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Relationship of parathyroid adenoma volume with preoperative biochemical parameters

Paratiroid adenom volümünün preoperatif biyokimyasal parametreler ile ilişkisi

Serhat Özçelik [1], Süleyman Baş [2], Mehmet Çelik [1], Sibel Temiz [1], Melike Özçelik [3], Pembegül Güneş [4], Hasret Cengiz [1], Yasemin Tütüncü [1], Hülya Ilıksu Gözü [5]

[1] Haydarpaşa Numune Training and Research Hospital, Department of Endocrinology and Metabolism, Istanbul, Turkey
[2] Haydarpaşa Numune Training and Research Hospital, Department of Internal Diseases, Istanbul, Turkey
[3] Kartal Lütfü Kırdar Training and Research Hospital, Department of Medical Oncology, Istanbul, Turkey
[4] Haydarpaşa Numune Training and Research Hospital, Department of Pathology, Istanbul, Turkey
[5] Marmara University Training and Research Hospital, Department of Endocrinology and Metabolism, Istanbul, Turkey

ORCID ID of the authors:
SÖ: 0000-0002-0521-5866
SB: 0000-0002-5883-445X
MÇ: 0000-0001-7364-370X
ST: 0000-0003-4993-9513
MÖ: 0000-0003-0406-715X
PG: 0000-0002-4982-5156
HC: 0000-0002-5216-3368
YT: 0000-0001-6975-7501
HIG: 0000-0001-7724-8168

Corresponding author / Sorumlu yazar:
Serhat Özçelik
Address / Adres: Adıyaman Üniversitesi, Eğitim ve Araştırma Hastanesi, Endokrinoloji ve Metabolizma Kliniği, Adıyaman, Türkiye
E-mail: ozserhat1981@gmail.com

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Abstract

Aim: Primary hyperparathyroidism (PHPT) is a clinical presentation of hypercalcemia resulting from autonomous excessive parathyroid secretion from parathyroid glands. Significant correlation between serum parathyroid hormone (iPTH), calcium (Ca), phosphorus (P) and 25-OH D3 levels and adenoma volume, have a predictive value to determine the size of parathyroid adenoma resection. In this study, we examined the relation between preoperative biochemical parameters and resected parathyroid adenoma volume.

Methods: Fifty-two patients with PHPT diagnosed in the endocrinology outpatient clinic of Istanbul Haydarpaşa Numune Research Hospital, between 2011 and 2014 were included in the study. Histopathological diagnosis of solitary parathyroid adenomas was made. Correlation analysis was performed between adenoma volume and preoperative serum iPTH, corrected Ca, P, 25-OH D3 and 24 hour urinary calcium levels. The study was designed a cross-sectional study.

Results: Fifty-two patients studied, 45 were female and 7 were male. The mean age of the patients was 53.538 ± 14.996 years. The mean preoperative iPTH level was 371.423 ± 341.8 pg / dl, corrected Ca level was 11.652 ± 0.947 mg / dl, phosphorus level was 2.285 ± 0.434 mg / dl and 25-OH D3 level was 11.442 ± 6.120 ng /dl. The calculated parathyroid adenoma volume averaged 1.612 ± 2 cm^3. Correlation between parathyroid adenoma volume with parathormone levels and 24 hour urine calcium levels was positive whereas 25-OH D3 levels were negatively correlated with adenoma volume.

Conclusion: The adenoma size correlates with iPTH and vitamin D levels in PHPT patients. These levels may have predictive value about adenoma volume.

Keywords: Parathyroid adenoma volume, Biochemical parameters

Öz

Amaç: Primer hiperparatiroidizm (PHPT), paratiroid bezlerinden otonom olarak aşırı parathormon salgılanması sonucu oluşan, hiperkalsemi veya normokalseminin görüldüğü klinik bir tablodur. Serum paratiroid hormonu (iPTH), kalsiyum (Ca), fosfor (P) seviyeleri ve vitamin D düzeyleri (25-OH D3) ile adenom hacmi arasında anlamlı bir ilişki bulunması, paratiroid adenomunun rezeksiyonunun boyutunu belirlemek için prediktif değere sahip olabilir.Biz de bu çalışmamızda preoperatif biyokimyasal parametreler ile paratiroid adenom volümü arasındaki ilişkiyi inceledik.

Yöntemler: İstanbul Haydarpaşa Numune Eğitim ve Araştırma Hastanesi Endokrinoloji polikliniğinde 2011-2014 yılları arasında primer hiperparatiroidi tanısıyla takip edilen, operasyon sonrasında histopatolojik olarak soliter paratiroid adenomu tanısı konmuş 52 hasta çalışmaya alındı. Adenom hacmi ile preoperatif serum parathormon (iPTH), düzeltilmiş Ca, P, 25-OH D3, 24 saatlik idrarda kalsiyum düzeyi arasında korelasyon analizi yapıldı. Çalışma cross-sectional olarak dizayn edildi.

Bulgular: Çalışmaya alınan elli iki hastanın 45'i kadın (%86,5), 7'si erkekti (%13,5). Hastaların yaş ortalaması 53,538 ± 14,996 yıldı. Hastaların ortalama preoperatif iPTH düzeyi 371,423 ± 341,857 pg/dl, ortalama düzeltilmiş Ca düzeyi 11,652 ± 0,947 mg/dl, ortalama fosfor düzeyi 2,285 ± 0,434 mg/dl, ortalama 25-OH D3 düzeyi 11,442 ± 6,120 ng/ml, 24 saatlik idrarda kalsiyum düzeyi 337,486 ± 213,658 mg/24 saat olarak bulundu. Hastaların hesaplanan paratiroid adenom volüm ortalaması 1.612 ± 2 cm^3 (0,0060-11,510) idi. Paratiroid adenom volümü ile parathormon düzeyleri ve 24 saatlik idrar kalsiyum düzeyleri arasında pozitif yönde, 25-hidroksi vitamin D düzeyleri arasında negatif yönde korelasyon saptandı.

Sonuç: PHPT hastalarda adenom boyutu parathormon ve vitamin D düzeyi ile korelasyon göstermektedir. Bu nedenle, preoperatif iPTH ve vitamin D düzeylerinin adenom boyutu hakkında prediktif değere sahip olabileceğini düşünmekteyiz.

Anahtar kelimeler: Paratiroid adenom volümü, Biyokimyasal parametreler

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Introduction

Primary hyperparathyroidism (PHPT) is a clinical presentation with hypercalcemia or normocalcemia resulting from autonomously excessive parathyroid secretion from parathyroid glands [1]. PHPT is a rare disease with a prevalence of 1-4 / 1000. It is more common in females than males [2]. The incidence has been increased with the recognition of asymptomatic patients due to routine calcium measurement. Organ complications such as specific bone diseases and nephrolithiasis are now less common due to the early detection of the disease [3,4]. The most common cause of PHPT is the solitary parathyroid adenomas. Parathyroid hyperplasia, multiple parathyroid adenomas, parathyroid carcinoma, and familial syndromes are more rare causes of hyperparathyroidism [1-5]. The primary etiology of primary hyperparathyroidism is a solitary parathyroid adenoma in approximately 85-90% of patients, and can usually be successfully treated with parathyroidectomy (approximately 95% of all) [6]. Significant correlation between serum parathyroid hormone (iPTH), calcium (Ca), phosphorus (P) levels and vitamin D levels 25-OH D3 with adenoma volume, together with imaging modalities, have been proposed to be predictive to determine the size of parathyroid adenoma resection [6,7]. However, the effect of existing parameters on the parathyroid adenoma volume is unclear [7]. We investigated the relationship, if any, between preoperative biochemical parameters and parathyroid adenoma volume in this study.

Materials and methods

Fifty-two patients diagnosed with primary hyperparathyroidism in the endocrinology outpatient clinic of Istanbul Haydarpaşa Numune Training and Research Hospital between the years of 2011 and 2014 were included in the study. The data of the patients were evaluated retrospectively. Histopathologically confirmed solitary parathyroid adenoma was the inclusion criteria. Patients with parathyroid carcinoma, parathyroid hyperplasia, multiple parathyroid adenomas, secondary or tertiary hyperparathyroidism were excluded from the study. Demographic characteristics such as iPTH, Ca, P, albumin, creatinine, calcium excretion rate at 24 hours, 25-OH D3 level, sex and age before surgery were collected from hospital records. The parathyroid adenoma volume was calculated using the length x thickness x width x 0.52 formula [8].

Statistical analysis

Data analysis was performed using SPSS version 22 for Windows, and the results were expressed as mean ± SD. Correlation analysis was performed between adenoma volume and preoperative serum parathormone (iPTH), corrected Ca, P, 25-OH D3, and 24 hour urinary calcium levels. Significance was accepted if the probability values were lower than 0.05.

Results

Out of fifty-two patients who were included in the study, 45 (86.5%) were female and 7 were male (13.5%). The mean age of the patients was 53.538 ± 14,996 years. The mean preoperative iPTH level was 371.423 ± 341.857 pg / dl, the mean corrected Ca level was 11.652 ± 0.947 mg / dl, the mean phosphorus level was 2.285 ± 0.434 mg / dl and the mean 25-OH D3 level was 11.442 ± 6.120 ng / dl. The urinary calcium level was 337.486 ± 213.658 mg / 24 hours. The calculated parathyroid adenoma volume averaged 1.612 ± 2 cm^3 (0.0060-11.510) (Table 1). Preoperative parathormone and 24-hour urinary calcium levels were positively correlated with adenoma volume whereas, 25-OH D3 levels were found to be negatively correlated (Table 2).

Table 1: Demographic characteristics of patients and laboratory parameters (preoperative)

	Values
Female (%) / Male (%)	45 (86.5) / 7(13.5)
Age (years)	53.538 ± 14.996 (19 - 84)
Parathormone (pg / dl)	371.423 ± 341.857 (95 - 2156)
Corrected calcium (mg / dL)	11.652 ± 0.947 (10.4 -15.4)
Phosphorus (mg/dl)	2.285 ±0.434 (1.4-3.3)
25-hydroxy vitamin D3 (ng/ml)	11.442 ± 6.120 (3.46-33.63)
24 hour urine calcium (mg/24 hour)	337.486 ± 213.658 (46 -1053)
Adenoma volume (cm^3)	1.612 ± 2 (0.006 -11.51)

Table 2: Correlation of parathyroid adenoma volume with laboratory parameters

	Correlation coefficient	p
Age (years)	-0.204	0.147
Corrected calcium (mg/dl)	0.147	0.299
Phosphorus (mg/dl)	-0.215	0.127
25-hydroxy vitamin D3 (ng/ml)	-0.277	0.047
Parathormone (pg / dl)	0.334	0.016
24 hour urine calcium (mg/24 hour)	0.286	0.042

Discussion

Primary hyperparathyroidism is the most common cause of hypercalcemia in patients admitted to the outpatient clinics. Although primary hyperparathyroidism can be seen at any age, it is most common in post-50s and postmenopausal women [9]. Early recognition of primary hyperparathyroidism in recent years and increased selection of localization studies have positively affected the diagnosis and treatment of the disease. However, due to the non-rare occurrence of recurrences, difficulties in the treatment of complications and being a relatively common endocrine disease, it remains an important entity [10]. Numerous studies have been carried out on the relationship between the volume of parathyroid adenoma and biochemical parameters, as well as the etiology of the disease. While some of these studies correlate biochemical parameters with parathyroid adenoma volume [7-11], some studies have not detected any correlation [12-13]. In this study we looked for this relationship in our Turkish population.

In our study, a positive correlation was found between iPTH and adenoma volume, but unlike many studies in the literature, there was no statistically significant correlation with serum Ca and P levels [7,11,14,15]. In the literature, Rutledge and colleagues first reported a significant association between serum iPTH and calcium levels and adenoma volume [7-11]. Subsequently, Bindlish and colleagues ended up with a positive correlation between iPTH and serum Ca values and solitary parathyroid adenoma volume in a relatively small study of 63 patients. However, there was no significant correlation between adenoma volume and phosphorus level [7]. Similarly, Moretz et al. [14] found a positive correlation between preoperative iPTH levels, serum calcium levels and adenoma volume. In a recently published study, Kizilgul and colleagues [15] suggested that preoperative serum calcium and iPTH levels may be useful in predicting parathyroid adenoma weight and volume.

On the other hand, in some studies, there was no significant relationship between biochemical parameters and

adenoma size in hyperparathyroidism [12,13]. Randhawa et al. [13] reported that biochemical parameters would not accurately predict the size of parathyroid adenoma in an analysis using data from 77 patients, and as a result, postoperative calcium levels also would not correlate with parathyroid adenoma size. Although Williams and colleagues [16] found significant correlations between PTH levels and adenomal weight, this correlation disappeared after two severely heavy adenomas extracted from analysis. Resembling to this result, in our study, adenoma volumes of 5 patients with iPTH values (779-2156 pg / dl) above 750 pg / dl were found above 3 cm^3 (3.01-6.8 cm^3) and in the case of removal of these patients from analysis, positive correlation lost its meaning.

Rao et al. [17] found an increase in adenoma volume in patients with vitamin D deficiency compared with those without vitamin D deficiency. The strong negative correlation between adenoma volume and 25-OH D3 was not impaired even in the case of extracting 5 patients with large adenomas and high iPTH values in our study. This suggests that 25-OH D3 levels play a decisive role in the growth of parathyroid adenoma. In our country, where 25-OH D3 deficiency is around 44-60% [18], in the regions of severe vitamin D deficiency, the developed parathyroid adenomas are also greater than those developed in the other parts. In support of this, the 25 -OH D3 levels of the 5 relating patients with large adenomas and high iPTH values were found to be below 8 ng / ml.

Primary limitations regarding this study are the selection bias due to the retrospective nature of the study and the small sample size.

Conclusion

In PHPT patients, adenoma size correlates with parathormone and vitamin D levels. For this reason, we think that preoperative iPTH and vitamin D levels may have a predictive value about adenoma size.

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Research article
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Can neutrophil to lymphocyte ratio and platelet to lymphocyte ratio be used as biomarkers for non-dipper blood pressure?

Nötrofil/lenfosit oranı ve platelet/lenfosit oranı non-dipper kan basıncı için biyobelirteç olarak kullanılabilir mi?

Özge Turgay Yıldırım [1], Ercan Akşit [2], Fatih Aydın [1], Ayşe Hüseyinoğlu Aydın [1], Evrin Dağtekin [1]

[1] Eskisehir State Hospital, Department of Cardiology, Eskisehir, Turkey
[2] Canakkale Onsekiz Mart University, Department of Cardiology, Canakkale, Turkey

ORCID ID of the authors:
ÖTY: 0000-0002-6731-4958
EA: 0000-0002-4478-4324
FA: 0000-0002-1017-1917
AHA: 0000-0002-3056-9981
ED: 0000-0003-4650-969X

Corresponding author / Sorumlu yazar:
Özge Turgay Yıldırım
Address / Adres: Yenidoğan Mahallesi Şehit Serkan Özaydın Sokak Eskisehir Devlet Hastanesi Kardiyoloji Polikliniği, 26060 Odunpazarı, Eskişehir, Türkiye
E-mail: ozgeturgay@gmail.com

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Abstract

Aim: Hypertension is a major risk factor for cardiovascular diseases and non-dipper status is associated with increased risk for cardiovascular events. Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) are related to inflammation and cardiovascular risk. The purpose of the study is to investigate the relationship between NLR and PLR with non-dipper status of hypertensive and normotensive patients.

Methods: A total of 482 patients were enrolled for the study. The study was planned as retrospective cohort study. Four groups were formed according to 24-h ambulatory blood pressure monitoring results. Group 1 was defined as hypertensive, non-dipper patients; group 2 as hypertensive, dipper patients; group 3 as normotensive, non-dipper patients and group 4 as normotensive, dipper patients.

Results: Mean age of the study population was 50.1±15.5 years, 38.1% were male. According to the statistical analysis of Group 1 (n=165), Group 2 (n=88), Group 3 (n=123) and Group 4 (n=91) NLR was statistically different among groups ($p<0.001$). Group 1 had significantly higher values compared to Group 2 ($p=0.001$), Group 3 ($p=0.002$) and Group 4 ($p=0.023$). In hypertensive patient group, PLR values of Group 1 was significantly higher than Group 2 ($p=0.002$). Pearson correlation analysis showed that NLR and PLR were correlated with BP variability ($r=-0.188$, $p<0.001$ for NLR and $r=-0.182$ and $p<0.001$ for PLR). Regression analysis showed NLR ($p=0.040$), PLR ($p=0.021$), age ($p=0.006$) and hypertension ($p<0.001$) were independent predictors of BP variability.

Conclusion: Our findings suggest that NLR and PLR can be used as inexpensive and easily accessible markers to detect non-dipper status in hypertensive patients.

Keywords: Neutrophil to lymphocyte ratio, Platelet to lymphocyte ratio, Hypertension, Ambulatory blood pressure monitoring, Non-dipper blood pressure

Öz

Amaç: Hipertansiyon, kardiyovasküler hastalıklar için önemli bir risk faktörüdür ve non-dipper kan basıncı kardiyovasküler olaylar için artmış risk ile ilişkilidir. Nötrofil lenfosit oranı (NLR) ve platelet lenfosit oranı (PLR) inflamasyon ve kardiyovasküler risk ile ilişkilidir. Bu çalışmanın amacı, hipertansif ve normotansif hastalarda NLR, PLR ve non-dipper kan basıncı arasındaki ilişkiyi araştırmaktır.

Yöntemler: Çalışmaya toplam 482 hasta alındı. Çalışma retrospektif kohort çalışma olarak planlandı. 24 saatlik ayaktan kan basıncı monitorizasyonu sonuçlarına göre dört grup oluşturuldu. Grup 1 hipertansif, non-dipper hastalar, Grup 2 hipertansif, dipper hastalar; Grup 3 normotansif, non-dipper hastalar ve Grup 4 normotansif, dipper hastalar olarak sınıflandırıldı.

Bulgular: Çalışma popülasyonunun yaş ortalaması 50,1±15,5 yıl idi ve %38,1'i erkekti. Grup 1 (n = 165), Grup 2 (n=88), Grup 3 (n=123) ve Grup 4 (n=91) NLR açısından karşılaştırıldığında sonuç istatistiksel olarak anlamlı farklıydı ($p<0,001$). Grup 1'de; Grup 2'ye ($p=0,001$), Grup 3'e ($p=0,002$) ve Grup 4'e ($p=0,023$) göre NLR değeri istatistiksel anlamlı yüksekti. Hipertansif hasta grubunda, Grup 1'in PLR değerleri Grup 2'den anlamlı olarak yüksekti ($p=0,002$). Pearson korelasyon analizine göre NLR ve PLR, diurnal kan basıncı değişkenliği ile korelasyon gösterdi (NLR için $r=-0,188$, $p<0,001$ ve PLR için $r=-0,182$, $p<0,001$). Regresyon analizinde NLR ($p=0,040$), PLR ($p=0,021$), yaş ($p=0,006$) ve hipertansiyon ($p<0,001$), kan basıncı değişkenliğinin bağımsız belirleyicileri olarak saptandı.

Sonuç: Bulgularımız, NLR ve PLR'nin hipertansif hastalarda non-dipper kan basıncı için ucuz ve kolay erişilebilir işaretleyiciler olarak kullanılabileceğini göstermektedir.

Anahtar kelimeler: Nötrofil lenfosit oranı, Platelet lenfosit oranı, Hipertansiyon, Ayaktan kan basıncı monitorizasyonu, Non-dipper kan basıncı

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Introduction

Hypertension is a major risk factor for cardiovascular diseases [1]. There are several methods for the diagnosis of hypertension. Ambulatory blood pressure monitorization (ABPM) is a commonly used method for detection and follow-up of hypertensive patients [2]. This technique also demonstrates the diurnal variability of the blood pressure (BP) so that we can determine the dipper and non-dipper status in patients. Decreased blood pressure variability is associated with hypertensive target organ damage and higher risk for cardiovascular events [3,4].

Inflammatory processes play an important role for pathophysiology of hypertension. There are studies that indicate blood pressure increase causes activation in inflammatory processes and that is the underlying mechanism which explains the relationship between hypertension and atherosclerosis [5,6]. Several inflammatory cytokines are related to blood pressure increase [7]. Also some inflammatory markers like mean platelet volume (MPV), high sensitivity C-reactive protein (hs-CRP), red cell distribution width (RDW) are related to diurnal variability of blood pressure [8,9]. Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are easily available, inexpensive markers which are obtained from complete blood count results. Recent studies showed the relationship between NLR, PLR and cardiovascular events [10,11]. We design the study to examine if there is a relationship between NLR, PLR and diurnal variability of BP in hypertensive and normotensive patients.

Materials and methods

Patient Population

The study population was chosen from 482 consecutive patients who admitted to outpatient clinic of cardiology department with ABPM results between October 2016 and October 2017. The study was retrospective cohort study. Patients with previous hypertension diagnosis, acute coronary syndrome, serious valve regurgitation or stenosis, coronary artery disease, echocardiographic findings of reduced left ventricular ejection fraction (LVEF < 55%), congenital heart diseases, abnormal kidney function, chronic liver disorders, chronic inflammatory disease, patients who had a recent history of acute infection were excluded from this study.

Patients were divided into four groups according to their dipping and hypertensive status. Patients with high ABPM results (waking ambulatory SBP/DBP >135/85 mmHg and/or sleeping SBP/DBP >120/70 mmHg) were categorized as hypertensive. Dipper status was defined as 10% or more nocturnal BP fall in systolic blood pressure compared to daytime values. Group 1 was defined as hypertensive, non-dipper patients; group 2 as hypertensive, dipper patients; group 3 as normotensive, non-dipper patients and group 4 as normotensive, dipper patients.

Evaluated Parameters

Demographic, clinical and echocardiographic data were obtained from hospital medical records. Total blood count and biochemical analyses were taken from the results of the admission before the ABPM.

Ambulatory 24-hour blood pressure monitoring

24-hour ambulatory blood pressure values were obtained by using a non-invasive oscillometric system. Blood pressure recordings are obtained every 30 minutes during day-time and one hour intervals during night-time. The cuff was placed around the non-dominant arm of the subjects. Dipper hypertension was defined as 10% or more nocturnal BP fall compared to daytime values.

Statistical Analysis

Data are presented as mean ± standard deviation (SD) and as proportions for categorical variables. The t-test or Chi-square test was used for comparisons of continuous and categorical variables, respectively. Distribution of the data for normality was tested by the Shapiro–Wilk test and homogeneity of group variances were tested by the Levene test. For the parameters which are not normally distributed, Mann Whithey U test is used. ANOVA model was used for comparisons across more than 2 groups. Pearson correlation test was used for correlation analysis. Regression analysis was performed to identify the independent associations of blood pressure variability. P-values <0.05 were considered statistically significant. The data were analyzed using SPSS 20.0 (IBM SPSS Ver. 20.0, IBM Corp, Armonk NY, USA).

Results

A total of 482 patients were included to the study. Mean age of the study population was 50.1 ± 15.5 years, 38.1% were male and 61.9% were female. Four groups were formed according to hypertension diagnosis and dipper and non-dipper patterns. Group 1 was consisted of 165 patients with hypertensive and non-dipper status; group 2 was consisted of 88 patients with hypertensive and dipper status; group 3 was consisted of 123 patients with normotensive and non-dipper status; and group 4 was consisted of 91 patients with normotensive and dipper status. Comparison and the baseline characteristics of the groups are shown in Table 1. 24-hour ABPM results of the study groups were shown in Table 2.

Table 1: Comparison of the baseline characteristics and laboratory results of the study groups

Variables	Group 1 (n=180)	Group 2 (n=88)	Group 3 (n=123)	Group 4 (n=91)	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Men, %	68 (41.2%)	50 (56.8%)	34 (27.6%)	26 (28.6%)	<0.001
Age, years	52.5 ± 15.0	48.7 ± 14.6	49.1 ± 16.2	44.3 ± 15.2	0.001
LVEF, %	58.0 ± 2.3	57.6 ± 1.7	57.9 ± 2.5	58.2 ± 2.3	0.507
FBG, mg/dL	101.6 ± 32.8	103.6 ± 31.6	98.2 ± 26.5	97.6 ± 40.1	0.590
BUN, mg/dL	14.4 ± 4.6	13.7 ± 4.5	13.6 ± 5.2	12.9 ± 4.2	0.180
Creatinine, mg/dL	0.8 ± 0.2	0.8 ± 0.2	0.7 ± 0.1	0.7 ± 0.1	0.070
HDL-C, mg/dL	50.1 ± 12.8	51.7 ± 14.3	53.2 ± 11.6	52.9 ± 12.1	0.433
LDL-C, mg/dL	128.2 ± 38.3	129.2 ± 27.3	121.0 ± 33.6	125.4 ± 45.6	0.050
Triglyceride, mg/dL	172.7 ± 109.0	138.9 ± 48.2	134.6 ± 79.1	138.5 ± 71.6	0.019
Hb, g/dL	14.1 ± 1.8	14.7 ± 1.8	13.6 ± 1.8	13.8 ± 1.7	<0.001
WBC, x10³/mm³	8.3 ± 2.3	8.2 ± 2.1	7.7 ± 1.9	7.8 ± 2.0	0.048
Neutrophils, x10³/mm³	5.5 ± 3.5	4.7 ± 1.7	4.5 ± 1.6	4.7 ± 1.7	0.006
Lymphocytes, x10³/mm³	2.3 ± 0.7	2.6 ± 0.8	2.4 ± 0.8	2.3 ± 0.6	0.006
Eosinophils, x10³/mm³	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.1	0.2 ± 0.1	0.092
Platelets, x10³/mm³	280.0 ± 77.6	270.9 ± 65.3	277.8 ± 67.9	268.1 ± 54.5	0.549
RDW, fL	43.0 ± 29.9	40.6 ± 3.4	41.0 ± 4.7	40.4 ± 4.0	0.648
MPV, fL	11.1 ± 7.1	11.6 ± 9.2	11.2 ± 8.4	10.4 ± 0.9	0.756
PDW, fL	12.4 ± 2.9	12.4 ± 2.5	12.2 ± 2.1	12.2 ± 2.1	0.752
NLR	2.696 ± 1.918	1.933 ± 0.916	2.357 ± 3.066	2.177 ± 1.154	<0.001
PLR	133.3 ± 49.9	112.2 ± 45.4	133.5 ± 90.3	121.7 ± 33.5	0.008

BUN: blood urea nitrogen, FBG: fasting plasma glucose, Hb: hemoglobine, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, LVEF: left ventricule ejection fraction, MPV: mean platelet volüme, NLR: neutrophil/lymphocyte ratio, PDW: platelet distribution width, PLR: platelet/lymphocyte ratio, RDW: red cell distribution width, WBC: white blood cell

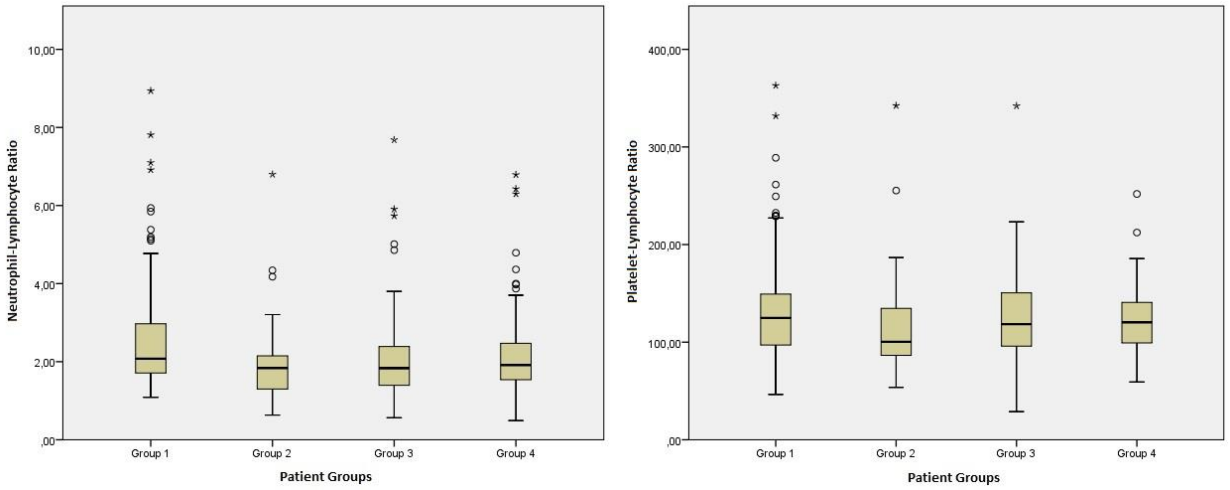

Figure 1: Neutrophil-lymphocyte ratio and platelet/lymphocyte ratio values of four study groups

Neutrophil lymphocyte ratio was statistically different among groups (p<0.001). Group 1 had significantly higher values compared to Group 2 (p=0.001), Group 3 (0.002) and Group 4 (p=0.023). NLR values were similar when values were compared among Group 2, Group 3 and Group 4 within each other (p>0.05). Platelet lymphocyte ratio was significantly different among all groups (p=0.008) (Table 1). Boxplot graph of four investigated groups were seen in Figure 1.

