layer pigmentation, fibroblastic cell proliferation (Figure 2), and collagen foci entrapped by fibroblastic cells (Figure 3). In the immunohistochemical evaluation of the lesion was positive for factor XIIIa, vimentin, and muscle spesific actin and negative for S100 and CD34. Based on these findings, the patient was diagnosed with dermatofibroma. The lesion was excised completely with negative surgical margins.

Written consent was taken from the patient.

Figure 1: A 3x3 cm immobile, firm, verrucous plaque seen on the extensor surface of the right leg.

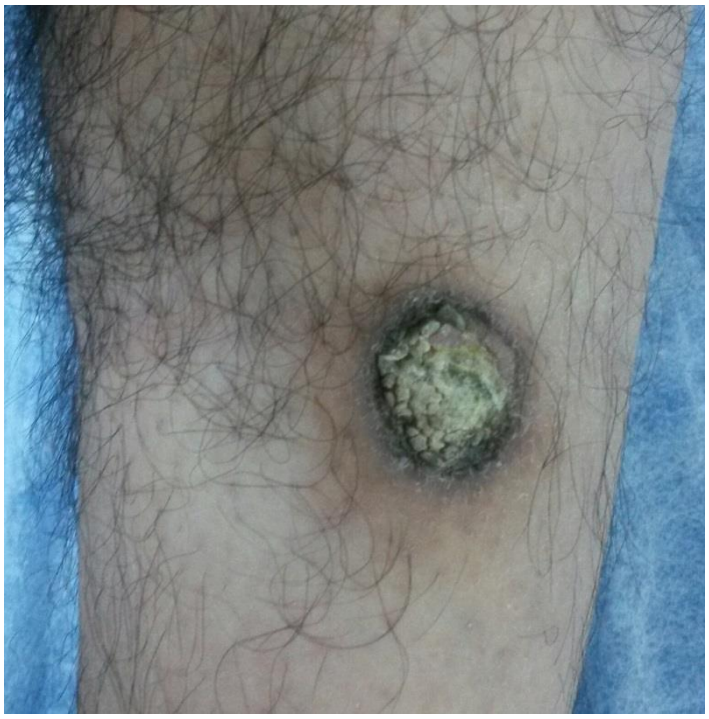


Figure 2: A lesion with acanthosis on the epidermis, increased basal layer pigmentation, and fibroblastic cell proliferation (H&E, X40).

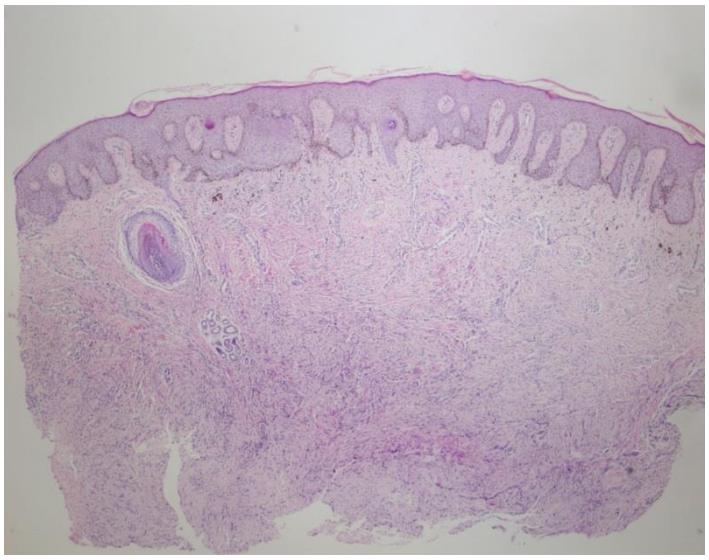
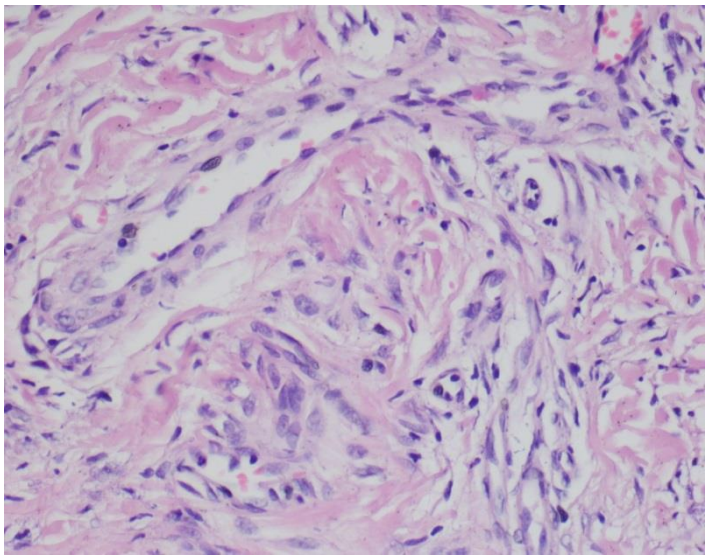


Figure 3: Collagen foci entrapped by fibroblastic cells (H&E, X400).



Discussion

DF commonly presents as firm, hyperkeratotic or dome-shaped papules varying in size from a few millimeters to 1 cm and rarely reaching 2 cm. While the lesions are usually hyperpigmented, they can vary from brown to pink in patients with low-pigmented skin [2]. Our patient was present with flesh-colored plaques with a verrucous surface. The lesions in dermatofibroma are usually solitary but 2-5 lesions can be seen in approximately 10% of the patients. In addition, rash and ulceration can also be seen, though rarely [3]. However, the lesion in our patient was asymptomatic.The etiology of DF remains uncertain but it is considered to have a traumatic origin such as an insect bite or follicular rupture [4]. Our patient did not have a trauma history. Multiple eruptive dermatofibromas have been reported in patients with systemic lupus erythematosus, human immunodeficiency virus, myasthenia gravis, mycosis fungoides, Sjogren's syndrome, pemphigus vulgaris, ulcerative colitis, and atopic dermatitis [1]. In DF, pressing the lesion with thumb and index finger causes a dimpled appearance on its surface and this helps in the differentiation of DF from other clinical conditions. Although the clinical diagnosis of DF is often easy to establish, it might be difficult to distinguish DF from

dermatofibrosarcoma protuberans, granular cell tumors, clear cell acanthoma, and melanoma [2, 3].

Typical histopathological findings of DF include dense polymorphic infiltrate of lymphocytes, plasma cells, and histiocytes as well as dermal findings particularly including thick collagen bundles in the peripheral area and increased capillary density. These findings may also be accompanied by acanthosis, epidermal hyperplasia, interlocking retes, and increased basal layer pigmentation. In the immunohistochemical evaluation, DF is often positive for factor XIIIa, vimentin, and muscle specific actin and negative for S100 and CD34 [2, 4].

The main histological types of DF are fibrocollagenous, cellular, histiocytic, lipidized, angiomatous, aneurysmal, clear cell, monster cell, myxoid, keloidal, palisading, osteoclastic and epithelioid dermatofibroma [4, 5]. Our patient was diagnosed as having fibrocollagenous type of DF. In DF, spontaneous resolution can occur in some patients after a long follow-up period. However, malignant transformation of the lesions is not likely. In the patients with cosmetic concerns, the lesions can be totally excised [3]. Similarly, the lesion in our patient was excised completely.

Dermatofibroma clinically presents as smooth-surface nodular lesions. In our patient, the lesion had a verrucous surface. Clinicians should keep dermatofibroma in mind particularly in the diagnosis of the patients presenting with verrucose lesions on the legs.

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