When hypertensive patient group were investigated, PLR values of Group 1 was significantly higher than Group 2 (p=0.002). Also Group 1 and 2 have significant differences in terms of lymphocytes (p=0.001). When normotensive patients were investigated, there were no statistically significant difference between white blood cell parameters between Group 3 and Group 4 (Table 3).

Table 2: 24-h ambulatory blood pressure monitorization results of the study groups

Variables	Group 1 (n=180) Mean ± SD	Group 2 (n=88) Mean ± SD	Group 3 (n=123) Mean ± SD	Group 4 (n=91) Mean ± SD	p
Day SBP, mmHg	138.1 ± 13.6	143.0 ± 10.9	117.4 ± 7.4	123.2 ± 7.0	<0.001
Day DBP, mmHg	81.8 ± 10.5	86.8 ± 9.1	69.5 ± 6.7	73.5 ± 6.0	<0.001
Night SBP, mmHg	136.3 ± 14.1	121.3 ± 9.5	110.9 ± 11.0	105.6 ± 7.3	<0.001
Night DBP, mmHg	79.3 ± 10.6	70.7 ± 8.0	64.1 ± 6.6	60.5 ± 6.3	<0.001
SBP, mmHg	136.9 ± 16.3	138.6 ± 10.5	116.4 ± 6.9	115.5 ± 13.1	<0.001
DBP, mmHg	81.3 ± 10.1	83.7 ± 8.7	68.4 ± 6.5	70.8 ± 6.0	<0.001
BP variability, %	1.1 ± 7.2	14.9 ± 3.9	4.8 ± 3.9	14.3 ± 3.7	<0.001

BP: blood pressure, DBP: diastolic blood pressure, SBP: systolic blood pressure

Table 3: Comparison of white blood cell parameters between Group 1-2 and Group 3-4

Variables	p value of Group 1 compared to Group 2	p value of Group 3 compared to Group 4
WBC	0.657	0.759
Neutrophils	0.056	0.578
Lymphocytes	0.001	0.595
Eosinophils	0.349	0.226
Platelets	0.377	0.285
RDW	0.478	0.408
MPV	0.637	0.357
PDW	0.965	0.998
NLR	<0.001	0.564
PLR	0.002	0.454

MPV: mean platelet volume, NLR: neutrophil/lymphocyte ratio, PDW: platelet distribution width, PLR: platelet/lymphocyte ratio, WBC: white blood cell

Pearson correlation analysis showed that NLR and PLR were correlated with blood pressure variability between night and day (r=-0.188, p<0.001 for NLR and r=-0.182 and p<0.001 for PLR). NLR levels were significantly correlated with night SBP (r=0.141, p=0.003) and night DBP (r=0.113, p=0.020). Pearson correlation analysis between NLR, PLR and ABPM results were shown in Table 4.

Table 4: Pearson correlation analysis of NLR, PLR and 24-hour ABPM values

	NLR		PLR	
	r	p	r	p
Day SBP	0.023	0.630	-0.033	0.495
Day DBP	-0.006	0.904	-0.065	0.180
Night SBP	0.141	0.003	0.095	0.050
Night DBP	0.113	0.020	0.051	0.295
SBP	0.054	0.267	-0.001	0.989
DBP	0.021	0.673	-0.042	0.387
BP variability	-0.188	<0.001	-0.182	<0.001

BP: blood pressure, DBP: diastolic blood pressure, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, SBP: systolic blood pressure

Regression analysis showed that NLR (p=0.040), PLR (p=0.021), age (p=0.006) and hypertension (p<0.001) were independent predictors of diurnal blood pressure variability.

Discussion

In this study we demonstrated that NLR is significantly higher in hypertensive non-dipper patients than hypertensive and non-dipper; normotensive and non-dipper; and normotensive and dipper patients. Also in hypertensive patient group; PLR is significantly higher in patients with non-dipper status compared to patients with dipper status.

24-hour ambulatory blood pressure monitorization is used for the diagnosis and follow-up of hypertension. It also gives valuable information about dipper and non-dipper status of patients. Non-dipper blood pressure pattern is defined as less than 10% drop of blood pressure in night-time blood pressure compared to day-time blood pressure [12]. Non-dipper blood pressure pattern is associated with cardiovascular mortality, end-organ damage and autonomic dysfunction [13-15]. There is evidence that number of endothelial progenitor cells is decreased in hypertensive non-dipper status meaning vascular repair mechanisms and endothelial homeostasis is disturbed [16]. Elevated blood pressure and decreased blood pressure variability may stimulate inflammation by increased expression of endothelial cytokines [6].

Chronic inflammation plays an important role in atherosclerosis, cardiovascular diseases, malignancy, chronic kidney disease, rheumatologic diseases and diabetes mellitus [17-22]. Neutrophils play a major role in inflammation by releasing cytokines and triggering immune system mechanisms. Increased NLR values are associated with atherosclerosis, severity of coronary artery diseases and worse cardiac outcome [23,24]. Increased platelet count is an indicator of increased platelet activity and increased platelet activity is in correlation with the severity of inflammation [25,26].

Increased platelet counts and decreased lymphocyte counts are associated with worse cardiac outcomes. No reflow after stent implantation after ST segment elevation myocardial infarction is more common in patients with high PLR values [27]. In non-ST segment elevated myocardial infarction patients, mortality outcome is higher with increased PLR values [28].

In our study we investigated the association between NLR, PLR and dipper, non-dipper status of hypertensive and normotensive patients. NLR values were highest in hypertensive non-dipper group when compared to hypertensive dipper, normotensive non-dipper and normotensive dipper groups. When the hypertensive patient group was examined separately, the lymphocyte count was significantly lower; NLR and PLR were significantly higher in non-dipper patient group. When non-dipper and dipper patients were compared in normotensive patients, no statistically significant difference was found in terms of whole blood count parameters, NLR and PLR. Correlation analysis revealed a statistically significant relationship between NLR and night systolic, night diastolic blood pressures and blood pressure variability. When the PLR was analyzed in the correlation analysis, a statistically significant relationship was found between this value and the night systolic blood pressure and BP variability. Moreover, NLR and PLR along with hypertension and age found to be an independent predictor for BP variability and non-dipper status. Kılıçaslan et al. [29] investigated NLR values in hypertensive and normotensive patients. This study included 150 subjects and NLR values were highest in non-dipper hypertensive patients. Sunbul et al. [30] found out that in hypertensive patients, PLR and NLR values are higher in non-dipper patients and PLR but not NLR was an independent predictor for non-dipper status. In our study both NLR and PLR values were independent predictors for BP variability. The difference may be caused because our study included normotensive patients and in our regression model, normotensive patients were not excluded and our sample size is wider.

Our study had some limitations. It would be better to compare inflammation markers like hs-CRP with our findings. We excluded conditions that would cause inflammation but still it would be better to include CRP levels to our regression model.

In conclusion, our findings suggest that NLR and PLR can be used as inexpensive and easily accessible markers to detect non-dipper status in hypertensive patients. Further investigations are needed to find the mechanism behind this relationship.

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Clinical and demographic characteristics of influenza B outbreak in Erzincan province of Turkey

Tükiye, Erzincan ilinde influenza B salgınının klinik ve demografik özellikleri

Edhem Ünver [1], Aytekin Çıkman [2], Faruk Karakeçili [3]

[1] Erzincan University, Faculty of Medicine, Department of Chest Diseases, Erzincan, Turkey
[2] Erzincan University, Faculty of Medicine, Department of Medical Microbiology, Erzincan, Turkey
[3] Erzincan University, Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Erzincan, Turkey

ORCID ID of the authors:
EÜ: 0000-0002-0322-8102
AÇ: 0000-0001-9259-7091
FK: 0000-0002-7368-7187

Corresponding author / Sorumlu yazar:
Aytekin Çıkman
Address / Adres: Erzincan Üniversitesi Tıp Fakültesi, Tıbbi Mikrobiyoloji Anabilim Dalı, P.O. Kutu 24030, Erzincan, Türkiye
E-mail: draytekin65@hotmail.com

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Abstract

Aim: Seasonal epidemics of influenza are responsible for significant morbidity and mortality worldwide. We aimed to investigate distribution of seasonal influenza viruses, and clinical and demographic characteristics of influenza B epidemics in Erzincan province of Turkey.

Methods: A total of 103 patients who presented to our hospital in spring the season in accordance with influenza case management schema in line with the recommendations by the World Health Organization and Ministry of Health were included in this study. Cepheid SmartCycler system, which is an integrated RNA replication and detection device based on microprocessor controlled I-CORE® (Intelligent Cooling / Heating Optical Reaction) module was used in order to detect Influenza A / Influenza B viruses.

Results: Influenza was positive in 28 (27.1%) of all patients who presented with suspected Influenza, with 23 (22.3%) being Influenza B and 5 (4.9%) Influenza A. Of patients with positive Influenza B, 18 (78%) had one or more chronic diseases. Of the patients, 15 (65%) were diagnosed with one of the chronic pulmonary disease, 8 (35%) one of the chronic cardiac diseases, and 3 (13%) diabetes mellitus. Leukopenia and thrombocytopenia were more common than leucocytosis. Seven patients were followed-up as inpatients. At the follow-up period, three of the patients were taken to the intensive care unit and 2 of them died. Whereas the remaining patients were discharged with recovery.

Conclusion: We observed that, Influenza B progressed more seriously than we expected. For this reason, we think that immunity level of the community against Influenza B should be raised with vaccination campaigns involving different subtypes of Influenza B.

Keywords: Influenza, Influenza B virus, Epidemics, Seasonal epidemics, PCR

Öz

Amaç: Mevsimsel influenza epidemileri, dünya çapında önemli morbidite ve mortalite nedenidir. Çalışmamızda Türkiye'nin Erzincan ilinde mevsimsel influenza virüslerinin dağılımı ile influenza B salgınının klinik ve demografik özelliklerinin araştırılması amaçlanmıştır.

Yöntemler: 2017 bahar döneminde Dünya Sağlık Örgütü ve Sağlık Bakanlığı'nın önerileri doğrultusunda influenza vaka yönetim şemasına uygun olarak, hastanemize başvuran 103 hasta çalışmaya dahil edildi. Özel eküvyon çubukları yardımıyla nazofarengeal sürüntü örnekleri alındı. Influenza A / Influenza B virüslerini tespit etmek için mikroişlemci kontrollü I-CORE® (Akıllı Soğutma / Isıtma Optik Reaksiyonu) modülünü temel alan entegre bir RNA çoğaltma ve algılama cihazı olan Cepheid SmartCycler Sistemi kullanıldı.

Bulgular: İnfluenza ön tanısı ile başvuran tüm hastaların 28 (%27,1)'i influenza pozitif bulunurken, 23 (%22,3)'ü Influenza B, 5 (% 4,9)'i Influenza A saptandı. Influenza B pozitif saptanan hastaların 18 (%78)'i bir veya daha fazla kronik hastalığa sahip olduğu saptandı. Hastaların 15 (%65)'i kronik akciğer hastalıklarından birine, 8 (%35)'i kronik kalp hastalıklarından birine, 3 (%13)'ü diabetes mellitus tanısı alan kişilerdi. Influenza B pozitif hastalarında en sık karşılaştığımız semptomlar; myalji, öksürük, ateş ve nefes darlığıydı. Lökopeni ve trombositopeni, lökositozdan daha sık saptandı. Hastaların 7'si yatırılarak takip edildi. Takip edilen dönemde hastaların 3'ü yoğun bakım servisine alındı, bu hastaların 2'si öldü. Diğer hastalar ise şifa ile taburcu edildi.

Sonuç: İnfluenza B'nin beklediğimizden daha ciddi seyrettiğini gözlemledik. Bu nedenle, İnfluenza B'ye karşı topluluğun bağışıklık düzeyinin, farklı tipte İnfluenza B alt tiplerini içeren aşılama kampanyalarıyla artırılması gerektiğini düşünüyoruz.

Anahtar kelimeler: İnfluenza, İnfluenza B virüsü, Epidemiler, Mevsimsel epidemiler, PCR

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Introduction

Influenza viruses from the orthomyxovirus familia have negative-polarity, single-chain, enveloped and segmented RNA [1,2]. These viruses are divided into three types as A, B and C. Recently, Influenza D virus which has been proven to cause illness in human as the fourth type has been described [3,4].

Influenza A (IA) and Influenza B (IB) types lead to high rates of morbidity and mortality in humans during yearly seasonal epidemics [5,6]. IA is a virus with pandemic potential, because it is an animal shelter. Especially migratory birds and pigs play an important role in the formation of subtypes again through viral mutation [7].

Since antigenic drift of IB is slower, these viruses do not lead to antigenic drift. Thus, IB is not expected to cause a pandemic [8]. However, especially since the 1980s, IB viruses have become widespread due to globalization and intense travels in recent years. From these years, phylogenetically two different subtypes of IB (B / Yamagata and B / Victoria) have emerged as a global problem [9]. Because these IB subtypes have become widespread, the World Health Organization (WHO) recommended to include these phylogenetic influenza subtypes to the influenza vaccines from 2012/13 influenza session [10].

Unlike the intensely investigated IA viruses, IB viruses have drawn a relatively less interest [11]. However, IB viruses are among the most important causes of morbidity and mortality in human population [12]. A complete understanding of the epidemiological, clinical, and biological features of IB is important in order to better control of this crucial pathogen.

Recently, IB has gain importance and commonly reported worldwide. Data about the incidence, disease burden and circulatory pathways of IB in Turkey are limited. In this study, we aimed to investigate distribution of seasonal influenza viruses, and clinical and demographic characteristics of influenza B epidemics in Erzincan province of Turkey.

Materials and methods

Patients and samples

A total of 103 patients who presented to our hospital between 01 March 2017 and 07 June 2017 in accordance with influenza case management schema in line with the recommendations by the World Health Organization (WHO) were included in this study [13]. Accordingly; patients with a fever of 38 ^{o}C which cannot be explained with other reasons or a history of fever together with at least one of the complaints of diffuse body pain, sore throat, headache, nasal discharge, cough, and shortness of breathing were accepted as an Influenza case. Whereas the persons aged under 2 years, above 65 years, and those with immunosuppression were considered as possible cases in the presence of fever. Shortness of breath or respiratory distress, changes in vital signs, hypoxia, changes in consciousness, severe dehydration, and bronchopneumonia or pneumonia on chest X-ray were considered as the indications for hospitalization. In accordance with the instruction by the WHO; patients younger than 2 years old and those with chronic pulmonary, cardiovascular, renal, hepatic, hematologic, metabolic, and neuromuscular disorders, and immunosuppression status were accepted as the patients at risk. Whereas the patients who did not fall into any of these groups were considered as health hosts.

All patients' age, gender, complaints and physical examination findings were recorded. As routine examinations; peripheral smear, levels of electrolytes, C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine phosphokinase (CK) and plasma creatinine were studied. Blood cultures were performed and postero-anterior chest X-rays were ordered at the admission and during follow-up of the patients with persistent fever.

Nasopharyngeal swab samples were collected from all patients. After the Nasopharyngeal swab samples were taken through swab rods, they were put into a viral transport medium (HiViral Transport Kit, India), and quickly sent to the laboratory following cold chain and biosafety rules in an appropriate carrier container without waiting.

Laboratory diagnosis

IA and IB viruses were studied in the samples that were sent to the laboratory, after appropriate preparation procedures. The laboratory analyses were performed using SolMag®12 Full Automated Nucleic Acid Isolation System and SolMag® Virus Nucleic Acid Isolation Kit (Taiwan R.O.C). In this system; first the sample was diluted with 1200 µl RNA Carrier free water. 20 µl of Carrier was pipetted into the sample tube. Sample of 480 µl was added on it. Reactive cartridges and pipette tips were respectively inserted. The samples were placed in the 'S' section of the sample rack, the Elution tube in the 'E' region, and the internal control in the 'IC' region. The study was then initiated in line with the recommendations by the manufacturer. 100 µl RNA was isolated as a result of the nucleic acid purification protocol, which took about 45 minutes.

Cepheid SmartCycler system, which is an integrated RNA replication and detection device based on microprocessor controlled I-CORE® (Intelligent Cooling / Heating Optical Reaction) module was used in order to detect Influenza A / Influenza B viruses. RealCycler FLURSV (Progenie Molecular, Spain), which enables real time PCR qualitative determination of RNA from IA and IB viruses simultaneously was used in the clinical samples. These study kits targeted M1 and M2 genes that are conservative gene regions of pathogen microorganisms. Whereas amplifications were assessed using SmartCycler II thermocycler (Cepheid). According to the instructions by the manufacturer, a master mixture of 23 µl was prepared, DNA samples of 2 µl were added and a total reaction volume of 25 µl was studied. The data were analyzed with SmartCycler system software using absolute quantification-adaptation point analysis method.

Ethical considerations

The study was approved by the Ethics Committee of Erzincan University (Approval No: 20.06.2017-9/5). Written informed consent was obtained from all participants. All participants were informed through "Informed Consent Form" and gave consent for the study. The relevant forms were received from the participants over 18 years old by themselves, and from the parents of the participants aged under 18 years.

Statistical analysis

Statistical evaluation of the data was carried out using Statistical Package for Social Sciences for Windows version 18.0 (SPSS, Chicago, IL, USA) software. Normality of the variables was analyzed using Kolmogorov-Smirnov test. The descriptive statistics are given as median and minimum-maximum values for the non-normally distributed variables. Mann-Whitney U tests was used in order to evaluate the variables with a disrupted distribution. Group comparisons were made with Chi-square test. P values less than 0.05 were considered statistically significant.

Results

In the study period; 59 of the patients were referred to the department of chest diseases, 26 to the pediatric diseases, 16 to the infectious diseases and 2 to the other outpatient clinics of our hospital. Influenza was positive in 27.1% (28/103) of all patients who presented with suspected Influenza, with 22.3% (23/103) being Influenza B and 4.9 (5/103) Influenza A. Of the IB positive patients, 10 (43%) were male and 13 (57%) were female with a mean age of 55 years and age range of 1-76 years.

All the patients with IA were identified in March when we began to this study. Whereas patients with IB were identified within a period of about 2 months between 13 March and 05 May (Figure 1). This duration correspondences to the spring season for our study area. In our study, we found that ending of IA endemic and beginning of IB endemic were at about the same dates.

Eighteen of the patients with positive IB were found to have one or more chronic diseases, when influenza B positive and influenza B negative patients were compared. Fifteen of these patients had one of the chronic pulmonary diseases such as asthma or chronic obstructive pulmonary disease, and this value was statistically significant ($p<0.001$). In addition, 8 patients had been diagnosed with one of the cardiac diseases (six hypertension), and this value was statistically significant ($p<0.05$). Three patients had been diagnosed with diabetes mellitus (DM), but these diseases were not found to be significant. Whereas, 5 patients had no any accompanying disease (Table 1).

The most common symptoms in Influenza B patients included myalgia, cough, fever and shortness of breath. Myalgia, cough, fever, headache, nasal discharge and sore throat were statistically significant ($p<0.05$), when influenza B positive and influenza B negative patients were compared. IB positive patients had no any gastrointestinal complaints such as abdominal pain, nausea, vomiting and diarrhea. Symptoms and incidences of the positive patients are presented in Table 1.

When laboratory findings were examined; increased CRP was found in 18, leukopenia in eight, thrombocytopenia in six and leukocytosis in three of the patients with positive IB. Leukopenia and thrombocytopenia were more common findings than leukocytosis. However, none of the laboratory findings was statistically significant.

All the patients referred to the hospital, were studied for IA and IB with PCR on the day of admission. Thus, all of the patients with positive outcome were diagnosed with IA or IB within the day of admission to the hospital. Oseltamivir therapy was initiated in the patients diagnosed with Influenza, on the same day. Seven patients were followed-up as inpatients. At the follow-up period, three of the patients were taken to the intensive care unit and 2 of them died. Whereas the remaining patients were discharged with recovery.

Table 1: Clinical and Demographic Characteristics of Influenza B positive and Influenza B negative patients

Clinical and demographic characteristics	Patient groups [a] Positive (n:23)	Negative (n:75)	p
Gender			
Woman	13 (%57)	30 (%40)	>0.05
Male	10 (%43)	45 (%60)	
Age (year)	55 (1-76)	39 (0-82)	0.008
symptoms			
Myalgia	21 (%91)	4 (%5)	<0.001
Cough	20 (%87)	35 (%47)	0.001
Fever	19 (%83)	24 (%32)	<0.001
Shortness of breath	13 (%56)	26 (%35)	>0.05
Headache	8 (%35)	2 (%3)	<0.001
Nasal discharge	8 (%35)	6 (%8)	0.004
Throat ache	6 (%26)	2 (%3)	0.002
Sputum	3 (%13)	15 (%20)	>0.05
Laboratory Findings			
CRP increase	18 (%78)	55 (%73)	>0.05
Leukopenia (<4.000 / mm3)	7 (%30)	9 (%12)	0.05
AST / ALT increase (>40 U / L)	8 (%35)	34 (%45)	>0.05
Thrombocytopenia (<150.000 / mm3)	5 (%22)	7 (%9)	>0.05
Increase in creatinine (>1.09 mg / dL)	5 (%22)	15 (%20)	>0.05
Leukocytosis (>10,000 / mm3)	3 (%13)	18 (%24)	>0.05
Chronic disease			
Chronic lung disease	15 (%65)	17 (%23)	<0.001
Chronic heart disease	8 (%35)	10 (%13)	<0.05
Diabetes mellitus	3 (%13)	6 (%8)	>0.05
Inpatient	7 (%30)	30 (%40)	>0.05
ICU Inpatient	3	0	-
Death	2	0	-

[a] Influenza B positive patients and Influenza B negative, n: Number of patients

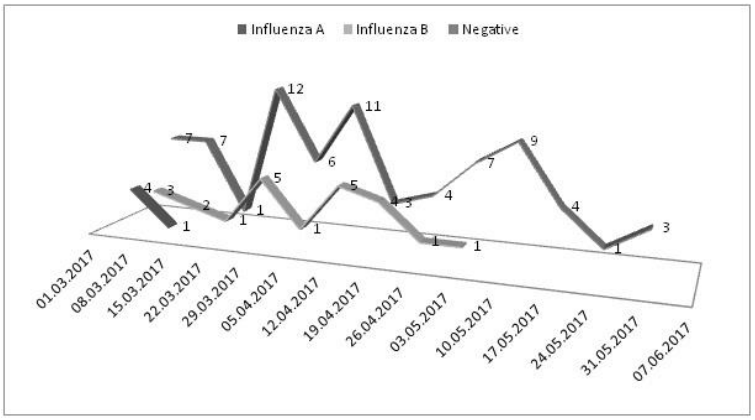

Figure 1: Distribution of the patients with positive IB by time period

Discussion

Seasonal influenza causes 3 to 5 million severe illnesses and 250,000 to 500,000 human deaths worldwide each year [14]. Traditionally, it is believed that IA accounts for majority of seasonal influenza cases [15]. However, IB constitutes an important part of seasonal influenza cases out of the periods of pandemics by IA [16].

Recent studies report significant increases in IB infections. The incidence of IB has been reported as 23.9% in a study from Spain, conducted between 2010 and 2016 [17]. There are several studies demonstrating that IB is more dominant in some periods in the epidemiology of seasonal influenza. Australian Influenza Surveillance Report stated that IB was the dominant type of Influenza in 2015 in Australia. According to the Australian Influenza Surveillance Report for January-October period; 61% of the cases were found as IB, and 38% IA (29% A (subtype unclear), 7% A (H3N2) and 2% A (H1N1) pdm09) [18]. In another study, Radovanov et al. [19] found that influenza

activity in the winter season in Vojvodina region increased over January and February months and peaked at the end of February, and that 53.4% of the positive cases were IB and 43.6% IA.

Weekly influenza surveillance reports are published in many countries worldwide due to several reasons such as tracking influenza viruses, predicting the possible epidemics, determination of the subtypes of influenza viruses, evaluation of severe influenza cases and identification of the high-risk groups in terms of the severity of diseases and mortality. Within this framework; especially WHO regularly publishes Influenza Surveillance Reports. When laboratory data of the WHO GISRS (Global Influenza Surveillance and Response System) were examined; the incidence of IA was found between 77.3% and 34.7%, and the incidence of IB between 65.3% and 22.7% in the period of 20 February – 14 May 2017. Whereas, IB type was reported to be more commonly encountered from the beginning of April through end of May [20].

In Turkey, Influenza Surveillance Reports are published by the Turkey Public Health Agency of Department of Infectious Diseases. Looking at the 2017 Weekly Influenza Surveillance Reports, IB type is seen to be more dominant in the period matching with our study. When the incidence of influenza viruses were examined over two months from the 12th week to the 18th week in 2017, IB virus has been reported to be more common than IA virus [21]. Our study covers approximately the same period. Similarly to the Turkey data, in our study IB virus was found to be the dominant type in our study area.

Influenza viruses may lead to pandemic in all seasons, particularly in winter [22,23). Influenza season typically starts at the beginning of October, peaks in January and February, and slightly raises at the end of March in the northern hemisphere where also cover our study area [24). Whereas IB usually leads to endemics in summer period and is encountered as the dominant type of influenza viruses [25,26]. Whereas in our study, majority of the cases were identified in March and April that fall into spring period.

Studies have reported similar rates of female and male patients with influenza infections. Although, there are studies with a larger number of female or male patients, none of these studies find a statistically significant difference between the genders [27]. No significant difference was found between the genders in the present study.

Influenza infections are seen in all age groups [15]. Some studies have reported that, children aged under 5 years and elderly people aged over 65 years are more frequently. Although IA and IB were investigated in 26 persons aged under 15 years who were considered as possible cases in line with the recommendations by the WHO and the Ministry of Health, only one child was found to have positive IB. Despite we had patients considered as possible cases in all age groups, the mean age was found as 55 years in our patients with IB, and this value was statistically significant (p=0.008). According to our data, we can say that IB cases were more common among the middle to advanced age group.

Clinical findings of influenza virus are variable and often progress with sudden-onset fever, headache, myalgia accompanied by cough and sore throat [28,29]. Higher fever, increased lymph gland growth, more common gastrointestinal system involvement, and less respiratory system findings may be observed in children than adults, because they previously have not encountered with the virus [30,31]. In our study; myalgia, cough, shortness of breath and fever were found in majority of the patients. There are studies reporting that, abdominal pain and complaints of gastrointestinal systems are more common during IB infections [31]. However, none of the patients with IB positive had complaints of gastrointestinal system. This may be related to the small number of our patients.

The incidence of chronic diseases has been found as high in patients who suffer from influenza. Studies have reported these diseases as particularly asthma, and chronic obstructive pulmonary disease, chronic cardiac diseases and diabetes mellitus [33,34]. In our study, 18 (78%) of the patients with IB had at least one chronic disease. Fifteen of our patients had chronic pulmonary diseases (13 asthma), eight chronic cardiac diseases (6 hypertension) and three DM. Chronic pulmonary diseases and chronic cardiac diseases were statistically significant in the IB positive group.

Until recently, it was thought that IA is more serious. However, some recent studies have shown that IB may progress at least as serious as IA [11,35]. Some studies have reported that IB may lead to serious outcomes especially in children and young adults [36]. Tran et al. [30] reported higher rates of mortality related to pediatric IB infections than IA. Whereas, some studies suggested that the most common type of influenza related with complications and mortality in elderly persons is IA/H3N2 followed by influenza B [36]. Whereas, in our study seven patients were followed-up on inpatient basis, three were taken to the intensive care unit and two of them died. Despite our patients were diagnosed with PCR at the day of admission and treatment was initiated, the rate of mortality was higher than we expected. However, this data should be supported by further studies with a larger number of cases.

The present study has some limitations. Referrals to the hospital were carried out in accordance with the influenza case management schema, and accordingly limited number of patients was enrolled to the study. In addition, other limitations may include that subtypes of Influenza A and B could not be determined, and the study reflects only a certain period of time.

In conclusion, we found that the community in Erzincan is sensitive to IB. This indicates that new and larger pandemics are inevitable in each seasonal influenza period. Immune memory of the community for IB should be improved. In this study, we found that IB can get ahead of IA in different periods of the year and in different regions, and even may be seen at a quite high rate. Therefore, we think that consideration of IB in the epidemiology of seasonal influenza is important. We recommend that, immunization level of the society should be raised with vaccination campaigns including different subtypes of IB, according to the needs of each country.

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Research article
Araştırma makalesi

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Which one is the first choice for rapid ventricular rate atrial fibrillation in emergency department: Metoprolol or Diltiazem? A randomized clinical trial

Acil serviste hızlı ventriküler hız atriyal fibrilasyonu için ilk tercih hangisidir: Metoprolol veya Diltiazem? Randomize bir klinik çalışma

Mehmet Barış Memiş [1], Rohat Ak [2], Tuba Cimilli Öztürk [3], Özge Onur [4], Özgür Ordu [5]

[1] Adıyaman Education and Research Hospital, Department of Emergency Medicine, Adıyaman, Turkey
[2] Sancaktepe Şehit Prof. Dr. İlhan Varank Education and Research Hospital, Department of Emergency Medicine, Istanbul, Turkey
[3] Fatih Sultan Mehmet Education and Research Hospital, Department of Emergency Medicine, Istanbul, Turkey
[4] Marmara University Faculty of Medicine, Department of Emergency Medicine, Istanbul, Turkey
[5] Fatih Sultan Mehmet Education and Research Hospital, Department of Cardiology, Istanbul, Turkey

ORCID ID of the authors:
MBM: 0000-0003-3591-2598
RA: 0000-0002-8324-3264
TCÖ: 0000-0002-4760-0076
ÖO: 0000-0002-0110-3533
ÖO: 0000-0001-7880-9430

Corresponding author / Sorumlu yazar:
Rohat Ak
Address / Adres: Sancaktepe Şehit Prof. Dr. İlhan Varank Eğitim ve Araştırma Hastanesi, Acil Tıp Anabilim Dalı, İstanbul, Türkiye
E-mail: rohatakmd@gmail.com

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Abstract

Aim: Atrial fibrillation (AF) is the most common cardiac arrhythmia managed by emergency physicians. Primary goals of treatment are hemodynamic stabilization, ventricular rate control, and prevention of embolic complications. The aim of this study is to compare the drug responses of the patients who presented to the ED with AF with rapid ventricular response (AFRVR), their need for the second dosage and echocardiographic parameters.

Methods: This is a prospective, single blind, randomized study. AFRVR patients were randomized and first group was given intravenous 0.25 mg/kg diltiazem as the calcium channel blocker; the second group was given intravenous 5 mg metoprolol. The vital findings and the clinical data of the patients in the 0, 2nd 5th, 15th and 30th minutes were recorded after each treatment. After the initial dosing, the patients having heart rate <110 beat/min in the 30th minutes were regarded as responders to the initial treatment. Nonresponders took second dosage of the same drug. After the rate control of all patients, a cardiologist performed the transthoracic echocardiography (TTE)'s of all participants.

Results: Fifty of the patients were given diltiazem, 50 of them were given metoprolol. 45 of them (45%) had no first dose response; whereas 55 (55%) of them had. The rate of incidence for the first dose response in the patients having diltiazem was higher than the patients having metoprolol, which was statistically significant. There is statistically significant difference between rates of the valvular heart disease seen for the patients in responsive /unresponsive groups for both drugs. But diltiazem is more successful in presence of valvular disease than metoprolol.

Conclusions: In this study, we found that diltiazem is more effective in the rate control of AFRVR in emergency department. This study showed that most of atrial fibrillation patients have valvular disease, and diltiazem is more effective than metoprolol in these patients. Ejection fraction, cardiac diameters are important in drug response.

Keywords: Atrial fibrillation, Diltiazem, Metoprolol, Rate control

Öz

Amaç: Atriyal fibrilasyon (AF), acil hekimleri tarafından yönetilen en yaygın kardiyak aritmidir. Tedavinin primer hedefleri hemodinamik stabilizasyon, ventriküler hız kontrolü ve embolik komplikasyonların önlenmesidir. Bu çalışmanın amacı, acil servise hızlı ventrikül yanıtlı AF ile başvuran hastaların hız yanıtlarını, ikinci doz ilaç gerkesinimlerini ve ekokardiyografik bulgularını incelemektir.

Yöntemler: Bu prospektif, tek kör, randomize bir çalışmadır. Hızlı ventrikül yanıtlı AF hastaları randomize edildi ve ilk gruba kalsiyum kanal blokeri olarak intravenöz 0,25 mg / kg diltiazem verildi; ikinci gruba intravenöz 5 mg metoprolol verildi. Her tedaviden sonra 0, 2, 5, 15 ve 30. dakikalardaki hastaların vital bulguları ve klinik verileri kaydedildi. İlk dozlamadan sonra 30. dakikada kalp atış hızı <110 atım / dk olan hastalar ilk tedaviye yanıt alınmış olarak kabul edildi. Cevap vermeyenler aynı ilacın ikinci dozunu aldı. Tüm hastalara hız kontrolünden sonra bir kardiyolog tarafından transtorasik ekokardiyografi yapıldı.

Bulgular: Hastaların 50'sine diltiazem, 50'sine metoprolol verildi. 45'inin (%45) ilk doz cevabı yoktu; 55'inde ilk doz cevabı (%55) vardı. Diltiazem alan hastalarda ilk doz cevap oranı, metoprolol alanlara göre istatistiksel olarak yüksek bulundu. Her iki ilaç için cevap veren / cevapsız gruplarda görülen kapak kalp hastalığı oranları arasında istatistiksel olarak anlamlı fark vardı. Ancak diltiazem, valvüler hastalık varlığında metoprololdan daha başarılı bulundu.

Sonuçlar: Çalışmamızda, acil serviste hızlı ventrikül yanıtlı AF kontrolünde diltiazemin daha etkili olduğunu bulduk. Bu çalışmada atriyal fibrilasyon hastalarının çoğunun valvüler hastalığı olduğunu ve bu hastalarda diltiazemin metoprololden daha etkili olduğunu göstermiştir. Ejeksiyon fraksiyonu, kardiyak çaplar ilaç yanıtında önemlidir.

Anahtar kelimeler: Atriyal fibrilasyon, Diltiazem, Metoprolol, Hız kontrolü

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in emergency department (ED) clinical practice. AF is associated with the increase in the incidence of mortality, stroke and other thromboembolic events, congestive heart failure and hospitalization, disturbed life quality, decreased exercise capacity and left ventricular dysfunction [1]. The left ventricular dysfunction is generally caused by the rapid ventricular rate, loss of atrial contractility and left ventricular filling pressure after the increased diastole. In accordance with the current guidelines, for the ventricular rate control, beta blockers or nondihydropyridine derivative calcium channel blockers are recommended as the chronic rate limiting treatment for the paroxysmal, persistent or permanent AF diseases.

Although the chronic AF maintenance treatments are standard in the guidelines, there are no wide ranged studies carried out in the ED for the patients who present with symptomatic disease and need the rate control. In patients with mild to moderate symptoms, slowing the rate often results in significant improvement or even resolution of symptoms. According to the current recommendations, it is effective to use esmolol, propranolol and metoprolol as the beta blocker for the intravenous therapy of AF with rapid ventricular response and diltiazem as the calcium channel blocker. However there is no prospective and extensive research carried out on the ED patients in relation to the 1st line medication for the acute rate control treatment and which patient responses to which treatment; the recommendations are weak evidentially.

The primary aim of this study is to compare the drug responses of the patients who presented to the ED with AF with rapid ventricular response and their need for the second dosage. The secondary purpose of this study is to determine whether there is a relation between the rate control responses to the medication groups and echocardiographic parameters.

Materials and methods

Study Design

This prospective, single blind, randomized study was carried out between 25.07.2015 and 25.11.2015 in the ED of Fatih Sultan Mehmet Research and Training Hospital, Istanbul, Turkey. Approval of the study was obtained from our hospital's Institutional Review Board. All the enrolled patients received information about the study and gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki. The study was done and is reported according to the CONSORT (Consolidated Standards of Reporting Trials) Group.

Study Setting and Selection of Participants

A convenience sample of ED patients who are >18 years old with AF with rapid ventricular response were evaluated in accordance with the inclusion criteria for the study. The patients who are hemodynamically stable and requiring rate control by medical treatment were included to the study and randomized after signing the consent form. Exclusion criteria were : <18 years old, systolic blood pressure< 90 mmHg, pulse < 60beat/min, temperature > 38°C, hemoglobin < 11.0 g/dL, Wolf Parkinson White Syndrome in ECG, 2nd or 3rd degree AV block, unstable clinics, having mental fog, being allergic to diltiazem and metoprolol (which is known), having contraindication to use calcium channel blocker or beta blocker due to any reason, usage of a beta blocker or diltiazem or any other AV nodal blocking agent, a history of cocaine or methamphetamine use in the 24 hours before arrival, having severe heart failure or pulmonary edema, being with suspected acute coronary syndrome, not consenting participation to the study, pregnancy and lactation period.

Interventions

After the identification of patients according to inclusion and exclusion criteria, patients' data were collected prospectively. All patients were monitorized in the observation room, 12 lead ECG was reviewed by an Emergency Medicine Specialist in charge for any contraindication to have any medication and the requirement of rate control.

Block randomization method was used for allocation of patients due to the small sample size. The first group (Group 1) was given intravenous 0.25 mg/kg (to a maximum dose of 30 mg) diltiazem (Diltizem-L®) as the calcium channel blocker by slow push in 2 minutes; the second group (Group 2) was given intravenous 5 mg metoprolol (Beloc®) by slow push in 2 minutes. The vital findings and the clinical data of the patients in the 0, 2nd 5th, 15th and 30th minutes were recorded after each treatment. After the initial dosing, the patients having heart rate <110 beat/min(bpm) in the 30th minutes were regarded as responders to the initial treatment. The patients who aren't responding the first dosage or having a decrease in heart rate firstly and afterward an increase as being >110 bpm in 30th minutes dedicated as unresponder and 2nd dosage of the same drug was given. The patients of Group 1 received intravenous 0.35mg/kg diltiazem (to a maximum dose of 30 mg) in 2 minutes; whereas the patients of Group 2 received intravenous 5 mg metoprolol in 2 minutes. After the application of the second dose, the patients having the heart rate 110 bpm in the 30th minute were regarded as responder to 2nd dose. The patients of Group 1 who did not respond the total dose were given diltiazem 5-15mg /hour by intravenous infusion and the patients of Group 2 were given metoprolol 5 mg as the 3rd dose in 2 minutes if still unresponder after 3rd dose of metoprolol, esmolol (Brevibloc ®) infusion was started. After the rate control of all patients, a cardiologist performed the transthoracic echocardiography (TTE)'s of all participants. PHILIPS EPIQ7 echocardiography device was used for examinations. The sizes of right, left atrium and ventricle, the heart valve motion and function disorders, the ejection fractions were recorded.

Outcome Measures

The primary efficacy outcome measure was HR < 100 bpm within 60 min of 1st or second dose drug administrations. The primary safety outcome measures were HR < 60 bpm, any complicating heart rhythm as 2nd or third degree heart block and SBP < 90 mm Hg.

Sample Size and Data Analyses

The standard deviations used to calculate the sample size were based on the study by Demircan et al and Fromm et al [2,3]. We estimated a sample size of 92 patients assigned in a 1:1 ratio to receive diltiazem and metoprolol would achieve 80% power to detect noninferiority using a one-sided, two-sample test.

As the data collected during the study were evaluated, IBM SPSS Statistics 22 (IBM SPSS, Turkey) was used for the statistical analyses. For the evaluation of the data, Shapiro Wilks was used to see the compliance of the parameters with the normal distribution. Besides the descriptive statistical methods (Mean, Standard Deviation, Frequency), Mann Whitney U test was used for the comparisons between the two groups of the parameters which did not present normal distribution in the comparison of the quantitative data. Continuity (Yates) Correction and Fisher's Exact test was used for the comparison of qualitative data. Significance level was $p<0.05$.

Results

Between July 2015 and November 2015, of 114 patients who were initially evaluated, 100 met all the inclusion criteria and enrolled in the study (Figure 1).

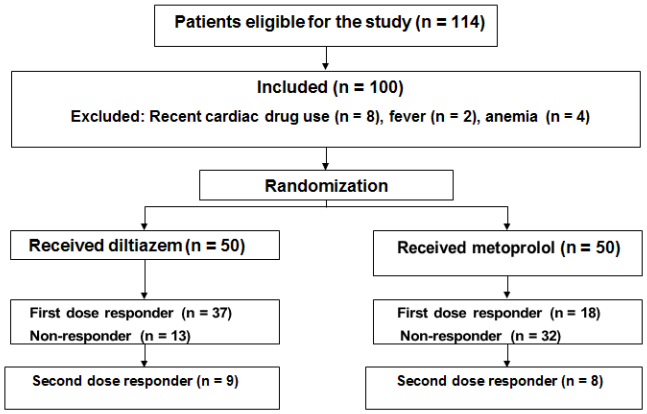

Figure 1: Patient enrollment chart

The study was carried out with 100 patients consisting of 55 male (55%) and 45 female (45%) between 25.07.2015-25.11.2015. The demographic data of the patients, the vital signs, their comorbid diseases and the drugs/medication they use are summarized in Table 1. There is no statistical difference between two groups.

Fifty of the patients (50%) were given diltiazem, 50 of them (50%) were given metoprolol. 45 of them (45%) had no first dose response; whereas 55 (55%) of them had. 48 of them (48%) had the second dose; whereas 52 of them (52%) did not need the 2nd dose. It was determined that there was 1 patient in Group 1 and 2 patients in Group 2 who responded in the 5th minute after the first dose however had heart rate increasing as being >110beat/min between the 5th and 30th minutes following. Those patients had the 2nd dose medication and were included in the group ' not responding the first dose'. 31 patients (64.6%) having the second dose did not respond to the second dose, however the rate was decreased for 17 patients (35.4%) by the 2nd dose. The total response was not seen in 28 of the patients (28%), whereas the total response was determined in 72 of them (72%). The rate of incidence for the first dose response in the patients having diltiazem was (74%) and higher than the patients having metoprolol (36%), which was statistically significant ($p:0.001$; $p<0.01$). The rate of incidence for the second dose response in the patients having diltiazem was (60%) higher than the patients having metoprolol (24.2%), which was statistically significant ($p:0.038$; $p<0.05$).

The rate of incidence for the total response in the patients having diltiazem was 92% and higher than the patients having metoprolol (52%), which was statistically significant ($p:0.001$; $p<0.01$). The responses of the patients in accordance with the medication given were summarized in the Table 2.

Ejection fraction (EF) values of the patients having medication response in Group 1 were significantly higher than the patients not having total medication response ($p:0.001$; $p<0.01$). The left atrium anterior- posterior diameter mean of the females responding to the treatment was significantly lower than the female not responding to the treatment ($p:0.043$; $p<0.05$). In accordance with the total response, there was no statistically significant difference between left atrium anterior posterior diameters of the males ($p>0.05$). In the same patient group, the left ventricular systole diameters of the patients not having total response were significantly higher than the patients "having total response" ($p:0.003$; $p<0.01$), and their left ventricular diastole diameters were significantly higher than "the patients not having total response" ($p:0.013$; $p<0.05$). Total echocardiographic findings of Group 1 are summarized in the Table 3. The evaluation of the echocardiographic findings according to the total responses of the patients having metoprolol (Group 2) is summarized in the Table 4.

Table1: Distribution of the general features in relation to the patients

	Diltiazem Mean±SD	Metoprolol Mean±SD	P
Age (year)	74.18±11.73	73.36±13.54	0.75
Heart rate	141.08±11.57	136.98±10.39	0.07
Respiration rate	20.66±3.55	20.52±2.38	0.82
Systolic blood pressure (mmHg)	149.5±23.21	155.38±22.28	0.20
Diastolic blood pressure(mmHg)	77.64±10.21	78.86±11.88	0.58
Temperature	36.1±0.19	36.1±0.22	0.96
Mean arterial pressure	101.58±12.71	104.35±14.58	0.31

Table 2: The evaluation of the first, second and total dose responses of the patients in accordance with the medication given

	Diltiazem n (%)	Metoprolol n (%)	p
First dose response	37 (74%)	18 (36%)	0.001**
Second dose response	9 (60%)	8 (24.2%)	0.038*
Total response	46 (92%)	26 (52%)	0.001**

Continuity (Yates) Correction, *p<0.05, **p<0.01

Table 3: The evaluation of the echocardiographic findings according to the total responses of the patients having diltiazem

Diltiazem	Total Response Exist (n=46) Avg±SD (Median)	None (n=4) Avg±SD (Median)	p
EF	55.43±8.42 (60)	23.75±10.31 (22.5)	0.001**
Right atrium anterior posterior diameter(cm)	4.83±0.87 (4.8)	5.1±0.54 (5.35)	0.215
Left atrium anterior posterior diameter(cm)	4.42±0.53 (4.45)	4.88±0.39 (5)	0.076
Left atrium anterior posterior diameter(cm) for females	4.37±0.47 (4.3)	5.10±0.14 (5.1)	0.043*
Left atrium anterior posterior diameter (cm) for males	4.47±0.60 (4.5)	4.65±0.49 (4.6)	0,675
Right ventricular diastolic diameter(cm)	2.92±0.37 (2.9)	3.1±0.27 (3)	0.297
Left ventricular systolic diameter(cm)	3.35±0.64 (3.2)	5±0.83 (4.95)	0.003**
Left ventricular diastolic diameter(cm)	5.25±19.57 (4.3)	5.35±0.37 (5.5)	0.013*
Left ventricular diastolic diameter(cm) for females	4.40±0.73 (4.3)	5.55±0.07 (5.5)	0.074
Left ventricular diastolic diameter(cm) for males	4.40±0.58 (4.3)	5.15±0.49 (5.15)	0.084

Mann Whitney U Test, *p<0.05, **p<0.01, EF: Ejection fraction

Table 4: The evaluation of the echocardiographic findings according to the total responses of the patients having metoprolol

Metoprolol	Total Response Exist (n=26) Avg±SD (Median)	None (n=24) Avg±SD (Median)	p
EF	59.62±1.96 (60)	47.08±7.79 (45)	0.001**
Right atrium anterior posterior diameter(cm)	4.31±0.89 (4.25)	5.22±0.51 (5.2)	0.001**
Left atrium anterior posterior diameter(cm)	3.92±0.36 (3.9)	4.53±0.42 (4.5)	0.001**
Left atrium anterior posterior diameter(cm) for females	3.93±0.23 (3.9)	4.50±0.43 (4.3)	0.003**
Left atrium anterior posterior diameter(cm) for males	3.91±0.42 (3.9)	4.54±0.42 (4.6)	0.001**
Right ventricular diastolic diameter(cm)	2.51±0.39 (2.35)	3.01±0.31 (3)	0.001**
Left ventricular systolic diameter(cm)	2.86±0.71 (2.7)	3.67±0.44 (3.6)	0.001**
Left ventricular diastolic diameter(cm)	4.07±0.69 (4.1)	4.52±0.7 (4.5)	0.004**
Left ventricular diastolic diameter(cm) for females	4.01±0.76 (4.1)	4.68±0.74 (4.8)	0.026*
Left ventricular diastolic diameter(cm) for males	4.10±0.67 (4.1)	4.42±0.69 (4.5)	0.044*

Mann Whitney U Test, *p<0.05, **p<0.01, EF: Ejection fraction

There is statistically significant difference between rates of the valvular heart disease seen for the patients in responsive /unresponsive groups for both drugs (Table 5). But diltiazem is more successful in presence of valvular disease than metoprolol. No hemodynamic instability observed among the patients within the study.

Table 5: The evaluation of rates of echocardiographic valvular heart disease for the patients having diltiazem/ metoprolol according to the total responses

		Response positive	Response negative	
Diltiazem	Valvular disease positive (44)	90.90%	9.09%	
	Valvular disease neg (6)	100%	-	
Metoprolol	Valvular disease positive (34)	35.29%	64.70%	P<0.01
	Valvular disease neg (16)	87.5%	12.5%	

Continuity (Yates) Correction, **p<0.01

Discussion

In this study, we found that diltiazem is more effective in the rate control of rapid ventricular rate atrial fibrillation in emergency department. This study showed that most of atrial fibrillation patients have valvular disease, and diltiazem is more effective than metoprolol in these patients. Ejection fraction, cardiac diameters are important in drug response and especially metoprolol response is dependent on the diameters of heart chambers.

AF is one of the most frequently seen arrhythmias in practice and associated with mortality, stroke and other thromboembolic events, left ventricular dysfunction and heart failure, decreased exercise capacity and the disturbed life quality [4].

Diltiazem and metoprolol used frequently for rate control of atrial fibrillation those have effects on slowing the AV nodal conduction and extending the AV nodal refractory period. In accordance with 2014 AHA Guideline these medications are recommended as the class I for the acute rate control of AF [5-7]. However, there is no recommendation which of the medications is required to be preferred primarily. The number of the randomized prospective studies on the issue is limited and the studies carried out are mostly related to the chronic therapy and complications of AF. Due to the lack of the studies on the emergency practices, it is not known which one has the priority in the emergency intervention.

There are only 2 studies carried out with small patient groups for comparison the rate control of these two medications in the emergency room in the literature. However, there is no structural evaluation of the heart by means of echocardiography in both studies [2,3].

The first study is carried out by Demircan et al [2] with 40 patients. The study shows that both medications are safe for the rate control however the patients with diltiazem have more rapid responses.

According to the study carried out by Christian Fromm et al, diltiazem is more effective in achieving heart rate in ED patients with rapid ventricular rate atrial fibrillation and there is no increase incidence of adverse effects beside metoprolol [3].

The rate control was maintained for 74% of the patients having diltiazem as rate-limiting agent for the first dose in our study, whereas the ratio was 36% among the patients having metoprolol; the difference is statistically significant. The ratios increased to 92% and 52% after the second dose. In the study by Fromm et al, 50% of the patients having diltiazem and 10.7% of the patients having metoprolol reached the target heart rate which is <100/min at the 5th minute and 95.8% of the group with diltiazem and 46.4% of the group with metoprolol at the 30th minute [3]. These findings are correlated with each other.

Martindale et al reviewed the literature to compare the efficacy of calcium channel blockers to β-blockers for acute rate control of atrial fibrillation with rapid ventricular response in the emergency department setting. Of the 1003 studies yielded by our initial search, two met inclusion criteria; and they reported that on the basis of the paucity of available evidence, diltiazem may be more effective than metoprolol in achieving rapid rate control, but high-quality randomized studies are needed at 2015. But none of the studies searched underlying heart condition effect for response to drugs [8].

In the study by Salih A et al [9], it is determined that 71% of the patients with AF have LV dilatation, 27% have LV function depletion and 26% have left ventricular hypertrophy.

In our study, we found that EF value is one of the determinant factors to maintain the rate control (p:0.001; p<0.01). As responses to the treatment are analyzed it is seen that there is no significant difference in the atrium diameters as diltiazem is concerned, however both diameters of the atrium are statistically significantly low in the patients giving response as metoprolol (p:0.001; p<0.01). There is statistically significant difference measured between the left ventricular systolic and diastolic in the use of diltiazem for the ventricular diameters, whereas the difference is statistically significant in both ventricle in the use of metoprolol.

Approximately 30% of the patients with AF have valvular heart disease [10,11]. AF due to LAD might be the early stage symptom of mitral stenosis and/or coronary failure.

More importantly as the patients in the diltiazem group are evaluated in accordance with the total response there is no statistically significant difference in terms of rate of incidence for valvular disease seen in the echocardiography (p>0.05), whereas the rate of incidence for valvular diseases of the patients not responding the medication in the metoprolol group is significantly high (91.7%, 46.2%, p:0.002; p<0.01). According to our study the use of beta blocker, in case of structural heart disease should be discussed due to the facts that the lower atrium diameters and compact valvular system are more important parameters for beta blocker response. The emergency department studies on this subject are limited. Kannel et al [12] found risk of AF for the patients having valvular disease history increased 1.8 times in males and 3.4 times in females. In the study carried out by Andrew et al, it is recommended that beta blockers and non dihydropyridine group calcium channel blockers are to be used as the primary medication for the patients with AF and valvular disease [13]. Moreover, Wang TJ et al show that there is increase in the AF risk due to the left atrial dilatation in obese patients [14]. There is no study in the literature showing the superiority of diltiazem or metoprolol used for the rate control in the patients having AF and valvular heart disease. In this study we show that diltiazem is more effective than the metoprolol for the rate control in the patients having AF and valvular heart disease.

Limitations

The study was conducted with the patients presented with rapid ventricular rate atrial fibrillation to the emergency department and underlying problems those may cause the acceleration of AF were tried to be excluded, but the patients with thyroid dysfunction might be included in the study due to the limited laboratory opportunities in the emergency department. The study team were not blind except the cardiologist who examined echocardiography. Regardless of the control of the pharmacy records via electronic system, there are patients whose records are not available and the usage and time of previous antiarrhytmic drug were reported as the patient said. Moreover, the long term drug compliance of the patients is unknown. The short term results of the patients are analyzed; there is no information about their subsequent follow-ups and treatment. Our study is limited with the patient group recognized as stable. Patients with known decompensated heart failure were excluded from the study. An inclusion bias may be consisted due to convenience sampling. The cardiologist who make echocardiography was studying between 08:00- 17:00 hours, Monday to Friday.

Conclusion

In this study we have determined that the stable patients having symptomatic atrial fibrillation with rapid ventricular response without any underlying correctable reason have better response to diltiazem as rate controlling treatment, especially for the patients with coexisting valvular disease. We did not determine any difference between the two medications in terms of their side-effects.

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Research article
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Evaluation of the effect of ultrasonic heating and exercise heating on muscles by ultrasound elastography: An experimental clinical trial

Egzersizle ısıtma ile ultrasonik ısıtmanın kaslarındaki etkisinin ultrason elastografi ile değerlendirimi: Deneysel bir klinik çalışma

Adnan Demirel [1], Murat Baykara [2], Tuba Tülay Koca [1], Ejder Berk [1]

[1] Kahramanmaraş Sütçü İmam University, Faculty of Medicine, Physical Medicine and Rehabilitation Department, Kahramanmaraş, Turkey
[2] Kahramanmaraş Sütçü İmam University, Faculty of Medicine, Radiology Department, Kahramanmaraş, Turkey

ORCID ID of the authors:
AD: 0000-0002-2974-8560
MB: 0000-0003-2588-9013
TTC: 0000-0002-4596-858X
EB: 0000-0002-0816-0960

Abstract

Aim: Ultrasound (US) has been used for therapeutic purposes for many years due to its biological beneficial effects. İn this report we compare the effect of therapeutic ultrasonic heating with exercise-heating on the gastrocnemius / soleus muscles by quantitative measurements of ultrasound elastography.

Methods: İt is designed as a single blind experimental clinical study. Fourty (40) healthy male patients aged between 19-23 years were included randomly in the study. To the first group, we applied a continuous wave therapeutic US on both calfs (symmetrically) consisting gastrocnemius / soleus muscle groups at a frequency of 3 Mhz, 2 w / cm^2 dose, for 6 minutes. To the second group, we applied a 15-minute jogging exercise program. Bilateral, symmetric measurements were made in the first 5 minutes with a wide band linear probe, US elastography before and after application.

Results: A statistically significant decrease in ultrasound elastography strain value (UESV) after therapeutic US in gastrocnemius / soleus muscle groups was observed ($p < 0.001$ / $p < 0.001$). There was no statistically significant change in UESV in the gastrocnemius / soleus muscle groups in the jogging group ($p = 0.792$ / $p = 0.187$). When the percentages of ultrasound elastography strain ratio (UESR) were examined, there was a significant difference in the change of percentages in the gastrocnemius / soleus muscle groups in both groups ($p = 0.005$/ $p = 0.001$). According to this, in both muscle groups, the elasticity increased and the stiffness decreased in group 1 and in group 2, the stiffness increased in some cases and decreased in some, and in overall it was observed to increase.

Conclusion: Therapeutic US-heating is an effective, reliable method that generally increases elasticity and reduces stiffness in calf muscles than exercise-heating.

Keywords: Sonoelastography, Therapeutic ultrasound, Therapy, Exercise

Öz

Amaç: Ultrason (US), biyolojik yararlı etkileri nedeniyle yıllarca tedavi amaçlı kullanılmıştır. Bu yazıda gastroknemius / soleus kaslarının egzersizle ısıtma ile terapötik ultrasonik ısıtmanın etkisini ultrason elastografi (UE) ile kantitatif ölçümleri karşılaştırdık.

Yöntemler: Çalışma tek kör deneysel klinik olarak tasarlanmıştır. Çalışmaya 19-23 yaşları arasında 40 sağlıklı erkek hasta randomize dahil edilmiştir. İlk grupta, 3 MHz frekansında gastroknemius / soleus kas gruplarını içeren her iki kalf kasları (simetrik olarak) üzerine 6 dakika, 2 w / cm^2 doz sürekli akım terapötik US uyguladık. İkinci gruba 15 dakikalık koşu egzersiz programı uyguladık. Bilateral, simetrik ölçümler ilk 5 dakikada geniş bant lineer prob, US elastografi ile uygulama öncesi ve sonrası yapıldı.

Bulgular: Gastroknemius / soleus kas gruplarında terapötik US sonrası ultrason elastografi strain değerinde (UESV) istatistiksel olarak anlamlı bir düşüş gözlendi ($p <0,001$ / $p <0,001$). Koşu grubundaki gastroknemius / soleus kas gruplarında UESV'de istatistiksel olarak anlamlı bir değişiklik yoktu ($p = 0,792$/ $p = 0,187$).

Ultrason elastografi gerim oranının (UESR) yüzdeleri incelendiğinde, her iki grupta da gastroknemius / soleus kas gruplarında yüzde değişiminde anlamlı bir fark vardı ($p = 0,005$ / $p = 0,001$). Buna göre, her iki kas grubunda da elastikiyet artmış ve grup 1'de ve grup 2'de sertlik azalmış, bazı durumlarda sertlik artmış iken bazılarında azalmış ve genel olarak artmıştı.

Sonuç: Terapötik US-ısıtma, genel olarak elastikiyeti arttıran ve baldır kaslarındaki sertliği egzersiz-ısıtmaya göre azaltan etkili ve güvenilir bir yöntemdir.

Anahtar kelimeler: Sonoelastografi, Terapötik ultrason, Terapi, Egzersiz

Corresponding author / Sorumlu yazar:
Tuba Tülay Koca
Address / Adres: Sütçü İmam Üniversitesi, Fiziksel Tıp ve Rehabilitasyon Bölümü, Kahramanmaraş, Türkiye
E-mail: tuba_baglan@yahoo.com

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Introduction

Heat is widely used to relieve pain in locomotor system diseases. Ultrasound (US) has been used for therapeutic purposes for many years due to its biological beneficial effects [1]. With therapeutic US, adverse bioeffects such as burns and serious bleedings may develop. For this reason, treatment should be started after considering the reduction of side effects, standardization, dosing and benefit-loss ratio [2,3]. Although US is a frequently used therapeutic agent in musculoskeletal injuries, there is limited number of clinical trials and guides to use.

Different exercise types were used in treatment modalities due to their numerous positive effects on muscles and tendons. In some studies it was demonstrated that stretching can reduce muscle stiffness and increase muscle elasticity by altering fascicule strain but not resting fascicule length [4]. Also exercise has fewer side effects and

is not affected by different users than US.

There is insufficient data on the effect of therapeutic-US on muscle elasticity. Although both US and exercise are commonly used in musculoskeletal disorders, the effects and treatment protocols are not fully established. The development of ultrasound technology resulted in the emergence of ultrasound elastography (UE) that can directly measure the mechanical properties of tissue, including muscle stiffness. When elasticity increases, we may say that stiffness decreases in the tissue. In our study, we were able to measure the changes in muscle tissue with therapeutic US-heating by UE quantitatively and compared the results with the changes occurred after jogging exercise. For the first time in the literature, we compared the effect of therapeutic US-heating on the elasticity of calf muscles with exercise-heating by UE quantitatively.

Materials and methods

Cases

It is designed as a single blind experimental clinical study. Forty (40) male cases aged between 19-23 years were included in the study. The US group consisted of 20 males and the jogging group consisted of 20 males of similar age, height and weight range. Those with known musculoskeletal complaints, deformities and sensorial deficits were not included in the study.

In the first group we applied continuous wave US at a frequency of 3 Mhz, 2 w / cm^2 dose for 6 minutes, onto the both calf, gastrocnemius / soleus muscle groups. In the second group, we applied a 15-minute jogging exercise program. Bilateral and symmetric measurements were performed with a broad band linear probe, sonoelastography before and after application. Ultrasound elastography strain value (UESV), strain ratio (UESR) values were calculated.

Therapeutic ultrasound

In our study, we performed continuous wave US (Chattanooga Intelect Mobile US, ELSA, Orthopedics) application at 3 Mhz frequency, 2 w / cm^2 dose, for 6 minutes. We used a gel to provide the skin to stay intact. No adverse effects due to the US were observed in any of the patients.

Ultrasound elastography (UE)

UE technique is a new functional US imaging technique developed in the last 5 years that can demonstrate the distribution of tissue elasticity. The low strain ratio indicated the decrease in tissue elasticity, softening of the tissue, loss of tendon integrity, and decrease in quality. Unlike other methods, this technique provided dynamic data [5].

A high-resolution ultrasonography system (AplioTM 400 Platinum, Toshiba Medical Systems Corporation, Tochigi, Japan) and a broad band convex probe (PVT-375BT) were used by a same trained radiologist. The gray-scale ultrasonographic posterior images of the calf region were obtained symmetrically, bilaterally, and separately. The elastography mode was activated, and pressure was applied when the muscles were captured in the same image during compression phase. The UE strain value (UESV) of the subcutaneous fat tissue in the same image and UESV of the central segments of the calf muscles were detected using the ROI. The UE strain ratio (UESR) of the muscles was calculated by dividing the fat values by the muscle values. All procedures were performed by the same experienced radiologist who was kept uninformed about the clinical diagnosis.

Statistical analysis

All statistical analyses were carried out using IBM SPSS version 19 (IBM Corp., Armonk, NY, USA). Descriptive data were presented in mean ± standard deviation (SD) or median scores according to their categories and distribution. The coherence of variables to normal contribution (normality) was analyzed by Shapiro Wilk test. The Pearson correlation analysis was used to analyze the level of the correlation between the variables.

Categorical data are reported as percentages and are compared using the chi-squared test. Continuous data are reported as mean with standard deviation or median with minimum and maximum and compared using parametric/non-parametric tests according to their normal or abnormal distribution. We also used histogram for this. A p value of <0.05 was considered statistically significant. As a result of the power analysis performed, the minimum number of subjects required in each group was determined as 20 so that the difference of 0.05 units between the two group could be statistically different. Type 1 error = 0.01, power of the test: %75. The study approved by local ethic committee (No: 2016/146) and complied with Helsinki declaration principles.

Results

Forty (n=40) male cases aged between 19-23 years were included in the study. Both groups consisted of 20 male cases. The groups were similar in terms of age, weight and height ($p = 0.13$ / $p = 0.06$ / $p = 0.15$). Descriptive data were shown at Table 1. The results of UESV before and after the administration of US onto gastrocnemius / soleus muscles in the US group and jogging group were summarized in Table 2. According to the data, a statistically significant decrease in UESV after US was observed in gastrocnemius / soleus muscle groups ($p < 0.001$ / $p < 0.001$). In the jogging group, UESV were not statistically different in gastrocnemius / soleus muscles ($p = 0.792$ / $p = 0.187$). When the percentages of UESR were examined, there was a significant difference in the change of percentages in the gastrocnemius /

soleus muscle groups in both groups (p = 0.005/ p = 0.001) (Table 3) (Figure 1, 2).

Table 1: Descriptive data of the study

Group	Age (year)	Height (cm)	Weight (kg)
US n/ Mean±std	40/21.10±1.36	40/174.41±5.64	40/71.53±10.96
Jogging n/ Mean±std	40/20.56±1.80	40/176.5±4.40	40/68.38±8.45
t/p	1.51/0.13	1.84/0.06	1.43/0.15

US: ultrasound, t: t value, p<0.05 statistically different

Table 2: UE strain values of gastrocnemius/soleus muscles in US and jogging groups, before/after

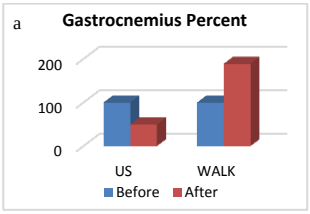
US group	n/ mean±std	t	p
GC_1	40/1.11±0.87	4.73	<0.001
GC_2	40/0.43±0.26		
SU_1	40/1.75±1.17	3.89	<0.001
SU_2	40/0.88±0.79		
Jogging group			
GC_1	40/0.55±0.38	0.26	0.792
GC_2	40/0.52±0.61		
SU_1	40/0.72±0.58	1.32	0.187
SU_2	40/1.05±1.46		

US: ultrasound, GC_1: gastrocnemius first, GC_2: gastrocnemius second, SU_1: soleus first, SU_2: soleus second, t: t value, p<0.05 statistically different

Table 3: The percental changes (UESR) in gastrocnemius/soleus muscles in US and jogging groups

Group, n=40	Gastrocnemius %	Soleus %
US	47.44±23.34	49.59±23.86
Jogging	161.80±251.74	188.9±270.66
t	2.86	3.24
P	0.005	0.001

US: ultrasound, UESR: ultrasound elastography strain ratio, t: t value, p<0.05 statistically different



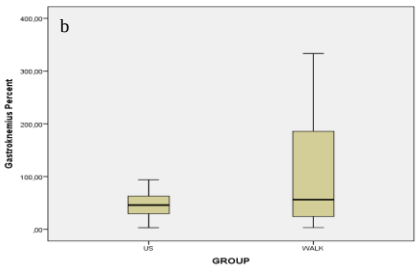
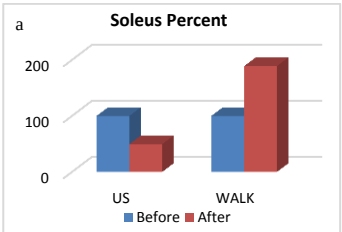


Figure 1a, 1b: Graphical presentation of percent changes in ultrasound elastography strain ratio in gastrocnemius muscle in ultrasound and jogging group



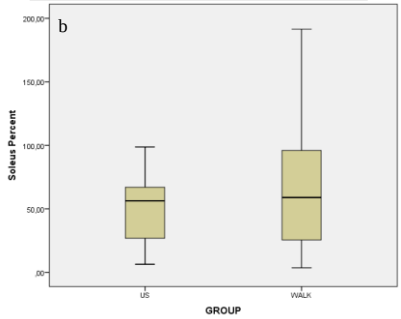


Figure 2a, 2b: Graphical presentation of percent change in ultrasound elastography strain ratio in soleus muscle in ultrasound and jogging group

Discussion

Therapeutic US is the most commonly used electro-physical agents in clinical practice [2]. It is totally different from the diagnostic US and is used in the treatment of diseased or damaged parts of the body. The US waves used in clinics have 0.8-3 MHz frequency and the average treatment dosage is 1.5 w / cm^2. The maximum dose can be 3 w / cm^2; higher doses can be used for the studies. In practice it is very important to use the head probe fully aligned. Water, petroleum jelly, various pomades, jellies can be used for this contact. Ultrasound can be applied in water for uneven surface areas such as hands, feet, elbows. One session takes 5-15 minutes once a day or every other day [6,7].

The impact of US on tissue has been a research topic for half a century. US effects cell tissue via thermal, shock wave and cavitation mechanisms [8]. While high-frequency applications benefit from both thermal and mechanical effects; the heat effect occurs more at low frequencies [9]. Due to the developments such as tranducer design, more accurate measurements and calibrations of acoustic power have been accomplished, US is started to be used in physiotherapy, surgery, chemotherapy and drug delivery etc.

The US is absorbed and it passes through the homogeneous tissues and transforms into heat energy. Heat can be effective on pain by increasing endorphins. US changes tissue metabolism. Increased circulation with vasodilatation helps to remove pain-stimulating metabolic waste [9,10]. Recent publications have shown that therapeutic US can pass cell membrane and induce various intracellular biochemical reactions as well as increase in cell proliferation, angiogenesis and results changes in DNA molecules, protein expression [10-12].

Topics such as dosimetry, transducer selection, duration, and safety for observing the physiological effects of therapeutic US have been the subject of various in vivo animal and in vitro artificial models [11,12]. Usually US thermal therapy appears to be disadvantaged over bones, but with appropriate application techniques, planar US can provide the required heat levels in the soft tissue under the bone in areas such as neck, shoulder, and head [13,14]. Therapeutic US has been used to treat the damage of joints, nerves and tendons. Some of the emitted radiation is absorbed by the healthy tissues around, like muscles.

Ohwatashi et al. [15] studied on a phantom, which is composed of pigskin and tissue-like material, was measured by ThermoGraph after application of 2.0 w / cm, 5 min US, ranging from 1-3 MHz. At 1 MHz application, the maximum temperature was measured in the near of the transducer, at 3 MHz application while the maximum temperature was found to be at bone tissue. Norte et al. [16] found that in arthroscopic knee joints, therapeutic US application to Hofman reflex, was observed to modulate the arthrogenic response according to SHAM.

After 3 hours of low-frequency therapeutic US application to triceps surae muscles of healthy volunteers, an increase of 3-4.0 ° C in temperature observed at a depth of 3 cm at the end of 1 hour [17]. In the case of Vasquez et al [18], after the continuous application of US administration, hypertrophy in the gastrocnemius muscle fibers was found to be excessive; it has

to be used in pulsed, focused modes to minimize the damage to the surrounding tissues. Montomery et al [19] have concluded that 20 min at 3.3 MHz, 1.5 w / cm^2 density can be used for therapeutic purposes without heating up.

There are only a few human studies about the effect of the US on muscle tissue. There is not enough guidance about the application method, severity and frequency of US application for muscle tissue, and safety precautions. In our study, we performed continuous wave ultrasound at a frequency of 3 Mhz, 2 w / cm^2 dose for 6 minutes period. As a result, we generally achieved positive results such as increase in the elasticity and reduced stiffness of calf muscles. Berko et al [20] found that elasticity significantly increases immediately postexercise in both biceps brachii and rectus femoris; resting differences between biceps brachii and rectus femoris elasticity, and dominant and nondominant biceps brachii elasticity, do not persist after exercise. Also they found the change in muscle elasticity with exercise is higher in younger children. In our study, we did not observe a significant difference in elasticity and stiffness in muscle groups after the exercise warming. In addition, when percentage ratios were examined, we generally concluded that the exercise was not effective as a heating method.

In both groups of muscles, the elasticity increased with US application and the stiffness decreased and additionally total stiffness decreased compared to the initial state. In the jogging group, the stiffness increased in some cases, but in general an absolute increase was observed. Accordingly, the US is a standard effective method of heating besides jogging exercise was not found effective.

Limitation of the study

Continuous US is generally used to produce thermal effects and reaches deeper than most superficial heating agents. However, although US is well-suited to heating tendons, ligaments, joint capsules and fascia; it is generally not the ideal agent for heating muscle tissue since muscle tissue has a relatively low absorption coefficient. Also, the muscles used in this study are large muscles, and the available US transducers may not be appropriate for heating these muscles.

Conclusion

Increased elasticity in gastrocnemius / soleus muscle groups with therapeutic US-heating was found to be superior to exercise-heating by US elastography.

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Melatonin, leptin, and ghrelin levels in nurses working night shifts

Gece vardiyasında çalışan hemşirelerde melatonin, leptin ve grelin düzeyleri

Sibel Söylemez [1], Ayşe Banu Çaycı Sivri [1], Ercan Şimşek [1], Burçak Polat [2], Bekir Çakır [2]

[1] Department of Biochemistry, School of Medicine, Gazi University, Ankara, Turkey
[2] Department of Clinic of Endocrinology and Metabolism, Atatürk Training and Research Hospital, Ankara, Turkey

ORCID ID of the authors:
SS: 0000-0002-5005-2277
ABÇS: 0000-0003-1379-5159
EŞ: 0000-0002 -9010-6196
BP: 0000-0002-7729-5586
BÇ: 0000-0001-7526-8827

Corresponding author / Sorumlu yazar:
Sibel Söylemez
Address / Adres: Gazi Üniversitesi Tıp Fakültesi, Biyokimya Anabilim Dalı, Ankara, Türkiye
E-mail: soylemezsibel@gmail.com

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Abstract

Aim: The levels of several hormones including melatonin, leptin, and ghrelin are regulated by circadian rhythm. Deregulated hormone levels due to disruption of circadian rhythm may result in medical conditions like metabolic syndrome (MetS). The aim of this cross-sectional study was to investigate the associations among circadian rhythm, melatonin, leptin, ghrelin and metabolic syndrome by determining melatonin levels of healthy nurses who were working on night-shift for at least 3 months and of those on day-shift for at least 3 months.

Methods: Venous bloods following 8-hour fasting of 50 nurses, who were aged at 20-40 age range and whose Body Mass Index (BMI) were >25, were collected. Those working on night-shift were named as night group and the control group of the study was named as day group. From the bloods collected; melatonin, leptin and ghrelin levels were evaluated by ELISA method, insulin was evaluated by immunochemically, whereas fasting blood glucose, cholesterol, triglyceride, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels were evaluated spectrophotometrically.

Results: Melatonin level was significantly lower in the night-shift group compared to the day-shift group (p=0.003). Leptin level was slightly but not significantly lower in the night-shift group (p=0.097). In contrast, ghrelin level and other biochemical parameters including triglyceride, fasting blood sugar (FBS), insulin, insulin resistance index (HOMA-IR) and cholesterol were increased in the night-shift group but these increments were not statistically significant.

Conclusion: Our results suggest that night-shift work might exhibit tendency towards MetS by disrupting circadian rhythm.

Keywords: Night shift, Metabolic syndrome, Melatonin, Leptin, Ghrelin

Öz

Amaç: Melatonin, leptin ve grelin dahil olmak üzere birçok hormonun seviyeleri sirkadiyen ritim tarafından düzenlenir. Sirkadiyen ritim bozulmasına bağlı düzensiz hormon düzeyleri metabolik sendrom (MetS) gibi sorunlara neden olabilir. Bu kesitsel çalışmada, en az 3 aydır gece ve en az 3 aydır gündüz vardiyasında çalışan sağlıklı hemşirelerin melatonin düzeylerini belirleyerek, melatonin, sirkadien ritim, leptin, grelin ve metabolik sendrom ilişkisinin araştırılması amaçlanmıştır.

Yöntemler: 20-40 yaş aralığında, Vücut Kitle İndeksi (BMI) > 25 olan 50 hemşirenin sabah 8 saatlik açlıkla venöz kanları alınmıştır. Gece nöbet tutan grup gece grubu olarak, gündüz çalışan kontrol grubu ise gündüz grubu olarak adlandırılmıştır. Alınan kanlarda melatonin, leptin ve grelin düzeyleri ELISA metodu ile, metabolik sendrom kriterlerinden olan insülin immünokimyasal olarak, açlık kan şekeri, kolesterol, trigliserid, yüksek yoğunluklu lipoprotein (HDL) ve düşük yoğunluklu lipoprotein (LDL) düzeyleri ise spektrofotometrik olarak incelenmiştir.

Bulgular: Melatonin düzeyleri gece grubunda, gündüz grubuna göre anlamlı derecede düşük bulunmuştur (p=0,003). Leptin düzeyleri gece grubunda düşük bulunmuştur ancak istatistiksel olarak anlamlı değildir (p=0,097). Aksine grelin düzeyleri ve diğer biyokimyasal parametreler olan trigliserit, açlık kan şekeri, insülin, insülin direnci ve kolesterol gece grubunda artmıştır, ancak bu artışlar istatistiksel olarak anlamlı değildir.

Sonuç: Bulgularımız gece vardiyasında çalışmanın sırkadiyen ritmin bozularak, MetS eğiliminin artabileceğini göstermektedir.

Anahtar kelimeler: Gece vardiyası, Metabolik sendrom, Melatonin, Leptin, Grelin

Introduction

Working night shift has deleterious effects on health by disrupting human body circadian rhythm. It was considered to be a risk factor for obesity and a wide range of chronic diseases and chronic medical conditions. Approximately 2-5% of workers have disorders associated with working night shifts [1,2]. The levels of several hormones including melatonin, leptin and ghrelin are regulated by circadian rhythm. Any deterioration in circadian rhythmicity may result in medical conditions like metabolic syndrome by changing hormone levels [3].

Melatonin, characterized at 1958 by Lerner et al., is secreted at night under dark condition and involved in the phasing of circadian rhythm. The circadian rhythm regulates physiological processes including immune system, antioxidant defenses, glucose regulation, and the control of sleep through melatonin signal [4,5].

The metabolic syndrome (MetS) lowers quality of life by increasing the risk of a range of disorders including type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and polycystic over syndrome (PCOS). A cluster of metabolic abnormalities including insulin resistance, abdominal (visceral) obesity, genetic susceptibility, high serum triglycerides, low high-density lipoprotein (HDL) levels, atherogenic dyslipidemia, elevated blood pressure, and chronic stress have been considered as components of MetS [6]. The prevalence of MetS was estimated to range from 20% to 30% in most countries and increases continuously. MetS is considered to be the most serious health problem for 21st century. The increased incidence of obesity in populations may be a major reason for the elevated prevalence of MetS worldwide [7].

Although the etiopathogenesis is still unclear, obesity lead to MetS by disrupting metabolic parameters including insulin resistance, blood pressure, cholesterol, and triglycerides [8]. Adipose tissue as an endocrine organ is involved in whole body homeostasis by secreting adipokines (adipocytokines) [9]. Leptin was characterized by Zhang et al. in 1994 as the first adipokine [10]. The primary function of leptin is to prevent the formation of obesity by regulating food intake of organism. While serum leptin level decreases in case of fasting and after weight loss, leptin production increases in obesity. The elevated level of leptin induce low grade inflammation, and affects cytokine production [11]. Ghrelin, another adipokine, was characterized by Kojima et al. in 1999 [12]. Ghrelin is mainly secreted by stomach to regulate food intake. In contrast to leptin, ghrelin secretion increases in starvation in a fast-acting manner. In addition, the involvement of ghrelin in the regulation of immunity and inflammation has been established in detail [13].

The aim of this study is to investigate the potential contribution of night-shift work on the development of metabolic syndrome. To this and, peripheral blood samples were taken from nurses working day-shifts and night-shifts, and the levels of melatonin, leptin and ghrelin were analyzed.

Materials and methods

Study participants

The study population comprised 50 female nurses working at a research hospital. The subjects were aged between 20 and 40 years in premenopausal period. They were healthy non-smoker individuals had no any medical treatment or no metabolic diseases such as thyroid, diabetes mellitus, hyperlipidemia, or hypertension. The night-shift group (NSG) consisted of 25 subjects that were required to work night shift for at least 3 months. The day-shift group (DSG) consisted of 25 subjects that were required to work day shift for at least 3 months. The physical (weight and height) and biochemical data were obtained for all subjects. The study protocol was approved by Institutional Ethics Committee. The study was carried out according to Declaration of Helsinki. All subjects gave written informed consent before participation.

Blood Sampling

A venous blood sample of 10 mL was drawn from all subjects at 8 o'clock in the morning after 8 hours of fasting and stored in pre-cooled biochemical tubes. In the NSG, the blood samples were obtained at the end of the night shift. In the DSG, the blood samples were obtained at the beginning of the day shift. Within 15 minutes of sample collection, the blood sample was spun at 1800 g for 10 min using a refrigerated centrifuge (4°C), and incubated for some time for phase separation. Then, the supernatant was transferred into polypropylene tubes and stored at –80 °C for analysis of relevant hormones or biochemical parameters.

Biochemical parameters

Plasma melatonin, leptin, and ghrelin concentrations were determined by enzyme-linked immunosorbent assay (ELISA) method. For this, commercially available melatonin (Catalogue Number: E-EL-H2016, Elabscience, Wuhan, China), leptin (Catalogue Number: KAP2281, DIAsource, Nivelles, Belgium), and ghrelin (Catalogue Number: E-EL-H1919, Elabscience, Wuhan, China) ELISA kits were used according to manufacturers' instructions.

Other relevant laboratory parameters including high and low density lipoprotein (HDL and LDL), fasting blood sugar (FBS), insulin, cholesterol, and serum triglyceride were determined on Cobas ® 8000 modular analyzer (Roche Diagnostics, Basel, Switzerland) via photometric and immunochemical methods.

Calculation of body mass index and insulin resistance index

Body mass index was calculated as the body mass divided by the square of the body height (kg/m2) for all participants. Insulin resistance index was calculated by using formula of homeostasis model assessment (HOMA-IR) method:

HOMA-IR = Fasting insulin (μU/mL) x Fasting glucose (mg/dL) / 405

Statistical analysis

Statistical analyses were performed using Predictive Analytics Software (PASW) statistical software (version 15.0 for Windows; SPSS Inc., Chicago, Illinois). Descriptive parameters were presented as median. Since the number of data is below 30, parametric conditions were not provided, and then nonparametric tests were used to analyses. For comparison of independent variables in the two groups, Mann-Whitney U tests were used. Correlation analysis was also performed with the nonparametric test, Spearman correlation. A p value less than 0.05 were accepted as statistically significant.

Results

The characteristics and laboratory parameters of the DSG and NSG were summarized in Table 1. Body mass indices (BMI) of all subjects were more than 25 kg/m2. No significant difference was found between the BMI values of the NSG (26.81, 25.71 - 32.05) and DSG (27.89, 26.99 - 29.69). Melatonin level was significantly lower in the NSG (p=0.003). Leptin level was also lower in the NSG but the difference was not statistically significant (p=0.097). Likewise, ghrelin level and other biochemical parameters including triglyceride, FBS, insulin, HOMA-IR, and cholesterol were found higher in the NSG albeit not statistically significant (p=0.308, p=0.356, p=0.915, p=0.923, p=0.884, respectively).

Correlation analyses for parameters of the DSG and NSG were done by Spearman's rho test. Strong positive correlation was found between HDL and melatonin levels (r: 0.602, p=0.001) in the NSG. In contrast, weak negative correlations were found between melatonin and insulin levels (r: -0.427, p=0.033) and between melatonin level and HOMA-IR (r: -0.420, p=0.036) in the DSG. A weak negative correlation was also observed between insulin and leptin levels in the NSG (r: -0.425, p=0.034).

Table 1: Comparison of characteristics and laboratory parameters in the day-shift and night-shift groups

Variables	Day-shift group Mean (Min.-Max.)	Night-shift group Mean (Min.-Max.)	p*
Melatonin (pg/mL)	534.11(295.39-657.54)	273.98 (202.33 - 390.29)	0.003
Leptin (ng/mL)	4.88 (2.8 - 7.31)	3.95 (1.64 - 5.8)	0.097
Ghrelin (ng/mL)	1.57 (1.08 - 3.43)	2.03 (0.9 - 4.36)	0.977
FBS (mg/dL)	86 (84 - 91)	88 (82 - 94)	0.356
Insulin (μU/mL)	8.83 (6.87 - 12.43)	10.1 (6.51 - 13.2)	0.915
HOMA-IR	2 (1.32 - 2.81)	2 (1.59 - 2.77)	0.923
Cholesterol (mg/dL)	182 (173 - 205)	193 (166 - 237)	0.884
Triglyceride (mg/dL)	88 (68 - 130)	109 (86 - 154)	0.308
HDL (mg/dL)	48 (43 - 53)	47 (37 - 58)	0.892
LDL (mg/dL)	101 (90 - 115)	117 (95 - 145)	0.084
BMI (kg/m^2)	27.89 (26.99 - 29.69)	26.81 (25.71 - 32.05)	0.985

*Mann-Whitney U test, FBS: Fasting Blood Sugar, HOMA-IR: Homeostatic Model Assessment-Insulin Resistance, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, BMI: Body Mass Index

Discussion

The metabolic syndrome (MetS) involves several metabolic abnormalities, and creates risks for wide range of disorders. Increased prevalence of MetS is a problem in developed and developing countries. Night-shift work is a reality in industrialized populations, and nearly 15% of all employees were estimated to work at nights regularly, including nurses. The effect of working style and condition on the health of nurses has been shown before [14,15]. It was established that the night-shift work makes strong tendency towards the development of MetS by disrupting circadian rhythm, but underlying mechanisms has not been elucidated yet [16]. For this; plasma melatonin, leptin, ghrelin and other relevant biochemical parameters were comparatively investigated in nurses' working day and night-shifts. These hormones were accepted as immune system regulators and the levels of them were regulated by circadian rhythm [3,17]. Our study found a significantly decreased level of plasma melatonin in the NSG. In addition, the HOMA-IR and the plasma levels of ghrelin, triglyceride, FBS, insulin, and cholesterol were increased in the NSG albeit not statistically significant (Table 1). This suggests that night-shift work is a risk factor for the MetS.

Several metabolic processes in human body, such as hormone secretion, are regulated by circadian rhythm. Although circadian rhythm is generated endogenously, it can be modulated by external factors such as the sunlight exposure and redox cycle. The most likely external factor to disrupt circadian rhythm is the contamination of night with light. The peak level of melatonin is reached under dark condition in the middle of night. The employees working at night shift are exposed to artificial light leading to melatonin deficiency in the body [5,18]. Similar to our findings, several studies found decreased levels of melatonin and urinary 6-sulfatoxymelatonin (the primary metabolite of melatonin) in night-shift workers [19]. Suppressed levels of melatonin may lead to MetS as well as cancers although the level of melatonin in response to light exposure during night varies depending on racial differences [20]. The primary mechanism in prevention of MetS by melatonin is considered to be through the antioxidant effect of melatonin. The roles of the oxidative stress in the development of MetS and the anti-oxidant effect of melatonin by direct radical scavenging or upregulating several antioxidant enzymes have been demonstrated before [5, 21]. Ulas et al. [15] have previously shown the increased levels of oxidative stress parameters in nurses working night shifts. Besides the lack of anti-oxidant effect, melatonin depletion is also associated with deterioration of various metabolic parameters such as increased triglyceride, FBS, insulin, HOMA-IR, and cholesterol levels in the MetS [22]. Although not statistically significant; triglyceride, FBS, insulin, HOMA-IR, and cholesterol levels were increased in the NSG compared with the DSG.

In a study of melatonin usage as a therapeutic agent, melatonin was given to animal models (rat, hamster) with MetS [23]. The study demonstrated a melatonin-induced protection against functional and metabolic impairment. In addition, a strong positive correlation between HDL and melatonin was found in that study, similar to the findings of the current study. The reduction in melatonin production has been linked to deficiency in insulin-signaling pathway and insulin resistance, and melatonin usage as a supplement has been recommended to protect against metabolic syndrome for the night-shift workers [24,25]. The weak negative correlations between the levels of melatonin and insulin and between the melatonin level and HOMA-IR in the DSG in our study support Cipolla Neto's proposal [25]. Solak et al. [26] previously established a relationship between leptin and insulin levels. Similarly, a weak negative correlation was observed between insulin and leptin level in the NSG in our study.

Obesity has already been defined as a risk factor for MetS [27]. It was proposed that short sleep duration and night-shift work lead to obesity [28,29]. Although, the mechanism between night-shift work and obesity has not been elucidated in detail, that the night-shift work induces more consumption of unhealthy food and associated with less energy expenditure were assumed to be main factors for obesity [30]. A recent study by Shea et al. revealed that a fluctuation in leptin level controlled by circadian rhythm may be responsible for obesity related to night-shift work [31]. Nowadays, the linkage between circadian rhythm and adipokines including leptin and ghrelin has been described [3]. Leptin and ghrelin are two main actors in energy

balance. The imbalance between them is the primary reason for obesity [32]. In our study, leptin level was decreased and ghrelin level was increased in night-shift workers albeit not significantly. These may cause more food intake by increasing appetite and thus lead to obesity in the long term. These results are in concordance with those of Taheri et al. [33] who used questionnaires, sleep diaries, and blood samples from 1024 individuals to investigate the effect of sleep duration on leptin, ghrelin, and BMI. They concluded that short or altering sleep duration elevated ghrelin levels and reduced leptin levels. This imbalance partially explained the increase in appetite after acute partial sleep deprivation [34]. Over-eating for a long period of time increases the circulating leptin levels to stop feeding. However, a sustained increase in leptin level disrupts the leptin system, and thus, hypothalamus develops a leptin resistance. This also explains why leptin level remains high in obese individuals compared with healthy individuals. Another factor accompanying the high leptin level is low-grade inflammation. Inflammation is another component of MetS, and leptin shows low-grade inflammation in contrast to melatonin [35,36]. So, obesity can make contribution to the development of MetS by formation of inflammation [37]. The metabolic syndrome is a multifactorial medical condition known as the black plague of the 21st century. Night-shift work was shown to be a risk factor for MetS formation [38]. Melatonin, leptin, and ghrelin are defined as immune system regulators and establish a linkage between metabolism and the immune system [17,39]. Melatonin-based therapeutic approaches have already been established [20,40]. However, underlying mechanisms has not been described in detail. The identification of these mechanisms and those at risk may be useful in the development of new treatment methods.

Limitations

An important limitation of our study was low sample size. This was in part due to the relatively strict exclusion criteria that we applied. We only enrolled the nurses who do not smoke, do not use any medication, have BMI>25, and do not have any metabolic disease, which narrowed down the population we can work with. Another important limitation was the enrollment of different nurses in the NSG and DSG. Studying the same group of nurses during a night-shift period and day-shift period was not possible since the nurses in this particular hospital have continuously worked day shift or night shift without switching between two shifts.

Conclusions

Our experimental data suggests that the reduction of melatonin level and impaired balance between leptin and ghrelin might contribute to the development of MetS. Melatonin system has already been targeted for therapeutic purposes; however, new therapeutic approaches targeting the melatonin, leptin, and ghrelin systems simultaneously might be developed for MetS. Further investigations are needed to describe how these agents may be used as targets in treatment of MetS.

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Shear Wave Elastography results of non-alcoholic fatty liver disease in diabetic patients

Non-alkolik yağlı karaciğer hastalığı bulunan diyabetik hastalarda Shear Wave Elastografi sonuçları

Birnur Yılmaz [1], Özgür Kürşat Şener [2], Halime Çevik [1]

[1] **Okan University Istanbul Hospital, Department of Radiology, Istanbul, Turkey**
[2] **Istanbul Oncology Hospital, Department of Radiology, Istanbul, Turkey**

ORCID ID of the authors:
BY: 0000-0001-8624-5807
ÖKŞ: 0000-0003-3800-1351
HÇ: 0000-0003-1622-7501

Abstract

Aim: To evaluate liver stiffness degree in non-alcoholic fatty liver disease with type II diabetes mellitus patients via Shear Wave Elastography (SWV) measurement. SWV elastography values were compared to degree of hepatic steatosis, liver aminotransferases, lipid profile and body-mass index.

Methods: In this case-control study, 110 patients with non-alcoholic fatty liver disease, followed by a general internal medicine outpatient clinic (57 male 53 female mean age 50.17) and a control group of 50 healthy adults (26 males 24 females mean age 48.26) without liver disease and sonographically grade 0 steatosis were admitted to the study. Right lobe of the liver parenchyma in each person was evaluated for a total of ten measurements. Sonographic grade of the hepatic steatosis in patients, SWV values and laboratory values simultaneously received were compared.

Results: SWV average speed value is calculated to be 2.26±0.57 m/s in patient group; 1.71±0.34 m/s in the control group; 2.15±0.63 m/s in patients with grade I steatosis; 2.25±0.42 m/s in patients with grade II steatosis, 2.72±0.43 m/s in patients with grade III steatosis. SWV values indicate a statistically significant difference in patient and control groups ($p<0.01$). There wasn't a statistically significant difference of liver SWV values among the three grades of steatosis.

Conclusion: Acoustic radiation force impulse can be used to detect of decreased stiffness in liver (on average 2 and over SWV values) with increase of triglycerides, aspartate aminotransferase and alanin aminotransferaz in patients.

Keywords: Liver steatosis, Acoustic radiation force impulse, Tip II diabetes mellitus

Öz

Amaç: Non-alkolik yağlı karaciğer hastalığı bulunan Tip II diyabetes mellituslu hastalarda, Shear Wave Elastography (SWV) ile karaciğer sertliği derecesini değerlendirmek amaçlandı. SWV elastografi değerleri ile hepatik steatoz derecesi, karaciğer aminotransferazları, lipit profili ve vücut kitle indeksi karşılaştırıldı.

Gereç ve Yöntemler: Bu vaka-kontrol çalışmasında, dahiliye kliniğine başvuran non-alkolik yağlı karaciğer hastalığı olan 110 hasta, (57 erkek, 53 kadın, ortalama yaş 50,17) ve kontrol grubunda karaciğer hastalığı olmayan 50 sağlıklı yetişkin (26 erkek, 24 kadın), yaş ortalaması (48,26) çalışmaya alındı. Her bireyde karaciğer parankiminin sağ lobundan toplam on ölçüm için alındı. Hastalarda hepatik steatozun sonografik derecesi, SWV değerleri ve eş zamanlı alınan laboratuvar değerleri karşılaştırıldı.

Bulgular: SWV ortalama hız değeri hasta grubunda 2,26±0,5 m/sn) olarak hesaplandı; Kontrol grubunda 1,71±0,3 m/sn; Grade I steatozu olan hastalarda 2,15±0,6 m/sn; Grade II steatozlu hastalarda 2,25±0,4 m/sn, grade III steatozlu hastalarda 2,72±0,4 m/sn. SWV değerleri hasta ve kontrol gruplarında istatistiksel olarak anlamlı bir fark olduğunu göstermektedir ($p<0,01$). Her üç grade karaciğer steatozu ile SWV değerlerinin arasında, istatistiksel olarak anlamlı bir farkı yoktu.

Sonuç: Akustik radyasyon forse impuls, kanda trigliserit, aspartat transaminaz ve alanin transaminaz artışıyla birlikte, karaciğerdeki (ortalama SWV değerleri 2 ve üzerinde ise) doku sertliğinin artışının tespitinde kullanılabilir.

Anahtar kelimeler: Karaciğer steatozu, Akustik radyasyon forse impuls, Tip II diabetes mellitus

Corresponding author / Sorumlu yazar:
Birnur Yılmaz
Address / Adres: Aydınlı Cad., No: 2, Okan Üniversitesi Hastanesi, İçmeler, Tuzla, İstanbul, Türkiye
E-mail: birnurtavasli@yahoo.com

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Introduction

In developed countries, Non-alcoholic fatty liver disease (NAFLD) is the most common diffuse liver pathology and NAFLD is related to insulin resistance and the metabolic syndrome [1,2]. The disease occurs up to 80% of obese people [3]. Non-alcoholic steatohepatitis (NASH) is the most advanced form at the NAFLD and is a major cause of cirrhosis [4]. Usually, NAFLD is detected and followed by abnormal liver function tests. NAFLD usually associated with insulin resistance and metabolic syndrome [4]. A spectrum of disease activity is being considered to cover in NAFLD. NAFLD is a spectrum of disease; it begins with fat accumulation in the liver (hepatic steatosis) without disturbance of liver function. By varying mechanisms and insults, inflammation and fibrosis is added to the fat accumulation (steatohepatitis). As disease progresses, over a 10-year period and also up to 20% of patients with NASH may develop cirrhosis of the liver, and 10% will suffer death related to liver disease [5].

Materials and methods

After approval from the Institutional Ethics Committee, and gathering written inform consent from volunteers, 110 patients with NAFLD, followed by a general internal medicine outpatient clinic (57 male 53 female mean age 50.17) and a control group of 50 healthy adults (26 males 24 females mean age 48.26) without liver disease and sonographically grade 0 steatosis were admitted to the study. Anyone having any other liver diseases (chronic alcohol abuse, cholestatic chronic hepatitis, autoimmune chronic hepatitis, Wilson's disease, HBV, HCV infection, haemochromatosis) and using any liver treatment was excluded from the study. Volunteers selected were completely healthy. Radiological evaluation in the NAFLD and the control group was carried out between November 2015 and September 2016 prospectively.

B Mode Ultrasound (US) grading of diffuse hepatic steatosis on ultrasound has been used to communicate to the clinician about the extent of fatty changes in the liver. Increase in liver echogenicity without obscuring periportal and diaphragmatic contours is graded as grade I; increased hepatic echogenicity with obscuration of periportal echogenicity and without diaphragm affected is graded as grade II, increased hepatic echogenicity with imperceptible periportal echogenicity and obscuration of diaphragm is graded as grade III. Craniocaudal length of the liver was measured midclavicular line averages 10-12.5 cm. Any liver that had a craniocaudal length longer than 15.5 cm in the midclavicular line was considered enlarged.

Acoustic Radiation Force Impulse Imaging (ARFI) measurement

The patients and control subjects underwent an ARFI examination using a commercial scanner (Siemens Acuson S3000™ 4 MHz (6C1) probe, Siemens Medical Solutions USA, Inc., Mountain View, CA, USA), which was performed by an US physician with three months of experience in ARFI elastography. The patients were examined in the left lateral decubitus position with the right arm elevated above the head. Scanning was performed with minimal scanning pressure applied by the operator; the patients were asked to stop breathing to minimize motion. The operator positioned the probe over the following region of interest: right lobe of the liver parenchyma, away from motion and vessels, including at least two times every segment at a depth between 3.0 and 4.0 cm. Ten SWV measurements were made for each person. A median value was calculated for each patient. SWV average values were obtained in all patients. Tissue stiffness was quantitatively assessed via VTQ. VTQ's were measured by detection of acoustic push pulses and measuring SWV which in increases with increasing tissue stiffness. The presence of steatosis and ratings were determined by sonographic criteria.

Laboratory tests

SWV values and laboratory values simultaneously received were compared. Routine liver function tests were performed immediately and patients with increase aminotransferases (ALT and AST) > 5 times the upper limit of normal were excluded from the further examination. Lipid profile was examined for triglycerides, very low density lipoprotein (VLDL), low density lipoprotein (LDL), and total cholesterol. We calculated body mass index (BMI) of patients and control group.

Statistical analysis

Statistical analysis was performed using SPSS 14.0 software package (SPSS Inc, Chicago, IL, USA). Data were expressed as means ± standard deviation (SD) $p< 0.05$ was considered statistically significant. The normal distribution for each variable was examined via the Kolmogorov-Smirnov test. Spearman correlation was used to reveal one to one interrelationships between SWV values and other variables. Analysis of variance (ANOVA) and Student's t-test were used for continuous variables with normal distribution. Nonparametric tests (Mann–Whitney U test and Kruskal Wallis test) were used for variables that were not normally distributed in the studied population.

Results

SWV values average speed value is calculated to be 2.26 ± 0.5 m/s in patient group (Figure 1); 1.71 ± 0.3 m/s in the control group (Figure 2) (Table 1).

Table I: SWV values in patient and control groups

	N	SWV Mean	SD
Patient	110	2.26	0.5
Control	50	1.70	0.3

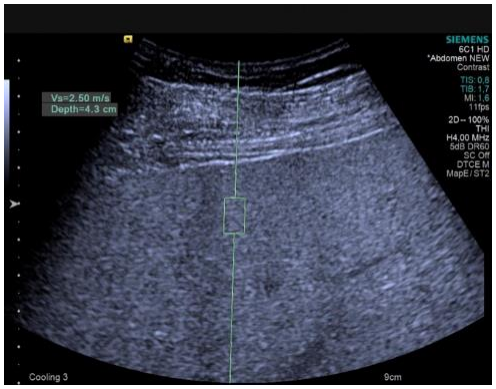

Figure 1: Image of liver stiffness measurement by ARFI in patients with hepatic steatosis (SWV: 2.50 m/s)

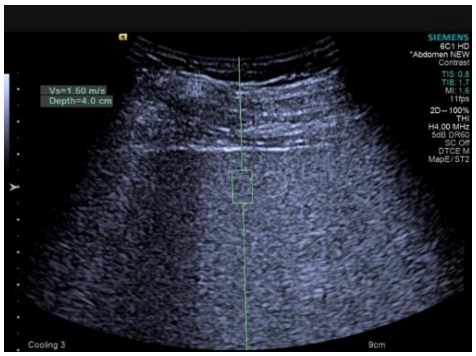

Figure 2: Image of liver stiffness measurement by ARFI in control group (SWV: 1.50 m/s)

SWV values average speed value is calculated 2.15 ± 0.6 m/s in patients with grade I steatosis; 2.25 ± 0.4 m/s in patients with grade II steatosis, 2.72 ± 0.4 m/s in patients with grade III steatosis (Table 2). SWV values indicate a statistically significant difference in patient and control groups ($p < 0.01$) (Table 3).

Table 2: Mean SMW values according to hepatic steatosis grades

Grade of liver steatosis	N	SWV Mean	Std. Deviation	Std. Error
I	43	2.15	0.6	0.06
II	54	2.25	0.4	0.08
III	13	2.72	0.4	0.12
Total	110	2.26	0.5	0.05

Table 3: SWV values in the degree grade of hepatic steatosis SWV values indicate a statistically significant difference in patient and control groups ($p < 0.01$)

SWV	Sum of Squares	df	Mean Square	F	p
Between Groups	3.492	2	1.746	5.968	0.003
Within Groups	31.304	107	0.293		
Total	34.796	109			

SWV values with statistically insignificant differences were detected between the degrees of hepatic steatosis grade. The triglyceride ($p < 0.01$), AST ($p < 0.01$), ALT ($p < 0.01$) show a significant difference between normal and pathological groups for SWV mean values. Liver craniocaudal length with increased triglycerides ($p < 0.01$), VLDL ($p < 0.01$), AST ($p < 0.01$) and ALT ($p < 0.01$) showed a statistically significant correlation with each increase in value. The triglyceride, VLDL, AST, ALT show a significant difference between normal and pathological groups for hepatomegaly liver size mean values. Similarly, the grade increases with increasing degree of liver craniocaudal length and increasing values of BMI, AST and ALT. Hence, an increase in the value of SWV indicated a statistically significant correlation. No significant difference found between normal BMI and high BMI SWV values statistically. SWV values did not show any statistically significant difference between patients with hepatomegaly and those having normal liver sizes.

Discussion

In order to avoid possible complications of liver biopsy and conventional B mode imaging may be in accurate measurement of liver stiffness, which correlates well with liver fibrosis, by ARFI elastography is a promising alternative imaging technology [6-8].

We found that ARFI elastography correlates well with significant fibrosis in NAFLD patients and is similar to results from a previous study in rats [9]. In order studies; it is reported that SWV is increased according to the degree of fibrosis observed by pathological specimens. Thus ARFI may be a better technic over other elastographic methods due to it is capability of both qualitative measurement [7,8]. As shown in previous studies presence of both steatosis and hepatic inflammation may complicate SWV measurement. Palmeri et al [10] found no relationship between SWV values and hepatocyte ballooning or inflammation while in another study decrease in SWV was reported proportional to do degree of steatosis. Based on current evidence it can be concluded that steatosis decreases SWV while with inflammation SWV values increase in NAFLD in ARFI elastography [6,11]. Some of NAFLD patients with different hepatic inflammatory activity levels shows significantly varied SWV values [1,12].

Conversely, our study demonstrated increase SWV in patients with hepatosteatosis but we didn't correlate SWV values with liver biopsy. We didn't know the extent of hepatic inflammation. This may be the cause of contradiction between previous studies and ours. These results may indicate that fibrosis started to develop in our patients.

There are several limitations in our study. First, we lack comparison with novel elastographic technologies such as Magnetic Resonance Elastography in NAFLD patients. Second, due to technical factors we are uncertain of whether our measurements failed diagnostic accuracy.

In this study we aimed only to measure stiffness of liver in NAFLD patients. Our case series is more than the other study which was planned as non-invasive.

Conclusion

The presence and severity of hepatic steatosis measured SWV values by ARFI elastography. SWV values were increased with the degree of hepatic steatosis. ARFI imaging can be used as a preliminary assessment examination with laboratory tests and at least 10 measurements, using the average value so that it may be more accurate. To detect decreased stiffness in liver (on average 2 and over SWV values) with increased of triglycerides, AST and ALT in patients ARFI can be most useful. This study shows that ARFI is a useful non-invasive tool for evaluation of decreased stiffness in liver on NAFLD.

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Relationship between atherosclerosis risks and lipoprotein-dependent phospholipase a2 activity in type 2 diabetic patients

Tip 2 diyabetli hastalarda ateroskleroz riski ile lipoprotein-bağımlı fosfolipaz a2 aktivitesi arasındaki ilişki

Durmuş Ayan [1], Ayşe Banu Çaycı Sivri [2], Seher Yüksel [2], İlhan Yetkin [3], Hakan Özdemir [4]

[1] Amasia Central Public Health Laboratory, Medical Biochemistry, Amasya, Turkey
[2] Gazi University Faculty of Medicine, Medical Biochemistry, Ankara, Turkey
[3] Gazi University Faculty of Medicine, Internal Disease, Ankara, Turkey
[4] Gazi University Faculty of Medicine, Radiology, Ankara, Turkey

ORCID ID of the authors:
DA: 0000-0003-2615-8474
ABÇS: 0000-0003-1379-5159
SY: 0000-0003-2373-7809
İY: 0000-0001-8905-3771
HÖ: 0000-0002-4458-3952

Corresponding author / Sorumlu yazar:
Durmuş Ayan
Address / Adres: Amasya Merkez Halk Sağlığı Laboratuvarı, Tıbbi Biyokimya, Amasya, Türkiye
E-mail: durmusayan@hotmail.com

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Abstract

Aim: Atherosclerosis is the most common macro-complication of diabetes and the most common cause of coronary artery disease. We aimed to investigate the relationship between the risk of atherosclerosis and lipoprotein-dependent phospholipase A2 activity in patients with type 2 diabetes.

Methods: The study was enrolled on 48 subjects: Group I: control group consisting of 20 healthy participants. Group II: 28 patients of type 2 diabetes mellitus before statin (rosuvastatin 10 mg/day) therapy. Group III: 28 patients of type 2 diabetes mellitus after statin (rosuvastatin 10 mg/day) therapy. Lp-PLA_2 activity was measured with immuno-turbidimetric method (plac test kit), HDL-C (High-Density Lipoprotein Cholesterol), LDL-C (Low-Density Lipoprotein Cholesterol), triglyceride, cholesterol and fasting blood glucose (FBG), levels were measured by spectrophotometric method using autoanalyzer (Architect C16000). LDL-C levels were measured by an assay for the direct quantification of LDL-C. Carotid intima-media thickness (IMT) was measured by B-mode ultrasonography method.

Results: Serum Lp-PLA_2 activity, serum LDL-C, triglyceride, cholesterol levels and IMT values of Group II (before 10 mg/gün rosuvastatin therapy) and Group III (after rosuvastatin therapy) patients were statistically significant higher than Group I (control group) ($p<0.01$) Serum Lp-PLA_2 activity, serum LDL-C, triglyceride, cholesterol levels and IMT values of Group II patients were statistically significant higher than Group III patients ($p<0.01$) and HDL-C levels only were lower than Group III (after 10 mg/gün rosuvastatin therapy) but It was not statistically significant ($p=0.198$).

Conclusion: According to our results, Increased Lp-PLA_2 activity is associated with risk of atherosclerosis in diabetic patients and plays an important role in the progression of atherosclerosis.

Keywords: Atherosclerosis, Diabetes, Statin therapy, Lp-PLA_2, Intima-media thickness

Öz

Amaç: Ateroskleroz diyabetik en sık makro komplikasyonudur ve koroner arter hastalığının en temel nedenidir. Çalışmamızda tip 2 diyabetli hastalarda ateroskleroz riski ile lipoprotein bağımlı fosfolipaz A_2 (Lp-PLA_2) aktivitesi arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Çalışmaya 48 kişi dahil edildi. Grup I: sağlıklı katılıcılardan oluşan kontrol grubu, Grup II: Statin (Rosuvastatin 10 mg/gün) tedavisi öncesi tip 2 diyabetli 28 hasta. Grup III: Statin (Rosuvastatin 10 mg/gün) tedavisi sonrası 28 tip 2 diyabetli hasta. Hiperlipidemisi olan diyabetik hastaların ve sağlıklı gönüllülerin serum örneklerinden, Serum Lp-PLA_2 aktivitesi immünotürbidimetrik yöntem (plac test kit) ile ve Serum HDL-C (Yüksek Dansiteli Lipoprotein Kolesterol), LDL-C (Düşük Dansiteli Lipoprotein Kolesterol), trigliserid, kolesterol ve açlık glikoz seviyeleri otoanalizör kullanılarak (Architect C16000) spektrofotometrik yöntemle ölçüldü. LDL-C ölçümü direct LDL kiti ile gerçekleştirildi. Karotis intima-media kalınlığı (IMK) B-mode ultrasonografi metodu ile ölçüldü.

Bulgular: Grup II (rosuvastatin (10 mg/gün) tedavisi öncesi) and Grup III (rosuvastatin (10 mg/gün) tedavisi sonrası) hastalarının serum Lp-PLA_2 aktivitesi, serum LDL-C, trigliserid, kolesterol düzeyleri ve IMK değerleri Grup I'e (kontrol grubu) göre istatistiksel olarak anlamlı düzeyde yüksek bulundu ($p<0,01$). Grup II'nin serum Lp-PLA2 aktivitesi, serum LDL-C, trigliserid, kolesterol düzeyleri ve IMK değerleri Grup III'e göre istatistiksel olarak anlamlı düzeyde yüksek bulunurken ($p<0,001$), serum HDL-C düzeylerinde istatistiksel olarak anlamlı bir fark elde edilemedi ($p=0,198$).

Sonuç: Sonuçlarımıza göre, artan serum Lp-PLA_2 aktivitesi diyabetik hastalarda ateroskleroz riski ile ilişkilidir ve ateroskleroz gelişiminde önemli role sahiptir.

Anahtar kelimeler: Ateroskleroz, Diyabet, Statin tedavisi, Lp-PLA_2, İntima-media kalınlığı

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Introduction

Diabetes increases the clinical risk of cardiovascular morbidity and mortality. This risk remains elevated with conventional low-density lipoprotein cholesterol (LDL-C) lowering therapies, such as statins [1]. Atherosclerosis is a major cause of coronary artery disease and most common macro complication of diabetes [2]. Atherosclerosis is a disease of the arterial wall, initiated by dyslipidemia and exacerbated by inflammation. An early event in the progression of the disease is the accumulation of LDL-C in subintima of arterial wall where it may become oxidized (oxLDL). Subclinical atherosclerosis precedes cardiovascular disease (CVD) and an increased intima-media thickness (IMT), measured by ultrasonography, and is regarded as an early indicator of generalized atherosclerosis [3]. Inflammation plays an important causal role in the initiation and progression of atherosclerosis lesion by promoting sustained plaque inflammation, large necrotic cores, thin fibrous caps, and thrombosis [4].

Lipoprotein-associated phospholipase A2 (Lp-PLA_2), known as a novel inflammatory biomarker, is involved in the pathophysiology of atherosclerosis [5]. Lp-PLA_2 is produced by monocyte, macrophage and T lymphocytes on the atherosclerotic process [6-8]. Lp-PLA_2 also is known as platelet-activating factor acetylhydrolase (AH) that carry out hydrolysis of platelet activating factor (PAF) [9,10]. Meanwhile, Lp-PLA_2 also hydrolyzes the modified phospholipids, lysophosphatidylcholine and oxidized fatty acid on the oxidized LDL-C that accumulate on the arterial wall during the atherosclerotic process [11]. Almost all prospective and nested case-cohort studies suggested that Lp-PLA_2 is proatherogenic [12]. Especially, Lp-PLA_2 enlightens about inflammation that occurs in the vascular area on the atherosclerotic process. That's why, expression of Lp-PLA_2 increase in necrotic core, rupture-prone plaque, atherosclerotic plaque. Due to these features, Lp-PLA_2 is referred to as a mediator of plaque progression [7].

Carotid atherosclerosis is a major risk factor for ischemic stroke [13,14]. While lipid metabolism and inflammation have been the major focus of atherosclerosis research for many years, there has been growing interest in Lp-PLA_2 due to it is a key enzyme both in lipid metabolism and in stimulating inflammation [15,16]. Development of the B-mode ultrasound technique has made it possible to noninvasively study the atherosclerotic process. IMT of the carotid artery has been used as a noninvasive indicator of the atherosclerotic process in the coronary arteries [17,18].

In our current study, we purposed to investigate the association between the Lp-PLA_2 activity and atherosclerosis risk in diabetic patients. Therefore we also aimed to find a possible link between lipid-lowering treatment (10 mg/day Rosuvastatin) and IMT.

Materials and methods

28 (14 male, 14 female) patients having applied to Gazi University Medical Faculty Hospital Diabetes and Obesity Clinic, between the ages of 18-65 with type-2 diabetes, diagnosed with hyperlipidemia and would receive an anti-hyperlipidemic treatment for the first time; and 20 (10 male, 10 female) healthy participants volunteering for the control group were included in this study. Carotid IMT of the patients and of the control group was measured in the same day. Then, an antihyperlipidemic treatment started to be applied to the patients by the Department of Obesity and Diabetes in Gazi University (standard 10 mg/day Rosuvastatin). Following the 3-month-Rosuvastatin treatment, the patients were recalled to the clinic. Carotid intima-media thickness was measured the same day in addition to routine examinations. While determining the groups, the control group was classified as Group I; patients before the Rosuvastatin treatment as Group II; and patients after the rosuvastatin treatment as Group III. Group II and Group III were two dependent groups having the same patients. They were named differently in order to indicate that they represent the results at different times and to compare these results. Following 10-12 hours fasting of the patients and of the control group, venous blood was taken and centrifuged at 4000 rpm for 10 minutes. After completing routine biochemistry tests, the venous blood was stored at -80^0 until the day of study. Patients were informed regarding the study and consent forms were signed. In addition, this study was approved by the Ethics Committee of Gazi University Medical Faculty. This study was funded by Gazi University Scientific Research Projects (SRP) unit (Project No: 01/2009-04).

While determining the patients to be included in the study; those who previously received an antihyperlipidemic treatment, those using drugs affecting lipid metabolism, those who had cardiovascular disease, cigarette and alcohol users, those having BMI>30, those who had an infection recently and those who disrupted the antihyperlipidemic treatment were excluded from the study. Moreover, the control group was entirely composed of healthy volunteers not using alcohol and cigarette, not taking any medication and not having any previous cardiovascular medical record. All participants were informed about the study and the consent forms were received.

Lp-PLA_2 measurement and routine biochemistry tests

Lp-PLA_2 activity was measured in serum samples with the PLAC Test (diaDexus Inc) reagent kit on Olympus AU 400 clinical chemistry analyzer. The PLAC test is a turbidimetric immunoassay using two highly specific monoclonal antibodies (2C10 and 4B4) against Lp-PLA_2. Lp-PLA_2 concentrations were given as ng/ml. Clinical and analytical sensitivities of the assay are 7 ng/ml and 4 ng/ml respectively. Reference intervals suggested by the reagent manufacturer are 120-342 ng/ml for females and 131-376 ng/ml for males. HDL-C (High-Density Lipoprotein Cholesterol), LDL-C (Low-Density Lipoprotein Cholesterol), triglyceride, cholesterol and fasting blood glucose (FBG), levels were measured by spectrophotometric method using autoanalyzer (Architect C16000). LDL-C levels were measured by an assay for the direct quantification of LDL-C.

Carotid ultrasonography

All participants were examined in the supine position (head turned 45°) by the same trained operator with a high-resolution B-mode ultrasonography equipped with a 10 MHz linear array transducer (GE LOGIQ 9). In our study, IMT values of right and left carotid arteries were measured by ultrasonography and then, measured values were divided into

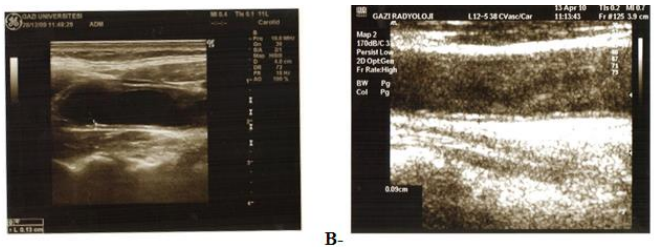
two average values were found and recorded by IMT value. IMT>0.9 mm values were considered to be pathological.

Statistical analysis

SPSS 15.0 for Windows program was used for the statistical analysis. Descriptive statistics were expressed as numbers and percentages for categorical variables; and as means, standard deviation, minimum, maximum and median for numeric variables. Normal distribution was determined by examining the distribution of skewness and kurtosis values, Kolmogorov-Smirnov (Lilliefors Significance Correction), Shapiro-Wilk tests and histogram graphs. Comparison of two independent groups not fulfilling the normal distribution requirement for numeric variables was performed by "Mann Whitney U" test; and the comparison of two dependent groups not fulfilling the normal distribution requirement was performed by Wilcoxon test. Statistical alpha significance level will be accepted as $p<0.05$. Due to the fact that the relations between numerical values did not meet parametric test requirement, it was examined by Spearman Correlation Analysis.

Results

Overall, the median age for the patients (n=28 (50% female, 50% male)) was 52.17 (39, 63) years and the median age for the control group (n=20 (50% female, 50% male)) was 48.02 (37-60) years. The baseline characteristics of all groups are shown in Table 1. The Lp-PLA2 activity levels were significantly higher in Group II than in Group III who receiving statin therapy (rosuvastatin 10 mg/day) ($p<0.01$). Moreover, the serum LDL-C, triglyceride and cholesterol levels were significantly higher in Group II than in Group III ($p<0.01$). Serum HDL-C levels were higher in Group III than Group II. However, it was not significant ($p<0.01$). IMT values were significantly lower in Group III than Group II ($p<0.01$). Pre and post-therapy results of IMT values which belong to a study patient were shown in Figure 1. According to the correlation results of Group II, exclusively, Lp-PLA2 activity was negatively correlated with HDL-C in Group II (r: -0.452, $p=0.016$). Lp-PLA_2 activity was not significantly correlated with LDL-C, triglyceride, cholesterol, IMT, FBG, BMI and age in Group II ($p>0.05$). According to the correlation results of Group III, Lp-PLA_2 activity was not significantly correlated with HDL-C, LDL-C, triglyceride, cholesterol, IMT, FBG, BMI and age in Group III ($p>0.05$). The correlation results of Group II and Group III are shown in Table 2.



A- B-

Figure 1: IMT (mm) measurement before statin (rosuvastatin 10 mg/dose) treatment (IMT: 1.13 mm (0.13 cm)) (A). IMT measurement after statin (rosuvastatin 10 mg/dose) treatment (IMT: 0.9 mm) (B) (*patient carotis IMT (mm) measurement from our study)

Table 1: Median and IQR values of all groups

Variable	Group I (n=20)		Group II (n=28)		Group III (n=28)	
	Median	IQR	Median	IQR	Median	IQR
Age (year)	48.02	37-60	52.17	39-63	52.17	39-63
Lp-PLA_2 activity (ng/ml)	172.4	44-293	304.9 [a]	171-553	213.6 [a,b]	91.7-500.7
Fasting glucose (mg/dl)	85.5	60-97	161 [a]	95-322	136 [a,b]	79-262
Total cholesterol (mg/dl)	163.5	115-220	225.5 [a]	148-332	200.5 [a,b]	100-293
Triglycerides (mg/dl)	99.5	35-237	168.5 [a]	79-376	146 [a,b]	55-464
HDL-C (mg/dl)	47.5	35-60	42	32-65	168.5	30-70
LDL-C (mg/dl)	89.5	52-124	137 [a]	73-235	119.5 [a,b]	45-211
Baseline maximal IMT (mm)	0.65	0.5-0.9	0.85 [a]	0,5-1.35	0.72 [a,b]	0.6-1.15
Body mass index (kg/m^2)	24.5	18-27	28 [a]	22-45	26.5 [a,b]	19-39

Abbreviations: Lp-PLA_2: Lipoprotein-associated phospholipase A_2, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, IMT: intima-media thickness, IQR: interquartile range, Group I (control), Group II (before rosuvastatin therapy), Group III (after rosuvastatin therapy), a: $p<0.01$ vs control (p values obtained Man-Whitney U test), b: $p<0.01$ vs Group II (p values obtained Wilcoxon test)

Table 2: Correlations between the Lp-PLA_2 activity and cardiovascular risk factors and carotid IMT values

Variable	Group II (n=28)		Group III (n=28)	
	r	p	r	p
Age (year)	0.127	0.518	0.290	0.135
Fasting glucose (mg/dl)	-0.044	0.823	0.090	0.648
Total cholesterol (mg/dl)	0.094	0.634	-0.213	0.275
Triglycerides (mg/dl)	0.162	0.412	-0.004	0.986
HDL-C (mg/dl)	-0.452	0.016*	-0.185	0.345
LDL-C (mg/dl)	0.263	0.177	-0.163	0.406
Baseline maximal IMT (mm)	-0.009	0.966	0.025	0.901
Body mass index (kg/m^2)	0.415	0.463	-0.141	0.474

Abbreviations: Lp-PLA_2: Lipoprotein-associated phospholipase A_2, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, IMT: intima-media thickness, r: Spearman's correlation coefficient, $p<0.05$*, $p<0.01$**

Discussion

In this study, we discussed whether Lp-PLA_2 enzyme activity, as an indicator of potential cardiovascular disease risk, has relevance with atherosclerosis being one of the major complications of diabetes. In the pre-treatment group (Group II) Lp-PLA_2 levels were significantly higher than the healthy volunteer control group (Group I) ($p<0.01$) and post-treatment group (Group III) ($p<0.01$). Furthermore, the IMT values of patients before the rosuvastatin treatment were significantly lower than the post-treatment IMT values ($p<0.01$). According to the acquired results, serum Lp-PLA_2 levels were associated with the risk of atherosclerosis progress especially in diabetic patients.

Our first finding concerning the relation between Lp-PLA_2 and the risk/progress of atherosclerosis is supported by the fact that carotid IMT values of the patients having increased Serum Lp-PLA_2 levels are high. The fact that diabetic patients' cholesterol and LDL-C levels are as high as to pose a risk for coronary artery diseases may lead to high serum Lp-PLA_2 levels and increased carotid IMT values. 80% of Lp-PLA_2 is dependent upon LDL-C; and the remaining 20% is dependent upon HDL-C. Along with dyslipidemia in diabetic patients, LpPLA_2-LDL-C levels increase and Lp-PLA_2-HDL-C levels decrease [19]. Lp-PLA_2-LDL-C levels decrease and they are rearranged with statin therapy. Lp-PLA_2-HDL-C levels are not affected by statin therapy [20]. The second finding of our study was that the diabetic patients who developed dyslipidemia had a statistically significant decrease in serum LDL-C, Lp-PLA_2 levels and in IMT values; and no statistically difference in serum HDL-C levels was found after 3 months of regular rosuvastatin treatment. These findings confirm the information given above.

Previous studies have revealed that there was a relation between Lp-PLA_2 and atherosclerosis. Okamura et al. [21] suggested that even the Lp-PLA_2 having an important function in

atherogenesis, its association with HDL-C plays the opposite role, as observed by high LDL-C-Lp-PLA_2 to the HDL-C-Lp-PLA_2 ratio in patients with atrial fibrillation. Allison et al. [22] demonstrated that an increment of one standard deviation in Lp-PLA_2 activity was associated with a higher risk of CVD in five years, however, not with mortality. Accordingly, Sabatine et al. [23] observed that an elevated level of Lp-PLA_2 is a predictor of adverse cardiovascular outcomes, independently of the traditional clinical risk factors in patients with stable coronary artery disease. Persson et al. [24] observed that this enzyme was strongly correlated with lipid fractions and the degree of carotid artery atherosclerosis; this study showed that the association with cardiovascular risk is stronger for activity than for mass, reinforcing the impact of activity in atherogenesis [24]. Lp-PLA_2, known as a novel inflammatory biomarker, is involved in the pathophysiology of atherosclerosis [5]. Lp-PLA_2 plays a role as a novel predictor of cardiovascular risk in a population at high risk for future CVD events [25-29]. In the study by Liu et al. examining the relation between subclinical atherosclerosis progress and Lp-PLA_2 activity, the carotid plaque status was determined by measuring the IMT thickness, and it was concluded that IMT and carotid plaque progress were significantly related to the increased Lp-PLA_2 activity. It was also reported that Lp-PLA_2 was a useful indicator for early prevention of cardiovascular diseases [30]. The results specified below were consistent with our findings.

However, Blake et al. [31] did not find any relevance between potential cardiovascular risks and Lp-PLA_2 contrary to our findings. Furthermore, it was reported by O'Donogheu et al. [33] that Lp-PLA_2 was not useful for risk classification following an acute coronary syndrome. It was reported that serum Lp-PLA_2 levels significantly decreased following the high-dose statin therapy and these levels may be associated with cardiovascular events independently of LDL-C.

Regarding that Lp-PLA_2 is associated with cholesterol and oxidized lipids in LDL-C and HDL-C, it is probable that drugs and environmental factors, capable of modulating the lipid metabolism, may change the mass and the activity of this enzyme. Schaefer et al. [32] compared the effect of atorvastatin with placebo in coronary heart disease patients, and observed a reduction of Lp-PLA_2 under therapy. In this way, O`Donoghue et al. [33] found that an intensive statin therapy was responsible for 20% of reduction in LDL-C-Lp-PLA_2, in average, the report by Saougos et al [34] the report by Joseph et al. [35], the report by White et al. [36].

Statin therapy is the first-stage therapy for the regulation of lipid profile for high-risk groups; but for patients with diabetic dyslipidemia, treatment with a single statin may not be effective enough on LDL-C. LDL-C and Lp-PLA_2 levels in patients who received statin therapy (10 mg Ezetimibe / 20 mg simvastatin, double dose 40 mg simvastatin or 20 mg atorvastatin and 10 mg rosuvastatin) at different doses for 6 months were examined by Le et al. Moreover, it has been found that 10 mg Ezetimibe / 20 mg Simvastatin treatment provides statistically more reduction in LDL-C and Lp-PLA_2 levels compared to other treatment options [37]. In another study conducted by Lee et al., the effect of the combination of 20 mg atorvastatin monotherapy and low dose 5 mg atorvastatin / 5 mg ezetimibe on LDL-C and Lp-PLA_2 activity was examined. While LDL-C levels decreased at similar rates with both treatments, it was concluded that Lp-PLA_2 levels decreased more effectively with 20 mg/day atorvastatin monotherapy [38]. Rosuvastatin (10 mg/day) monotherapy known to be more effective than atorvastatin treatment in decreasing HDL-C levels is almost as effective as atorvastatin in decreasing LDL-C [39] and causing [40] less rhabdomyolysis than other statin group drugs was administered for 3 months. A statistically significant decrease was found in serum LDL-C, Lp-PLA_2 and IMT levels ($p < 0.01$). However, no statistically significant increase was found in HDL-C levels ($p = 0.198$).

Limitation of the study

Although the research has reached its aim, there are some unavoidable limitations, First of all, to generalize the result for larger groups, the study should have involved more participants according to gender and different age ranges. Second, due to the lack of previous studies in the research area, the adequate comparison in discussion section was not achieved. Therefore, more regional researches which belong to the Turkish population should be done.

Conclusions

In our study, patients with type 2 diabetes (n=28) were treated with 10mg/gün Rosuvastatin monotherapy during the three months and at the same time, IMK values were measured in after and before treatment. According to our results, serum Lp-PLA_2 activity, serum LDL-C, triglyceride, cholesterol levels and IMT values of Group II (before rosuvastatin therapy) patients were statistically significantly higher than Group III (after rosuvastatin therapy) patients and HDL-C levels only were lower than Group III (after rosuvastatin therapy) however, It was not statistically significant (p=0.198). According to our results, Increased Lp-PLA_2 activity is associated with risk of atherosclerosis in diabetic patients and plays an important role in the progression of atherosclerosis.

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An evaluation of the effect on depression and anxiety levels of the frequency of providing informing to the relatives of patients treated in intensive care unit

Yoğun bakım ünitesinde tedavi gören hastaların yakınlarının bilgilendirilme sıklığının depresyon ve anksiyete düzeylerine etkisinin değerlendirilmesi

Çiğdem Ünal Kantekin [1], Arzu Esen Tekeli [2], Özgül Karaaslan [3],Gamze Talih [1],Yunus Hacımusalar [3]

[1] Department of Anesthesiology, Bozok University, School of Medicine, Yozgat, Turkey
[2] Department of Anesthesiology, Yüzüncü Yıl University, School of Medicine, Van, Turkey
[3] Department of Psychiatry, Bozok University, School of Medicine, Yozgat, Turkey

ORCID ID of the authors:
ÇK: 0000-0001-6758-7764
AET: 0000-0002-6525-7267
ÖK: 0000-0003-0829-5088
GT: 0000-0003-4743-9734
YH: 0000-0002-1777-2707

Abstract

Aim: Treatment in the Intensive Care Unit (ICU) is a stressful experience, not only for the patient but also for their family. The aim of the study was to investigate the effects on anxiety and depression levels of the relatives of patients in ICU who were given information once a day or three times a day by the same physician.

Methods: In this cross sectional study the relatives of the patients hospitalized in the ICU of two university hospitals were randomly separated into two groups. Group 1 comprised 50 individuals closely related to patients in the ICU and they were given information about the patient once a day. Group 2 comprised 49 individuals closely related to patients in ICU and they were given information 3 times a day at 4-hour intervals. After 7 days, all the participants in Groups 1 and 2 completed the Beck Depression Inventory (BDI) and the Penn State Worry Questionnaire (PSWQ).

Results: The BDI points of Group 1 were determined to be statistically significantly higher than those of Group 2 ($p<0.01$). The PSWQ points of Group 1 were determined to be statistically significantly higher than those of Group 2 ($p<0.023$).

Conclusion: By providing information to the relatives of patients 3 times a day rather than once a day created confidence that the patient was being well cared for, involvement with physician in the decision-making process and the feeling that the physician could be reached, thereby strengthening the physician- family relationship. This leads to lower rates of anxiety and depression.

Keywords: Intensive care unit, Relatives of patients, Depression, Anxiety

Öz

Amaç: Yoğun bakım ünitesi (YBÜ)'nde tedavi görmek sadece hastalar için değil aynı zamanda hastaların aileleri için oldukça stresli bir deneyimdir. Bu çalışma ile hasta yakınlarının aynı hekim tarafından günde bir defa bilgilendirilmesi ile günde üç defa bilgilendirilmesinin endişe ve depresyon düzeyleri üzerine etkisini araştırmayı amaçladık.

Yöntemler: Bu kesitsel çalışmada iki üniversite hastanesinin YBÜ'lerinde yatan hasta yakınları randomize olarak iki gruba ayrılmıştır. Birinci gruptaki 50 hasta yakınına günde bir defa bilgi verilirken ikinci gruptaki 49 hasta yakınına 4 saat ara ile günde 3 defa bilgi verilmiştir. 7. Günün sonunda aynı hasta yakınlarından Beck depresyon ölçeği (BDÖ) ve Penn state endişe ölçeği (PSEÖ) doldurmaları istenmiştir.

Bulgular: Günde bir defa bilgilendirilen hasta yakınlarının BDÖ puanları günde 3 defa bilgilendirilen gruba göre anlamlı derecede yüksekti ($p<0,01$). Günde bir defa bilgilendirilen hasta yakınlarının PSEÖ puanları günde 3 defa bilgilendirilen gruba göre anlamlı derecede yüksekti ($p=0,023$).

Sonuç: Hasta yakınlarına günde bir defa bilgi vermek yerine üç defa bilgi vermek hasta yakını-hekim güven ilişkisini güçlendirerek, hasta yakınlarının hastaya iyi bakıldığından emin olmalarına, hekimin ulaşılabilir olduğunu hissetmelerine neden olmaktadır. Hekimle hasta yakını ilişkisinin güçlenmesi kaygı ve depresyon oranlarının daha düşük olmasını sağlamaktadır.

Anahtar kelimeler: Yoğun bakım ünitesi, Hasta yakını, Depresyon, Anksiyete

Corresponding author / Sorumlu yazar:
Çiğdem Ünal Kantekin
Address / Adres: Bozok Üniversitesi, Tıp Fakültesi, Anesteziyoloji Anabilim Dalı, Adnan Menderes Bulvarı, No: 44, Yozgat, Türkiye
E-mail: drcgdm@hotmail.com

Ethics Committee Approval: Bozok University Clinical Ethics Committee, 2017-KAEK-189-2018.04.24_04.
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Introduction

Treatment in the Intensive Care Unit (ICU) is a stressful experience, not only for the patient but also for their family. A severe life-threatening situation for the patient can cause negative effects on the family. Assurance that the treatment administered to the patient in ICU is sufficient is one of the most important factors in reducing the concerns of relatives. There are studies in literature that have measured emotional, somatic, cognitive and motivation-based symptoms of relatives in depression or that have evaluated how they feel at a specific time or in a specific condition independently of the situation in which they are in [1,2]. However, to the best of our knowledge, there has been no study that has examined the effect on anxiety and depression of the frequency of giving information. While there is a previous study that has reported no statistically significant relationship between the anxiety of relatives and the support given in terms of information about the patient, another study emphasized that lack of information was the primary cause of anxiety [1,3]. It has also been reported that the most important needs of family members were to receive sufficient information and to feel that the hospital staff were interested in the patient [4].

Anxiety and depression scales can be used to determine the specific needs of the patient's relatives and to observe changes in the emotional state of the relatives. The Beck Depression Inventory (BDI) is a self-reporting scale formed from the data obtained from clinical observations not based on a specific institution, which measures emotional, somatic, cognitive and motivation-based symptoms in depression. The Penn State Worry Questionnaire (PSWQ) was developed in 1990 as a scale to evaluate the general tendency to pathological anxiety.

The aim of the current study was to investigate the effects on anxiety and depression levels of the relatives of patients in ICU who were given information once a day or three times a day by the same physician.

Materials and methods

Approval for this cross sectional study was granted by the Local Ethics Committee (Local ethics committee approval number: 2017-KAEK-189-2018.04.25-04).The relatives of patients hospitalized in the ICU of two university hospitals were randomly separated into two groups. Group 1 comprised 50 individuals closely related to patients in the ICU and they were given information about the patient once a day, which was the normal practice in both university hospitals. Group 2 comprised 49 individuals closely related to patients in ICU and they were given information 3 times a day at 4-hour intervals. After 7 days, all the participants in Groups 1 and 2 completed the BDI and PSWQ. The scales were evaluated by a psychiatrist blinded to the study. Exclusion criteria were length of stay in ICU <7 days, alcohol or substance abuse, cognitive impairment, a known psychiatric disease, the use of any psychotropic drug with anxiolytic or antidepressant properties for any reason other than psychiatric disease, or refusal to participate in the study. The scales were completed by the relatives while the patient was alive, and in cases where the patient got dead in ICU, those relatives were not included in the study.

Statistical analysis

Statistical analyses of the study data were performed using SPSS v22.0 software (Statistical Package for the Social Sciences, IBM Inc., Chicago, IL, USA). The sociodemographic data were evaluated with descriptive statistical methods. The distribution of the groups was assessed using the Kolmogorov-Smirnov test. In the comparison between two independent groups of quantitative variables with normal distribution, the t-test was used, and for variables not showing normal distribution, the Mann Whitney U-test was applied. A value of $p<0.05$ was accepted as statistically significant.

Results

The 50 participants in Group 1 who were given information once a day comprised 28 (56%) females and 22 (44%) males with a mean age of 39.60±9.9 years, and education level of university in 16 (32%) cases, high school in 22 (44%) and middle school in 12 (24%).

The 49 participants in Group 2 who were given information three times a day comprised 26 (53%) females and 23 (47%) males with a mean age of 41.60±5.91 years, and education level of university in 14 (28.5%) cases, high school in 21 (42.8%) and middle school in 14 (28.5%) (Table 1). The BDI points of Group 1 were determined to be statistically significantly higher than those of Group 2 ($p<0.01$). The PSWQ points of Group 1 were determined to be statistically significantly higher than those of Group 2 ($p<0.023$) (Table 2).

Table 1: Sociodemographic Data of the Relatives of Patients

	Group 1 information given once a day (n=50)	Group 2 information given 3 times a day (n=49)
Age(years) (mean±SD)	39.60±9.91	41.60±5.91
Gender Female	28 (56%)	26 (53%)
Male	22 (44%)	23 (46.9%)
Level of Education	University 16 (32%)	University 14 (28.5%)
	High school 22 (44%)	High school 21 (42.8%)
	Middle school 12 (24%)	Middle school 14 (28.5%)

n: number of cases, SD: standard deviation

Table 2: Beck Depression Inventory Points and Penn State Worry Questionnaire

	Group 1 information given once a day (n=50) Median (min- max)	Group 2 information given 3 times a day (n=49) Median (min- max)	u	p
Beck Depression Inventory	23 (11-63)	12 (2-35)	277	<0.01
	mean±SD	mean±SD	t	p
Penn State Worrry Questionnaire	43.32±10.48	37.92±12.71	2.309	0.023

n: number of cases, SD: standard deviation, min: minimum, max: maximum

Discussion

In almost all countries, ICU are units with defined visiting times, with their own internal rules, and the ICU personnel on one side and relatives of the patient on the other side [5]. To see a family member in ICU because of a life-threatening disease, who is unconscious and cannot communicate, can increase levels of anxiety and depression in relatives of the patient. When a family member is admitted to ICU, relatives experience emotions such as shock, uncertainty, denial, anger, hopelessness, hope, guilt, worry and fear which create emotional, cognitive and social stress [6,7]. The most important factor causing this is the possibility of losing a family

member. Appleyard et al reported that the most significant cause of worry for the family is not having confidence in the care given to the patient [1]. Chaitin et al. [8] emphasized that for the satisfaction of the relatives of the patient, the most important factors were the physician's interest in the patient, not giving conflicting information, allocating sufficient time to give information, the accessibility of the ICU team, providing continuous care, effective listening to the patient and their family, and providing emotional support in the decision-making process. In the current study, that the anxiety and depression rates of the group who were given information 3 times a day were low can be considered to be associated with confidence that the doctor was interested in the patient, knowing that the physician could be reached and decreasing the feeling of uncertainty about the medical status of the patient with frequent information.

In a study by Lautrette et al. [9], with meetings of family members of patients lost in ICU and providing informative brochures, the incidence of anxiety, depression and post-traumatic stress disorder in family members was seen to decrease dramatically. In the current study, the relatives of patients who were lost in ICU were not included in the study. However, despite the continuation of a critical disease status, the anxiety and depression points of the group given more information were significantly low.

In a prospective study by Myhren et al. [10], the relatives of patients were seen to be highly satisfied in respect of communication, but the satisfaction of communication with doctors was determined to be at a significantly lower level than the satisfaction of communication with nurses. The reason for this is that under daily working conditions, the relatives of the patients encounter nurses more often and can establish direct communication. In the current study, the physicians meeting the relatives at least 3 times a day rather than once a day was seen to have positive effects on their emotional status.

There are several studies in literature that have investigated the requirements of the relatives of patients in ICU. These studies have reported the most important requirements to be the receipt of sufficient information and to feel that the ICU personnel are interested in the patient [11]. In the current study, the low rates of anxiety and depression in the group given information 3 times a day could be due to assurance that sufficient interest was being taken in the patient because they were given sufficient information.

This study have some limitations as having been used self-report scale in the evaluation of the patients, not having been used structured psychiatric interview, having been designed as cross sectional study and not having known the anxiety and depression levels of the patients' relatives before our study period.

In conclusion, the results of this study showed that by providing information to the relatives of patients 3 times a day rather than once a day created confidence that the patient was being well cared for, involvement with physician in the decision-making process and the feeling that the physician could be reached, thereby strengthening the physician-family relationship. As the relatives of the patient feel emotionally better with the strengthening of the physician-family relationship, this leads to lower rates of anxiety and depression.

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Research article
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Effects of high-dose tranexamic acid in total hip replacement: A prospective, double-blind, randomized controlled study

Total kalça protez ameliyatlarında yüksek doz traneksamik asitin etkileri: Prospektif, çift-kör, randomize kontrollü çalışma

Seher Orbay Yaşlı [1], Zeynep Tosun [2], Mehmet Halıcı [3], Selda Kahraman Kayaaltı [4]

[1] Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Erciyes University, Kayseri, Turkey
[2] Department of Anesthesiology and Reanimation, Erciyes University Faculty of Medicine, Kayseri, Turkey
[3] Department of Orthopedics and Traumatology, Erciyes University Faculty of Medicine, Kayseri, Turkey
[4] Division of Anesthesiology, Develi State Hospital, Kayseri, Turkey

ORCID ID of the authors
SOY: 0000-0001-5163-3893
ZT: 0000-0001-5441-4303
MH: 0000-0003-0372-6360
SKK: 0000-0002-8176-0188

Corresponding author / Sorumlu yazar:
Seher Orbay Yaşlı
Address / Adres: Erciyes Üniversitesi, Diş Hekimliği Fakültesi, Ağız Diş Çene Hastalıkları Anabilim Dalı, Kayseri, Türkiye
E-mail: syasli@erciyes.edu.tr

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Abstract

Aim: Different studies support the use of tranexamic acid (TA) to decrease the rate of transfusions in total hip replacement. This study aimed to investigate the effects of high-dose TA in total hip replacement.

Methods: Sixty American Society of Anesthesiologist (ASA) class I-III 60 adult patients were randomly assigned into 2 groups as group TA and group control (C) for this study. While, TA was administered at dose of 50 mg/kg to group TA, the group C received 100 cc normal saline (NS). In all subjects, blood samples were taken pre-surgery and 24 hours after the operation in order to study hemoglobin (Hgb), hematocrit (Hct), platelet count, prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, D-dimer, blood urea nitrogen (BUN), creatinine, and cystatin-c. The amount of intraoperative bleeding and number of given packed of red blood cell (PRBCs) were recorded.

Results: The amount of blood loss and number of PRBCs given were significantly lower, and Hgb values at discharge were significantly higher in group TA compared with group C. In group TA postoperative cystatin-c levels, compared with the preoperative period, were significantly low. The length of hospital stay was significantly short in group TA.

Conclusion: TA was given intravenously before incision reduces intraoperative blood loss and the use of PRBCs in total hip replacement. This approach also provided higher Hgb values at discharge. The provision of TA shortened length of hospital stay and did not negatively affect renal function.

Keywords: Tranexamic acid, Total hip replacement, Blood transfusion

Öz

Amaç: Farklı çalışmalar total kalça protezi ameliyatlarında transfüzyon oranını azaltmak için traneksamik asit (TA) kullanımını desteklemektedir. Bu çalışmada total kalça protezi ameliyatında yüksek doz TA'nın etkilerinin araştırılması amaçlanmıştır.

Yöntemler: Bu çalışma için American Society of Anesthesiologist (ASA) sınıf I-III 60 yetişkin hasta, grup TA ve grup kontrol (C) olarak 2 gruba ayrıldı. TA grubuna 50 mg / kg'dan traneksamik asit, kontrol grubu (C grubu) hastalarına ise 100 cc normal salin (NS) uygulandı. Tüm olgularda hemoglobin (Hgb), hematocrit (Hct), trombosit sayısı, protrombin zamanı (PT), parsiyel tromboplastin zamanı(PTT), fibrinojen, D-dimer, kan üre azotu (BUN), kreatinin ve sistatin-c değerlerinin çalışılması için hastalardan operasyondan 24 saat önce ve sonra kan örnekleri alındı. İntraoperatif kanama miktarları, transfüze edilen eritrosit süspansiyonu (PRBC) sayısı kaydedildi.

Bulgular: Grup TA'da kan kaybı miktarı verilmiş olan eritrosit süspansiyonu sayısı grup C'ye göre istatistiksel olarak anlamlı düşük bulundu. Taburculuktaki hemoglobin değerleri grup TA'da grup C'ye göre istatistiksel olarak anlamlı yüksek bulundu. TA grubunun postoperatif sistatin-c değerleri preoperatif periyottaki değerlerinden istatistiksel olarak anlamlı düşük bulundu. TA grubunun hastanede kalış süreleri istatistiksel anlamlı olarak düşük bulundu.

Sonuç: Total kalça protezi ameliyatlarında insizyondan önce uygulanan 50 mg/kg traneksamik asit intraoperatif kan kaybı miktarını ve verilen eritrosit süspansiyon sayısını azaltır. Aynı zamanda bu yaklaşımla taburculukta daha yüksek hemoglobin değerleri sağlanır. Bu prosedür böbrek fonksiyonlarını etkilemediği gibi hastanede kalış sürelerinin de kısalmasına neden olur.

Anahtar kelimeler: Traneksamik asit, Total kalça protezi, Kan transfüzyonu

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Introduction

Total hip replacement (THR) is associated with a significant amount of blood loss, often requiring allogenic blood transfusions. Our current population is aging; more and more people are living longer and maintaining active lifestyles, leading to more patients undergoing THR. With the anticipated increase in THR surgery, a strain will be placed on the already limited supply of allogenic blood. Moreover, allogenic blood transfusions are not risk-free. Patients can receive blood-borne pathogens, sustain immunologic reactions, become coagulopathic, be overtransfused, and become volume overloaded. One of the ways to decrease these complications is the use of antifibrinolytic agents. Recent studies showed that therapy with aggressive crystalloid infusion and the use of packed red blood cells (PRBCs) early in resuscitation induced early coagulopathy and increased bleeding [1,2].

Antifibrinolytic drugs are used to provide hemostasis, decrease bleeding, and allogenic blood transfusions. Tranexamic acid (TA) exerts its antifibrinolytic effect by blocking lysine binding sites on plasminogen molecules and thereby inhibiting the interaction of plasminogen and the heavy chain of plasmin with lysine residues on the surface of fibrin. Although plasmin can still be formed under these circumstances, it is unable to bind to and degrade fibrin. Suppression of fibrinolysis by tranexamic acid is manifested in surgical patients by reductions in blood levels of D-dimer, but the drug has no effect on blood coagulation parameters [3].

The effectiveness of antifibrinolytic drugs has been investigated in cardiovascular, hepatic, orthopedic, and many other operations. TA has been shown to decrease bleeding for some specific orthopedic procedures [4,5]. High-dose TA administration is often used in cardiovascular surgery. We thought that high-dose administration of TA for THR could be effective on both intraoperative blood loss and the need for intraoperative and postoperative PRBCs.

Materials and methods

The study protocol was approved by the Medical Ethics Committee of Erciyes University Hospital. Written, informed consent was obtained from the patients.

We investigated 60 patients who were American Society of Anesthesiologist (ASA) physical status I to III, aged between 18 and 75 years, and were scheduled to undergo primary THR with combined spinal-epidural anesthesia.

The indications for surgery were primary osteoarthritis (n=51), femoral neck fracture (n=4), and rheumatoid arthritis (n=5). All patients' hips were replaced by a cemented prosthesis using the posterior approach. A subfascial drain was used in all patients and removed 24 hours later.

We performed the study as randomized, double-blind and placebo controlled; accordingly, the patients were assigned into two groups. The patients were assigned as TA group and control (C) group using the coin toss method. The TA group (n=30) received a total dose of 50 mg/kg TA (Transamine® %10 ampule) mixed in normal saline (NS); total volume of 100 ml via infusion, which started 15 minutes prior to the skin incision and took a total time of 30 minutes, meaning that it continued during part of the surgery. Group C (n=30) received NS in place of TA in the same manner and the same volume.

Patients were excluded if they had a history of drug sensitivity; coagulopathy; thrombocytopenia; hepatic or renal failure; deep vein thrombosis (DVT) or embolism; severe aortic or mitral valve stenosis; neurologic or cerebrovascular disease; if they had received aspirin or platelet antiaggregant treatment in the week before surgery, or nonsteroidal anti-inflammatory agents in the 2 days before surgery. Patients were also excluded if their preoperative plasma creatinine was greater than 130 μmol litre-1; they had a history of myocardial infarction or chronic arteriopathy; had unstable angina in the previous 12 months; or their mental states prevented them from understanding the study proposal. Eligible patients were informed of the objectives and procedure of the study and were required to give written informed consent before being enrolled.

The patients received no premedication on the day of the procedure. Demographic information and ASA status were recorded preoperatively for all patients. Monitoring included electrocardiography, pulse oximetry, noninvasive blood pressure, respiratory rate, and urine output through a Foley catheter.

After the patients were placed sitting position or in the lateral decubitis position, a lumbar epidural catheter was inserted in the L3-L4 or L4-L5 interspaces and combined spinal-epidural anesthesia was performed. Bupivacaine 0.5% was used for the spinal injection. The TA and NS solutions for all patients were prepared by the same anesthesia technician and administered by the same anesthesiologist. The duration of surgery, hospital length of stay, quantity of infused fluids, and transfused blood or blood products were recorded. During surgery, the loss of about 1000 mL blood was replaced with NS and/or 6% hydroxyethyl starch (Voluven®). Pre-surgery and 24-hour postoperative blood samples were taken from all patients to measure hemoglobin (Hgb), hematocrit (Hct), prothrombin time (PT), partial thromboplastin time (PTT), platelet count, blood urea nitrogen (BUN), creatinine, fibrinogen, D-dimer and cystatin-c values.

Intraoperative blood loss and intraoperative and postoperative numbers of given PRBCs was measured by same anesthesiologist who was unaware of each patient's group assignment. The patient's groups were learned by anesthesiologist only at the end of the study. Intraoperative blood loss was measured as the difference between the weights of used gauze and the original unused gauze, plus the difference between the volume accumulated in suction bottles and the volume of irrigation. The decision to give PRBCs was made by the anesthesiologist in view of the patients' age, cardiovascular status, and the amount of blood loss. Usually, blood loss under 1000 mL was replaced intraoperatively with NS and/or 6% hydroxyethyl starch. The decision to transfuse a patient for the postoperative period was made by the duty physician after the clinical assessment of anemia in orthopedic ward. A Hgb level of less than 8 g/dL−1 was considered a transfusion trigger except in patients who could have poor tolerance to these levels because of associated conditions such as chronic obstructive pulmonary disease (COPD), cerebral arterial insufficiency, or patients who presented signs, symptoms, or both of hypoxia such as tachycardia, dyspnea, or syncope. The transfusion trigger was placed at less than 10 g/dl for these patients.

For thromboprophylaxis, all patients received 40 mg enoxaparin (Clexane®, Lovenox®) subcutaneously, starting the day before surgery and continuing for 7-10 days.

Postoperative bleeding from the drain was not included in the calculation. However, observational information about postoperative bleeding was taken from the duty orthopedic doctor.

Statistical analysis

Data were analyzed using SPSS software version 21.0 (IBM Corporation, Armonk, NY, USA). Variables were checked using the Kolmogorov-Smirnov test. The independent samples t-test and Mann-Whitney U test were used in the analysis of quantitate data, the paired-sample t-test and Wilcoxon test were used for repeated measures, and the Chi-square test was used in the analysis of qualitative data. Differences were considered statistically significant if $P< 0.05$. Power analysis was used to determine the sample size. Based on a previous study, power analysis was performed according to the "peroperative blood loss amount" parameter. The number of cases was calculated as 26 for each group at 95% power, 95% safety margin ($\alpha = 0.05$, $\beta = 0.95$) [6].

Results

Age, sex, height, weight, ASA physical status, and the duration of surgery were similar between the groups. The length of hospital stay was significantly shorter in the group TA than in the C group ($p < 0.05$) (Table 1).

Intraoperative blood loss was significantly less in the group TA than in the group C (600mL vs 1450mL; $p < 0.05$) (Table 2). The amount of PRBCs given intraoperatively and postoperatively was significantly less in the group TA than in the group C ($p < 0.05$) (Table 2). Hemoglobin and Hct values were similar between the two groups before surgery and 24 hours after surgery; however, Hgb values were higher at hospital discharge in the group TA than in the group C (Table 3).

No significant differences were noted between the two groups with regards platelet count, PT, PTT, BUN, creatinine or fibrinogen values either before or 24 hours after surgery. Also, no significant differences were noted for D-dimer and cystatin-c values between the two groups (Table 3, 4). At the same time, D-dimer values were significantly higher in group C for postoperative period than intraoperative period. Furthermore, cystatin-c values were significantly lower in group TA for postoperative period than intraoperative period. We encountered no clinical venous thromboembolic events in either group.

Table 1: Demographic data, durations of surgery and lengths of hospital stay of the groups

	Group TA (n=30)	Group K (n=30)
Age (years)	53.5±12.7	54.6±14.9
Weight (kg)	79.0±11.4	72.8±11.8
Gender (M/F)	21/9	19/11
Height (cm)	166.6±8.8	164.6 ±9.1
ASA (I/II/III)	10/18/2	17/12/1
Duration of surgery (minute)	135 (60-225)	135 (60-210)
Length of hospital stay (days)	5 (4-6) *	7 (5-10)

Demographic data: mean ± standard deviation or number of patients. Length of hospital stay and duration of surgery: median (minimum–maximum). *p < 0.05

Table 2: Blood loss and transfusion

Parameter	Group TA (n=30)	Group K (n=30)
Intraoperative blood loss (m L)	600(200-1700)*	1450(400-3000)
Numbers of given PRBCs		
intraoperative	0 (0-1) *	1 (0-5)
postoperative	0 (0-1) *	1 (0-6)

Values are median (minimum–maximum). PRBCs: packed of red blood cells, *p < 0.05

Table 3: Red blood cell and coagulation data

Parameter	Group TA (n=30)	Group K (n=30)
Hemoglobin (gr/dl)		
Before surgery	14.1± 1.6	13.2 ± 1.9
24 hours after surgery	11.2± 1.2	10.6 ± 1.5
At discharge	10.8± 1.1	*10.1 ± 0.7
Hematocrit (%)		
Before surgery	42.9± 5.2	40.1 ± 5.3
24 hours after surgery	33.8± 3.4	31.9 ± 4.2
Platelet count (10^9/L)		
Before surgery	270 ± 63	272 ± 80
24 hours after surgery	207 ± 43	192 ± 51
PT (sec)		
Before surgery	11.2± 0.9	11.5 ± 1.1
24 hours after surgery	13.2± 1.9	13.3 ± 1.8
PTT(sec)		
Before surgery	27.0± 3.1	29.7 ± 7.3
24 hours after surgery	29.3± 3.6	31.2 ± 4.4
Fibrinogen (mg/dL)		
Before surgery	349 ± 76	349 ± 112
24 hours after surgery	438 ± 79	400 ± 113
D-dimer (mcg/L)		
Before surgery	2178 ± 6524	1307 ± 2229
24 hours after surgery	2130 ± 1975	2873 ± 2909

Values are mean ± SD. *P < 0.05.Group TA versus Group K

Table 4: Indicators of renal function's data

Parameter	Group TA (n=30)	Group K (n=30)
BUN (mg/dL)		
Before surgery	14.7± 4.4	16.0 ± 6.4
24 hours after surgery	11.2± 4.4	13.5 ± 7.1
Creatinine (mg/dL)		
Before surgery	0.79 ± 0.14	0.78 ± 0.23
24 hours after surgery	0.71 ± 0.18	0.70 ± 0.22
Cystatin-c (mg/dL)		
Before surgery	0.9± 0.2	0.9 ± 0.3
24 hours after surgery	0.8± 0.3	0.9 ± 0.3

Values are mean ± SD. Group TA versus Group K

Discussion

Orthopedic surgery, where the nature of the procedures makes it impossible to fully cauterize the exposed bone surfaces, blood loss tends to be significant, particularly for total joint replacement of hip and knee, often requiring extensive dissections through fibrotic, muscular, and bony tissues [7]. However, allogeneic blood is a scarce and expensive resource as well as having risks of viral disease transmission, immunologic and allergic reactions. These handicaps have led to the development of different methods to reduce or avoid allogeneic blood transfusion, such as restrictive transfusion protocols, use of autologous blood and administration of pharmacological agents. Although strategies to reduce perioperative blood loss during major surgery have been available for many years, they began to be used routinely only when the complications of transfusion became evident [8].

Many studies have reported different doses and methods of administration of TA. Commonly, 10 to 20 mg/kg is injected as an initial bolus dose, and then either the same amount is again injected after a few hours or a continuous infusion is provided during surgery of total hip replacement [9-12].

The clinical benefit of high doses of TA was first demonstrated in dose–response trials of adults undergoing cardiac surgery. Dose of 100 mg/kg was more effective than 50 mg/kg and equally effective to 150 mg/kg in a trial [13].

Timing is one of the important points about administration of TA because TA acts on the early phase of the fibrinolytic cascade, before binding of plasminogen to the fibrin surface, and a reduction of %80 in the activity of tissue plasminogen activator is needed to suppress fibrinolysis [14]. Lemay et al. reported that a 10 mg/kg IV bolus dose and continuous infusion of 1 mg/kg per hour may produce a therapeutic plasma concentration of TA. At the end of the study

they found that TA is not effective on intraoperative and total blood loss but is effective on decreasing frequency of blood transfusion [15]. In this study TA had administrated just before skin incision and TA might have reached effective plasma concentration after binding of fibrin to plasminogen which prevents binding of TA to plasminogen. In our study administration of TA had started 15 minutes before skin incision and found effective on decreasing intra operative blood loss and allogenic blood transfusions. In another study TA had administrated at the end of the surgery and found ineffective on blood loss [16].

The other important point about TA is effective plasma concentration, which is not known for in vivo inhibition of fibrinolysis. In vitro studies show that 10-15 mg/L concentrations of TA at plasma decrease the tissue plasminogen activator at a ratio of %80 [17]. Associated with this condition a study had executed with Garneti et al. [18] who reported that one IV bolus injection at a dose of 10 mg/kg before surgery is not effective on blood loss. As a different from other many studies about TA, transfusion of PRBCs were higher in group TA than control group.

Fibrinolytic activity is biphasic after surgery. Fibrinolytic activity which is increased in the initial phase is terminated after approximately 1 hour and then a deceleration occurs in fibrinolytic activity because of increased Plasminogen activator inhibitor (PAI) release. Fibrinolytic activity increases again after about 24 hours later [8,19]. TA was administered as IV bolus in the Ekbäck et al.'s study [20] and maintained with infusion. At the end of the study TA was found effective on blood loss. They also have studied D-dimer values which were significantly less in group TA than control group. We have also studied D-dimer values and changes of D-dimer values were not differing preoperatively or postoperatively in our group TA. This condition is correlated with higher expectation of fibrinolytic activity in group K, to which TA was not administered, than in our group TA.

Many studies which were executed in total hip replacement reported that TA is effective on postoperative blood loss [8-12,21]. Three study have reported that TA is effective on intraoperative blood loss which we detected [3,20,22]. In our study; intraoperative mean blood loss was recorded 600 mL (200-1700 mL) in group TA, despite that, 1450 mL (400-3000 mL) in group K which means TA is effective on intraoperative blood loss.

The major concern with antifibrinolytic agents is that their use may increase the risk of thrombosis [23,24]. In one study, whole-body enhanced CT was undertaken postoperatively to detect not only deep vein thrombosis but also pulmonary embolization, and they found that TA administration did not increase the incidence of either deep vein thrombosis or pulmonary embolization, as reported by other studies [11,12,22,25]. Tranexamic acid, being a potent antifibrinolytic drug, stabilizes a clot that has already formed and prevents further clot formation [26,27]. Hourlier et al. [28] compared effect of administration of TA as bolus and infusion and they also found that TA is safe in both applications.

No study has been found in the literature on the effects of TA on renal functions. In our study renal functions have been evaluated via cystatin-c values. Serum creatinine and urine output are known as insensitive and nonspecific parameters for renal function evaluation. Thus, a great variety of bio-markers has been identified and then applied in the clinical settings in recent years [29]. Among the potential markers, serum cystatin-c performs a consistent accuracy in various conditions. In our study we found that postoperative cystatin-c values were significantly lower than preoperative cystatin-c values in group TA.

Although there are many studies which evaluate the effectiveness of TA, there is no consensus about dose regime and time of administration for TA. TA effectiveness varies for different surgical types. High dose TA administration is often used in cardiovascular surgery. We thought that high dose administration of TA for total hip replacement can be effective on both intraoperative blood loss and needs of intraoperative and postoperative PRBCs. As result of our study we found that high dose administration of TA reduces intraoperative blood loss and needs of intraoperative and postoperative PRBCs in total hip replacement.

Conclusion

Administration of 50 mg/kg TA via infusion which starts 15 minutes prior to skin incision and takes time total of 30 minutes reduces intraoperative blood loss and needs of intraoperative and postoperative PRBCs. Also this approach provides higher Hgb values at discharge and shorter length of hospital stay. And it does not affect renal functions negatively. New studies are needed on the effectiveness, cost, and reliability of TA.

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Association between monocyte to HDL cholesterol ratio and mitral annulus calcification

Monosit HDL-kolesterol oranı ile mitral annülüs kalsifikasyonu arasındaki ilişki

Hilal Erken Pamukcu [1], Mert Aker [1]

[1] **Dışkapı Yıldırım Beyazıt Education and Research Hospital, Department of Cardiology, Ankara, Turkey**

ORCID ID of the authors
HEP: 0000-0001-8116-5090
MA: 0000-0003-2435-6610

Abstract

Aim: Mitral annulus calcification (MAC) is characterized by degenerative calcification of the mitral valve annulus, MAC and atherosclerosis are similar in regard to risk factors and pathogenesis. Monocyte count to high density lipoprotein (HDL) cholesterol ratio (MHR) is an inflammatory marker that is associated with several atherosclerotic diseases. We aimed to show the association of MHR levels with the presence of MAC.

Methods: This retrospective cohort study was conducted with MAC (+) patients who admitted to our echocardiography laboratory which constituted the study group (n=200) and MAC (-) patients which constituted the control group. Demographic features like age and sex, presence of hypertension and diabetes mellitus were similar between groups. Laboratory and echocardiographic parameters were recorded and evaluated for statistical analysis.

Results: When groups were compared according to echocardiographic parameters; left atrial diameter, pulmonary artery systolic pressure (PASP) were found to be positively correlated with the presence of MAC (r=0.271, p<0.001; r=0.329, p<0.001, respectively). MHR was significantly higher in study group {15.3 (11.9-20.6) vs. 10.8 (8.6-16.9) p<0.001}. In correlation analysis, MHR value was found to be positively correlated with presence of MAC (r=0.273; p <0.001).

Conclusion: We found that the presence of MAC was associated with higher MHR, and MHR was significantly correlated with MAC.

Keywords: Mitral annulus calcification, Monocyte, HDL

Öz

Amaç: Mitral annülüs kalsifikasyonu (MAK) mitral kapak annülüsünün dejeneratif kalsifikasyonu ile karakterizedir, MAK ve ateroskleroz risk faktörleri ve patogenez bakımından benzer özellikler taşır. Monosit sayısının yüksek dansiteli lipoproteine (HDL) oranı (MHO) birçok aterosklerotik hastalıkla ilişkili bir inflamatuvar belirteçtir. Biz MAK varlığı ile MHO derecesinin ilişkisini ortaya koymayı amaçladık.

Yöntemler: Bu retrospektif kohort çalışma ekokardiyografi laboratuvarımıza başvurmuş 245 [MAK(+) 200 çalışma grubu hastası, MAK(-) 45 kontrol grubu hastası] ile yapılmıştır. Grupların demografik özellikleri; yaş, hipertansiyon ve diyabetes mellitus varlığı açısından benzerdi. Tümünün laboratuvar ve ekokardiyografik parametreleri değerlendirildi.

Bulgular: Gruplar ekokardiyografik veriler olan sol atriyum çapı, pulmoner arter sistolik basıncı (PASB) açısından karşılaştırıldığında MAK varlığı ile pozitif yönde ilişkili saptandı(sırasıyla, r=0,271, p<0,001; r=0,329, p<0,001). Monosit HDL kolesterol oranı, MAK (+) grupta MAK (-) gruba göre istatistiksel olarak anlamlı derecede yüksekti {15,3 (11,9-20,6) vs. 10,8 (8,6-16,9) p<0,001}. Korelasyon analizine göre Monosit HDL oranı MAK varlığıyla anlamlı olarak ilişkili saptandı (r=0,273; p<0,001).

Sonuç: Sonuçlarımız MAK bulunan hastalarda MHO'nun anlamlı derecede yüksek olduğunu ve MAK ile MHO'nun anlamlı derecede korele olduğunu ortaya koymuştur.

Anahtar kelimeler: Mitral annülüs kalsifikasyonu, Monosit, HDL

Corresponding author / Sorumlu yazar:
Hilal Erken Pamukcu
Address / Adres: Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, Kardiyoloji Bölümü, Dışkapı Ankara, Türkiye
E-mail: hilalerkenn@gmail.com

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Introduction

Mitral annulus calcification (MAC) is characterized by degenerative calcification of the mitral valve annulus [1,2]. Many studies have shown a strong association between MAC and cardiovascular risk factors [3,4]. MAC was considered a passive, degenerative, age-related process, but it can also result from an atherosclerotic process [5]. On the basis of pathological features seen in specimens of patients with MAC, it was suggested that MAC and atherosclerosis are different forms of the same disease [6]. The association of MAC with atherosclerotic diseases such as coronary artery disease and carotid disease has been shown in previous studies [7,8]. There is a close association of atherosclerosis and systemic inflammation, growing evidence also regarding the association between MAC and inflammation [9,10].

Monocytes play a major role both in the initiation and progression of atherosclerosis HDL prevents monocyte recruitment into the arterial wall via a decrease in the expression of adhesion molecules and thus inhibiting adhesion of monocytes to endothelium [11]. Recently It had been shown that high monocyte count and low high density lipoprotein (HDL) levels are associated with inflammation [12,13] and it has been reported that the monocyte count to high density lipoprotein (HDL) cholesterol ratio (MHR) is a new prognostic marker in several cardiovascular diseases [14].

Given that both MAC and MHR are associated with cardiovascular risk factors and both are chronical inflammatory processes we hypothesized the possibility of association between presence of MAC and higher MHR levels.

Materials and methods

After approval of the local ethics committee, we started a retrospective cohort study.

Sample size

The sample size was calculated via the G* Power package program in post Hoc analysis, and the study was completed with 200 patients as study group and 45 patients as control group. The power of the study was calculated as 95% with the effect size of 0.60 at significance level of 0.05.

Study population

Between January 2017 and September 2018, a total of 200 consecutive MAC (+) patients who were admitted to our echocardiography laboratory were enrolled to study group. Age and sex-matched control group was composed of 45 MAC (-) patients who were admitted to our echocardiography laboratory due to suspicion of heart disease or other causes. All patients' demographic features and laboratory and echocardiographic parameters were evaluated retrospectively from our hospital data base.

Patients with severe valvular heart disease, coronary artery disease, history of rheumatoid fever, prosthetic valves, heart failure, malignancy, renal or hepatic dysfunction, acute or chronic infection or inflammatory condition, hematologic diseases including anemia or with chronic obstructive pulmonary disease were excluded.

Hypertension was defined as the documentation of systolic blood pressure≥ 140 mmHg and/or a diastolic blood pressure of ≥90 mmHg in at least two measurements, or the active use of any antihypertensive agent. Diabetes mellitus was defined as fasting plasma glucose levels more than 126 mg/dL or glucose level over 200 mg/dL at any measurement or active use of antidiabetic medications.

Transthoracic echocardiographic examination was performed using the Philips Epic 5 (Philips Healthcare, Andover, Massachusetts) instrument with a 1-5 MHz transducer. Standard parasternal long and short-axis views, and apical 2 and 4-chamber views were obtained for all patients. Left ventricular (LV) and left atrial (LA) diameter were measured from the M-mode images in parasternal long axis view [15]. Peak tricuspid regurgitant velocities were recorded by the continuous wave Doppler technique and a modified Bernoulli equation was used to estimate systolic pulmonary artery pressure (PASP). The modified Simpson's method was used for calculating the LV ejection fraction using the apical 4-chamber views [15].

MAC was defined as the presence of an echodense tracing, visualized throughout the systole and diastole, distinguishable from the posterior mitral leaflet and located anterior and parallel to the posterior LV wall and an intense echocardiographic structure at the junction of the atrioventricular groove and the posterior or anterior mitral leaflet on the parasternal long-axis, apical 4-chamber or 2-chamber, or parasternal short-axis 2D echocardiography views, ≥ 2 mm wide (when measured from the leading anterior to the trailing posterior edge at its greatest width) [16].

Samples of peripheral venous blood were drawn from the antecubital vein in the morning, after 12 h of fasting, and immediately studied at the laboratory without any time delay. Blood samples were taken into standardized tubes containing dipotassium ethylene dinitro tetraacetic acid (EDTA) for complete blood count (CBC). Coulter Counter LH Series (Beckman Coulter Inc., Hialeah, Florida, USA) was used for CBC analysis. Plasma levels of triglyceride, high-density lipoprotein, low-density lipoprotein, glucose, and creatinine were evaluated using an automated chemistry analyzer (Aeroset, Abbott, Holliston, MN, USA) using commercially available kits (Abbott, USA). Monocyte count was calculated using data obtained from the CBC differential analysis (using an automated blood cell counter). The reference value for monocyte in our laboratory is 0.2–1.2 × 103/dL and for HDL-C is 40–60 mg/dL. HDL-C levels were measured using a Beckman Coulter AU680 (Beckman Coulter Inc, CA, USA).

Statistical analysis

The statistical analyses were performed using SPSS Version 23 software (Armonk, NY, USA: IBM Corp). Categorical data are presented as numbers and percentages; Kolmogorov Smirnov test was performed in order to test normality for numerical variables. Continuous variables are presented as mean ± standard deviation when normally distributed and median and interquartile ranges (IQR) otherwise. Student's T test was performed in order to analyze significance of means; Mann Whitney U test was performed in order to analyze significance of differences of medians between two independent groups. Association between two continuous variables was measured by Pearson or Spearman correlation

coefficient as appropriate. A p value of <0.05 was considered statistically significant.

Results

Demographic features, presence of hypertension and diabetes mellitus were similar between groups. Demographic and echocardiographic features of the study groups have been represented in Table 1.

When groups were compared according to echocardiographic parameters, Left ventricular ejection fraction (LVEF) of study group was 60 (55-60) and control group was 60 (60-65) was lower and left ventricular end diastolic diameter (LVEDD) were higher in the study group (p=0.044 and p=0.006 respectively). But all of these parameters were in normal ranges according to guidelines. Left atrium diameter {40 (36-43) vs 36 (34-39), p<0.001} and pulmonary artery systolic pressure (PASP) was significantly higher in study group than control group {27 (20-30) vs 35 (28-40), p<0.001} (Table 1).

Table 1: Baseline characteristics and echocardiographic parameters of the groups

Parameters	Control group MAC (-) (n=45)	Study group MAC (+) (n=200)	p
Male, n (%)	21 (46.7%)	72 (36%)	0.123 [a]
Age, years	71.3	72.7	0.351 [b]
Hypertension, n (%)	32 (71.1%)	151 (75.5%)	0.331 [a]
Diabetes Mellitus, n (%)	20 (44.4)	100 (50)	0.306 [a]
LVEF , %	60 (60-65)	60 (55-60)	0.044 [c]
LVEDD, mm	44 (41-47)	46 (43-49)	0.006 [c]
LA diameter, mm	36 (34-39)	40 (36-43)	<0.001 [c]
Ascending aorta diameter, mm	35 (33-36)	35 (33-38)	0.295 [c]
PASP, mmHg	27 (20-30)	35 (28-40)	<0.001 [c]

a: Pearson chi-square, b: Student's T test, c: Mann Whitney-U test, LVEF: Left ventricle ejection fraction, LVEDD:Left ventricle end diastolic diameter, LA:left atrium, PASP: Pulmonary artery systolic pressure

Laboratory results of the groups have been represented in Table 2. Lipoprotein levels of the groups were different; patients in the study group have more dyslipidemic properties. Serum fasting glucose levels were higher in the study group {101 (89.5-119.5) vs. 115 (95.7-161.2), p=0.009} According to blood cell counts, monocyte values were higher in the study group {0.6 (0.5-0.78) vs. 0.5 (0.4-0.65), p=0.003}. Also monocyte to HDL cholesterol ratio was higher in the study group than control group {15.3 (11.9-20.6) vs. 10.8 (8.6-16.9) p<0.001}.

Table 2: Laboratory parameters of the groups

Parameters	Control group MAC (-) (n=45)	Study group MAC (+) (n=200)	p
Total cholesterol mg/dl	202.5±68	177.5±44	0.264 [a]
LDL-C mg/dl	136±28	127.2±36	0.106 [a]
HDL-C mg/dl	47.2±11.2	42.6±11.0	0.018 [a]
Triglyceride mg/dl	126 (96-186.7)	138.5 (99-215)	0.881 [b]
Glucose mg/dl	101 (89.5-119.5)	115 (95.7-161.2)	0.009 [b]
BUN mg/dl	39 (33-43.7)	45.5 (32-64)	0.193 [b]
Creatinine mg/dl	0.9 (0.8-1.02)	1.0 (0.8-1.22)	0.175 [b]
Albumin g/dl	4.1 (3.95-4.4)	3.9 (3.4-4.2)	0.001 [b]
Calcium mg/dl	9.5 (9.3-9.85)	9.3 (8.8-9.7)	0.004 [b]
Phosphorus mg/dl	3.3 (3.1-3.75)	3.6 (3.2-4.1)	0.022 [b]
Hemoglobin g/dl	13.6 (12.2-14.4)	12.7 (11.1-13.8)	0.003 [b]
RDW (%)	14.1±1.6	15.1±2.1	0.210 [a]
White blood cells 10^9/l	7.3 (6.2-8.8)	7.6 (6.3-9.3)	0.689 [b]
Neutrophils 10^9 /l	4.3 (3.5-5.8)	4.9 (3.8-6.0)	0.230 [b]
Lymphocytes 10^9 /l	2.1 (1.6-2.5)	1.8 (1.4-2.3)	0.093 [b]
Monocytes 10^9/l	0.5 (0.4-0.65)	0.6 (0.5-0.78)	0.003 [b]
Monocytes to HDL-C ratio	10.8 (8.6-16.9)	15.3 (11.9-20.6)	<0.001 [b]
Platelets 10^9/l	250 (195.5-296)	229 (193-281)	0.229 [b]
Mean platelet volume fL	8.4 (7.6-9.5)	8.6 (7.9-9.2)	0.501 [b]

Data are given as mean ±SD, median (interquartile range), a: Student's T test, b: Mann Whitney U test, BUN: Blood urea nitrogen, LDL-C: Low-density lipoprotein cholesterol, HDL-C, High-density lipoprotein cholesterol, RDW: Red cell distribution width

In correlation analysis MHR was found correlated with presence of MAC (r=0.273; p<0.001) Also serum albumin level was negatively correlated with left atrial diameter (r=-0.248, p=0.001), PASP were found to be positively correlated with presence of MAC (r=0.271, p<0.001; r=0.329, p<0.001, respectively) (Table 3). There was a positive correlation between PASP and LA diameter (r=0.465, p<0.001).

Table 3: Correlation between MAC and laboratory parameters

	r	p
Monocytes to HDL-cholesterol ratio	0.273	<0.001
Serum albumin	-0.248	0.001
LA diameter	0.271	<0.001
PASP	0.329	<0.001

r: Spearman-rho correlation coefficient, LA: left atrium, PASP: Pulmonary artery systolic pressure

Discussion

This present work demonstrates that MHR is significantly associated with the presence of MAC when compared with elderly individuals who have similar comorbidities and similar demographic characteristics. In some previous studies the demographic characteristics and risk factors of the control group were different, MAC (+) patients were more hypertensive and older than control group [17]. In our work, study and control groups were similar according to hypertension, age and presence of diabetes mellitus. Our study is the first to address the relationship between the MHR level and the presence of mitral annular calcification. We also found that dyslipidemia and impaired fasting glucose is also independently related with the presence of MAC.

In the main pathophysiology of MAC, calcium and phosphorus metabolism was thought to be in relation with this process [18]. In our study, median calcium level of MAC (+) group was lower and median phosphorus level was higher than control group but all these levels were in normal ranges. In our MAC (+) group left atrial diameter and SPAB were significantly higher than control group; this finding suggests that MAC may be associated with diastolic dysfunction.

MAC is known to be in close relationship with cardiovascular risk factors and many atherosclerotic diseases [3,19]. Correlation between MAC and carotid artery atherosclerosis, coronary and peripheral artery disease and aortic atheroma were demonstrated [7,20,21].

MAC is also considered to be a form of atherosclerosis, similar risk factors with atherosclerotic diseases and pathologic findings in MAC supports this idea [7].

Atherosclerosis is a chronic inflammatory disease characterized by strong immunological activity [22]. In the previous literature there were some data demonstrating the relationship between inflammation and MAC. A few studies demonstrated that inflammatory mediators increase in patients with calcification of valves [9, 23]. Varol et al. [10] reported the correlation between the neutrophil to lymphocyte ratio and MAC, which is an indirect inflammatory marker. Yayla et al. [17] reported the close association of ongoing inflammation as shown by the platelet lymphocyte ratio, another novel inflammatory marker, with the presence of MAC.

Monocyte activation is considered to be strongly associated with almost all aspects of chronic inflammation and cardiovascular diseases [24,25]. As a result of some stimuli, circulating monocytes become macrophages. Monocytes and macrophages can trigger an inflammatory cascade involving the production of cytokines [26]. On the other hand, high-density

lipoprotein cholesterol (HDL-C) molecules affect these pro-inflammatory and pro-oxidant effects of monocytes by inhibiting the migration-activation of monocytes and the proliferation-differentiation of the progenitor cells of monocytes [27-29].

Monocytes show pro-inflammatory and pro-oxidant effects, but HDL-C shows the opposite effects. Hence, it is logical to combine these parameters as a ratio and this ratio can be used as an indicator of oxidative stress and inflammation. The ratio of monocyte to HDL has recently emerged as a new cardiovascular prognostic marker. The association of MHR and cardiovascular diseases has been examined in a few studies. Kanbay et al. [30] reported that MHR is associated with worse cardiovascular outcomes in patients with chronic kidney disease.

In another study, in patients with acute ST-segment elevation myocardial infarction (STEMI), MHR values at admission were independently correlated with in-hospital adverse cardiovascular events and stent thrombosis and mortality [31]. In two different studies MHR values were found to be in relation with in-stent restenosis [32,33]; also MHR was found to be correlated with presence and severity of ectasia [13].

Limitations

There are some limitations in our study. First, this was a retrospective analysis of patients with MAC, focusing on the association of laboratory and echocardiographic parameters with the presence of MAC in a random time limit. Though we demonstrated a relationship with MHR and MAC, this observational finding may not establish a causal relationship. Although we excluded patients with coronary artery disease from study, data of atherosclerosis at other locations (carotid, aorta, etc.) were unavailable.

Conclusion

We have shown that MHR was significantly higher in patients with MAC when compared with controls with similar features, MHR was correlated with the presence of MAC. We also found that left atrial diameter and PASP was significantly higher in patients with MAC when compared with controls. All these findings reveal the importance of MHR in demonstrating inflammation, which is an important step in development of many cardiovascular diseases. Our results showing high MHR ratio in MAC (+) individuals support the idea that inflammation plays a role in MAC pathophysiology. The difference of MHR values of groups appears to be mainly tended to originate from monocyte counts. The difference between groups according to monocyte levels was more pronounced than the difference in HDL levels. This result can be interpreted as a finding supporting the place of inflammation in the pathophysiology of MAC. Further prospective studies are needed to establish the pathophysiological and clinical significance of increased MHR in patients with MAC.

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Relation of peritumoral, prepectoral and diffuse edema with histopathologic findings of breast cancer in preoperative 3T magnetic resonance imaging

Preoperatif 3T manyetik rezonans görüntülemede tümör çevresi, pektoral kas önü ve yaygın ödemin meme kanserinin histopatolojik bulguları ile ilişkisi

Ayşegül Akdoğan Gemici [1], Safiye Tokgöz Özal [1], Elif Hocaoğlu [1], Gözde Arslan [2], Ebru Sen [3], Serdar Altınay [4], Ercan İnci [1]

[1] Health Science University, Bakirkoy Dr.Sadi Konuk Training And Research Hospital, Department of Radiology, Istanbul, Turkey
[2] Maltepe University, Department of Radiology, Istanbul, Turkey
[3] Health Science University, Bakirkoy Dr.Sadi Konuk Training And Research Hospital, Department of General Surgery, Istanbul, Turkey
[4] Health Science University, Bakirkoy Dr.Sadi Konuk Training And Research Hospital, Department of Pathology, Istanbul, Turkey

ORCID ID of the authors
AAG: 0000-0002-7707-1849
STÖ: 0000-0003-1690-4744
EH: 0000-0002-2506-4794
GA: 0000-0003-0991-1380
ES: 0000-0002-0121-4540
SA: 0000-0003-0267-8360
Eİ: 0000-0002-3791-2471

Corresponding author / Sorumlu yazar:
Ayşegül Akdoğan Gemici
Address / Adres: Sağlık Bilimleri Üniversitesi, Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi, Radyoloji Bölümü, İstanbul, Türkiye
E-mail: aysegulakdogan@yahoo.com

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Abstract

Aim: Preoperative breast magnetic resonance imaging (MRI) findings can provide rich information about the prognosis of the disease. Morphologic and dynamic features are especially used for it. We aimed to compare peritumoral, prepectoral, and diffuse edema identified in MRI with histopathologic findings, and to show how prognostic information can be gathered from the identification of edema.

Methods: We conducted a retrospective cohort study with forty-six women who underwent breast DCE-MRI as part of the pre-surgical evaluation between January and August 2018 were included in the study. Signal enhancements similar to water that were localized to the prepectoral or peritumoral areas or diffuse enhancements on T2A-weighted sequences were considered as edema. The presence of edema was compared with clinicopathologic parameters such as cancer type, tumor size, histologic grade, ER-PR receptor positivity, Her2 positivity, Ki-67 labelling index and lymphovascular invasion.

Results: The mean age of the participants was 53.15±11.75 (range, 27-80) years. Eleven patients had diffuse edema, 27 patients had peritumoral edema, and 5 patients had prepectoral edema. Nineteen luminal A cancers, 17 luminal B, 9 triple-negative, and 1 Her2 cancer were seen. Peritumoral edema was associated with lymphovascular invasion positivity (p=0.002). Tumor size and the level of Ki-67 was associated with peritumoral edema (p=0.001, p=0.009). The odds of observing prepectoral edema showed no statistically significant difference in the presence of lymphovascular invasion positivity and other parameters. The presence of diffuse edema showed significant differences depending on tumor size measurements (p=0.026).

Conclusion: Edema in breast MRI can provide information about histopathologic findings, particularly about lymphovascular invasion. The authors suggest that different edema types could be mentioned in radiology reports as a matter of routine given that such findings can provide information about the prognosis.

Keywords: Breast cancer, Edema, Magnetic resonance imaging, Lymphovascular invasion

Öz

Amaç: Preoperatif meme manyetik rezonans görüntüleme (MRG), meme kanserinin prognozu konusunda zengin bilgiler sağlar. Bunun için özellikle morfolojik ve dinamik özellikler kullanılır. Çalışmamızda meme MRG'de peritümöral, prepektoral, diffüz ödemin meme kanserinin histopatolojik prognostic parametreler ile ilişkisin araştırmayı ve meme MRG'den prognoz ile ilgili edinilen bilgileri değerlendirmeyi amaçladık.

Yöntemler: Ocak-Ağustos 2018 tarihleri arasında hastanemizde meme kanseri tanısı almış ve ameliyat öncesi değerlendirmede kontrastlı dinamik meme MRG çekilen 46 hasta çalışmaya dahil edildi. T2A sekansta tümör çevresinde, pektoral kas önünde ya da tüm memede izlenen su ile benzer sinyal ödem lehine değerlendirildi. Her bir ödem tipi; kanser tipi, tümör boyutu, histolojik evre, ER-PR reseptör pozitifliği, Her2 reseptör pozitifliği, Ki67 proliferasyon indeksi ve lenfovasküler invazyon gibi klinikopatolojik parametreler ile değerlendirildi.

Bulgular: Ortalama yaş 53.15±11.75 (aralık 27-80) idi. Meme MRG'de 11 hastada diffüz, 27 hastada peritümöral, 5 hastada prepektoral ödem bulgusu izlenmekteydi. 19 lüminal A, 17 lüminal B, 9 üçlü negatif, 1 Her2 kanser mevcuttu.Peritümöral ödem LVI pozitifliği ile ilişkili bulundu (p=0.002). Tümör boyutu ve Ki-67 indexi peritümöral ödemle ilişkilidir (p=0.001, p=0.009).Prepektoral ödem ile değerlendirilen parametreler arasında ilişkili görülmedi. Diffüz ödem tümör boyutuna göre farklılık gösterir (p=0.026).

Sonuç: Meme MRG'de görülen peritümöral ödem LVI pozitifliği açısından bilgi vericidir. Farklı ödem tipleri prognoz açısından bilgiler taşıdığından rutin raporlamalarda belirtilmelidir.

Anahtar kelimeler: Meme kanseri, Ödem, Magnetik rezonans görüntüleme, Lenfovasküler invazyon

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Introduction

Magnetic resonance imaging (MRI) of the breast is the most accurate method for the detection of breast cancer, and the specificity of the method has increased with the introduction of diffusion models suggested in recent studies, which allow the acquisition of radiomics data [1,2]. MRIs have been used to establish the diagnosis, determine the treatment options, and monitor the treatment course in patients who receive oncologic therapy. A combination of clinicopathologic data with MRI findings can provide rich information about the prognosis of the disease [3]. Studies showed that rim enhancement in a mass lesion observed in breast MRI could be associated with aggressive tumor biology, and background parenchymal enhancement other than the mass was associated with a poor prognosis [4,5]. There are studies in the literature that showed a relationship between immunohistochemical subtypes and MRI findings [6,7]. To our knowledge, the first study in the literature that associated focal-diffuse breast edema observed on the T2A-weighted sequences was published by Takayoshi Uematsu in 2014, and peritumoral edema has been regarded as an indicator of poor prognosis [8]. The aim of the present study was to compare peritumoral, prepectoral, and diffuse edema identified in preoperative breast MRI with histopathologic findings, and to show how prognostic information can be gathered from the identification of edema.

Materials and methods

This study was approved by our institutional review board, and conducted according to The Declaration of Helsinki. An informed consent was obtained from all the participitants.

Patient cohort

Women with a recent diagnosis of breast cancer who underwent DCE-MRI as part of the pre-surgical evaluation between January and August 2018 were included in the study. In premenopausal patients, DCE-MRI examinations were made between days 7 and 14 of the menstrual cycle. All patients underwent a Tru-Cut biopsy before undergoing a DCE-MRI in our department.

Breast DCE-MRI protocol

All breast DCE-MRIs were performed using a 3T scanner (Verio, Siemens Healthcare, Erlanger, Germany) with a phase-array eight-channel bilateral breast receive coil. An intravenous catheter was inserted into the left or right arm before the examination. First, prior to the administration of the contrast material, axial turbo-spin echo inversion recovery fat-sat T2-weighted sequences were acquired using the following parameters: TR = 3000-3500 ms, TE = 79 ms, field of view (FOV) = 20-24 cm, matrix = 288 × 192, slice thickness = 4 mm with no gap, flip angle = 90°, and number of excitations (NEX) = 2. Finally, dynamic contrast-enhanced sequences that contained axial T1-weighted 3D fast spoiled gradient recall echo sequences (TR = 5.3, TE = 2.5, FOV = 20-24 cm, matrix = 256 × 256, slice thickness = 4 mm) were acquired. The DCE-MRI included one precontrast acquisition and five postcontrast acquisitions after the injection of gadolinium diethylenetriaminepentaacetic acid (Magnevist; Bayer HealthCare, Wayne, NJ). The contrast was injected at a dose of 0.1 mmol/kg body weight using an automated pump, followed by a 20 mL saline flush, both at a rate of 2 mL/s.

Image analysis

All DCE-MRI intensity characteristics and morphology and kinetic features were analyzed by two breast radiologists with 3-5 years' experience. After observing the malignant masses on a contrast-enhanced dynamic series, signal enhancements similar to water that were localized to the prepectoral or peritumoral areas or diffuse enhancements on T2A-weighted sequences were considered as edema. When disagreement occurred between the two readers, consensus was reached. The presence of edema was compared with clinicopathologic parameters such as cancer type, tumor size, histologic grade, ER-PR receptor positivity, Her2 positivity, Ki-67 labelling index, and lymphovascular invasion (LVI).

Pathologic Evaluation

The histologic type and grade, invasive tumor size, and lymph node status were determined through an examination of surgical specimens by a pathologist with ten years' experience in breast pathology. LVI was assessed on hematoxylin and eosin-stained sections and defined as carcinoma cells in a definite endothelial-lined space in the peritumoral breast surrounding the invasive carcinoma. Expressions of ER, PR and HER2 were assessed using immunohistochemical staining, and expressions of ER and PR were quantified using the Allred score, considering a total Allred score of greater than 2 as positive for ER or PR [9]. An HER2 value of 0 or 1 was considered to be negative, and a value of 3 was considered to be positive. An HER2 value of 2 was considered equivocal; silver-enhanced in situ hybridization was performed for equivocal cases. An HER2/chromosome enumeration probe 17 (CEP17) ratio of 2.0 or greater, or an HER2/CEP17 ratio of less than 2.0 with an average HER2 copy number of 6.0 or greater, was considered positive [10]. Hormone receptor (HR)-positivity was defined as the presence of tumors that expressed ER and/or PR. For the Ki-67 expression status, immunohistochemical nuclear staining was performed [11].

Statistical Analysis

The Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) software package was used for the statistical analysis. Along with descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) to evaluate the study data, the Mann-Whitney U-test was used to make paired comparisons of quantitative data without normal distribution. Pearson's Chi-square test, Fisher's exact test, and the Fisher-Freeman-Halton test were used to compare qualitative data. In multivariate analyses, the effects of other factors on the types of edema were analyzed using backward stepwise logistic regression analysis. The level of significance was set at $p<0.05$.

Results

The study was conducted in 46 women in our university hospital between January and August 2018. The mean age of the participants was 53.15±11.75 (range, 27–80) years. The descriptive statistics are shown in Table 1. Table 2 shows the relationships between different edema types and histopathological parameters.

Table 1: Distribution of general characteristics

Pathology	IDC	40 (87.0)
	ILC	2 (4.2)
	Invasive micropapillary carcinoma	1 (2.2)
	Mixed carcinoma	1 (2.2)
	Mucinous carcinoma	1 (2.2)
	Pleomorphic carcinoma	1 (2.2)
Type of Edema	Diffuse	11 (23.9)
	Peritumoral	27 (58.7)
	Prepectoral	5 (10.9)
ER	Absent	10 (21.7)
	Present	36 (78.3)
PR	Absent	16 (34.8)
	Present	30 (65.2)
HER2	Absent	39 (84.8)
	Present	7 (15.2)
Ki-67	Min-Max (Median)	2-60 (20)
	Mean±SD	22.26±16.24
	≤15	21 (45.7)
	16-40	19 (41.3)
	>40	6 (13.0)
Histologic grade	Grade 1	12 (26.1)
	Grade 2	24 (52.2)
	Grade 3	10 (21.7)
Perineural invasion	Absent	37 (80.4)
	Present	9 (19.6)
In situ	Absent	15 (32.6)
	Present	31 (67.4)
Lymphovascular invasion	Absent	29 (63.0)
	Present	17 (37.0)
Postoperative tumor size	Min-Max (Median)	1-16 (2.5)
	Mean±SD	2.75±2.26
T stage	T 1	18 (39.1)
	T 2	26 (56.5)
	T 3	1 (2.2)
	T 4	1 (2.2)
Cancer subtype	Luminal A	19 (41.3)
	Luminal B	17 (37.0)
	Triple-negative	9 (19.6)
	Her2	1 (2.2)

IDC: invasive ductal carcinoma, ILC: invasive lobuler carcinoma, ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor 2

Table 2: Evaluation based on the type and presence of edema

	Diffuse edema		Peritumoral edema		Prepectoral edema	
	Present n (%)	Absent n (%)	Present n (%)	Absent n (%)	Present n (%)	Absent n (%)
ER						
Negative	3 (27.3)	7 (20)	5 (18.5)	5 (26.3)	2 (40)	8 (19.5)
Positive	8 (72.7)	28 (80)	22 (81.5)	14 (73.7)	3 (60)	33 (80.5)
[a]p	0.682		0.719		0.295	
PR						
Negative	5 (45.5)	11 (31.4)	10 (37)	6 (31.6)	3 (60)	13 (31.7)
Positive	6 (54.5)	24 (68.6)	17 (63)	13 (68.4)	2 (40)	28 (68.3)
[a]p	0.477		[b]0.702		0.325	
HER2						
Negative	9 (81.8)	30 (85.7)	24 (88.9)	15 (78.9)	5 (100)	34 (82.9)
Positive	2 (18.2)	5 (14.3)	3 (11.1)	4 (21.1)	0 (0)	7 (17.1)
[a]p	0.999		0.424		0.999	
Ki-67						
≤15	3 (27.3)	18 (51.4)	8 (29.6)	13 (68.4)	2 (40)	19 (46.3)
16-40	8 (72.7)	11 (31.4)	16 (59.3)	3 (15.8)	2 (40)	17 (41.5)
>40	0 (0)	6 (17.2)	3 (11.1)	3 (15.8)	1 (20)	5 (12.2)
[c]p	0.056		0.009*		0.832	
Histologic grade						
Grade 1	2 (18.2)	10 (28.6)	5 (18.5)	7 (36.8)	1 (20)	11 (26.8)
Grade 2	5 (45.5)	19 (54.3)	15 (55.6)	9 (47.4)	2 (40)	22 (53.7)
Grade 3	4 (36.4)	6 (17.1)	7 (25.9)	3 (15.8)	2 (40)	8 (19.5)
[c]p	0.426		0.391		0.683	
In situ						
Negative	5 (45.5)	10 (28.6)	10 (37)	5 (26.3)	4 (80)	11 (26.8)
Positive	6 (54.5)	25 (71.4)	17 (63)	14 (73.7)	1 (20)	30 (73.2)
[a]p	0.462		[b]0.445		0.033*	
Lymphovascular invasion						
Negative	6 (54.5)	23 (65.7)	12 (44.4)	17 (89.5)	3 (60)	26 (63.4)
Positive	5 (45.5)	12 (34.3)	15 (55.6)	2 (10.5)	2 (40)	15 (36.6)
[a]p	0.722		[b]0.002**		0.999	
Postoperative tumor size						
Min-Max (Median)	1.5-16 (3)	1-5 (2)	1.1-16 (3)	1-3.5 (1.5)	1.5-4.8 (2.5)	1-16 (2.5)
Mean±SD	4.15±4.03	2.32±1.09	3.40±2.72	1.84±0.76	3.02±1.34	2.72±2.36
[d]p	0.026*		0.001**		0.348	
Cancer type						
Luminal A	4 (36.4)	15 (42.9)	11 (40.7)	8 (42.1)	2 (40)	17 (41.5)
Luminal B	4 (36.4)	13 (37.1)	11 (40.7)	6 (31.6)	1 (20)	16 (39)
Triple-negative	3 (27.3)	6 (17.1)	5 (18.5)	4 (21.1)	2 (40)	7 (17.1)
HER2	0 (0)	1 (2.9)	0 (0)	1 (5.3)	0 (0)	1 (2.4)
[c]p	0.864		0.726		0.468	

ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor 2, [a] Fisher's Exact Test, [b] Pearson Chi-square Test, [c] Fisher Freeman-Halton Test, [d] Mann-Whitney U Test, *p<0.05, **p<0.01

Peritumoral edema was strong related with higher tumor size (p=0.001). Also there was a strong correlation between peritumoral edema and lymph node positivity (p=0.004).

Peritumoral edema according to the Ki-67 classification showed the significant difference (p=0.009; p<0.05). In paired comparisons performed to find out the source of the difference, peritumoral edema were significantly lower in cases with a Ki-67 value of 15 and lower (p<0.05), and significantly higher (p=0.003) in cases with a Ki-67 value of 16–40 (p<0.05). Peritumoral edema in cases with a Ki-67 value above 40 did not show a significant difference (p>0.05) as shown in Figure 1.

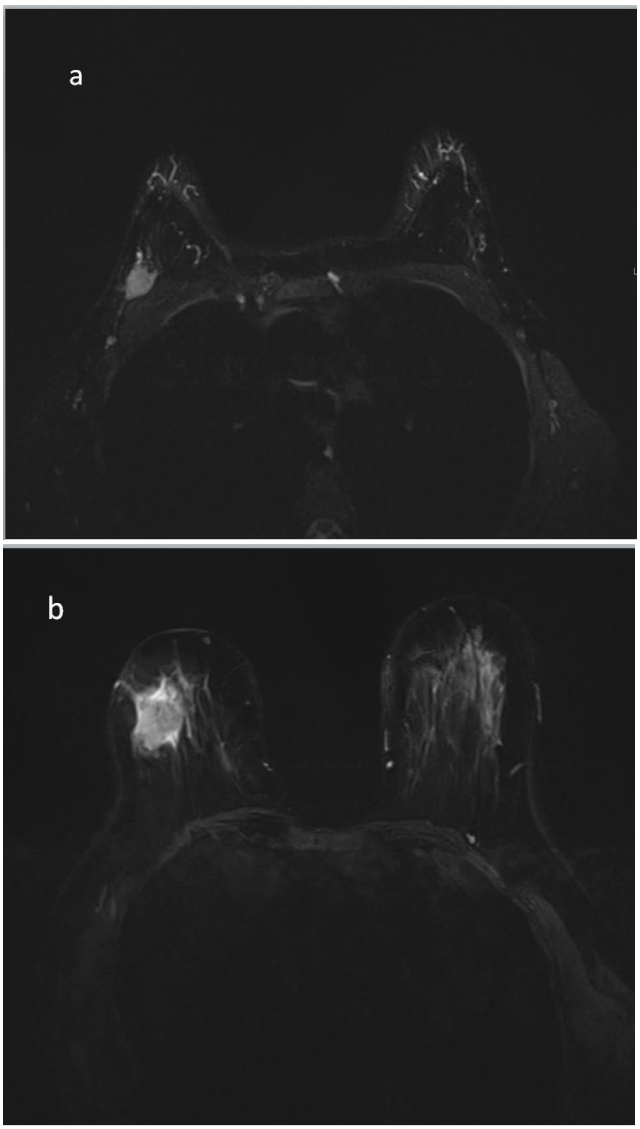

Figure 1: a,b. Fat-suppressed T2-weighted axial breast MR image in a 45-year-old woman with triple- negative invasive ductal carcinoma. Ki67 labelling index was 60 and no peritumoral edema was shown (a). Fat-suppressed T2-weighted axial breast MR image in a 35-year-old woman with triple- negative invasive ductal carcinoma. Ki67 labelling index was 35 and presence of peritumoral edema was shown (b).

The presence of diffuse edema showed significant differences depending on tumor size measurements (p=0.026; p<0.05). The tumor sizes in patients with diffuse edema were significantly higher than in patients without diffuse edema.

Prepectoral edema were significantly higher in the event of an in-situ positivity (p=0.032). The presence of prepectoral and diffuse edema did not show a significant difference in the presence of lymphovascular invasion positivity or other parameters (p>0.05).

When we evaluated the effects of Ki-67, lymphovascular invasion, tumor size and T stage on peritumoral

edema with a Backward Stepwise logistic regression analysis, the model was found to be significant (p=0.001; p<0.05) with an explanatory coefficient of 80.4%. The odds ratio of the effect of positive lymphovascular invasion was 9.422-fold higher (95% Cl: 1.467-60.525), while the odds ratio of the effect of tumor size was 3.806 (95% Cl: 1.448-10.003) higher (Table 3).

For the presence of diffuse edema, Ki-67, tumor size and T-stage were included in the logistic regression analysis. The model was found to be significant (p=0.012) with an explanatory coefficient of 76.1%. The effect of a T-stage being 2 or higher was significant in the model, with an odds ratio of 9.444-fold (95%Cl: 1.089-81.882) higher (Table 4).

Table 3: Multivariate analysis of risk factors that affect peritumoral edema

	p	ODDS	95% CI	
			Lower	Upper
Ki-67	0.611	1.013	0.964	1.065
Lymphovascular invasion	0.018*	9.422	1.467	60.525
Tumor Size	0.007**	3.806	1.448	10.003
T stage (≥2)	0.582	2.126	0.145	31.210

*p<0.05, **p<0.01

Table 4: Multivariate analysis of risk factors that affect diffuse edema (Logistic regression analysis)

	p	ODDS	95% CI	
			Lower	Upper
Ki-67	0.709	0.989	0.933	1.049
Tumor Size	0.331	1.268	0.786	2.046
T stage (≥2)	0.042*	9.444	1.089	81.882

*p<0.05

Discussion

We should highlight that the pathophysiology of peritumoral, prepectoral, and diffuse edema in women with a mass lesion in the breast is not clear. Baltzar et al. [12] suggested that peritumoral edema might arise from tumor angiogenesis and cytokine release around the mass. Research suggested that increased levels of a substance called hyaluronan in the peritumoral stroma could increase T2 relaxation [13]. In recent literature, the increased peritumoral signal intensity in T2A-weighted sequences was mostly related to LVI positivity. Some studies reported the presence of edema by providing its grade, and there are more published studies that assessed the frequency of the presence of breast edema as absent or present [3]. Mori et al. [14] compared ADC values in the peritumoral area with the presence of LVI and performed a quantitative and easily reproducible assessment. The presence of edema in the present study was evaluated as absent or present on T2A-weighted sequences, and a significant relationship was found between LVI and peritumoral edema among other types of edema.

LVI is a pathologic finding that points to the presence of tumor embolisms within the vascular structures around the tumor [15]. No clear relationship has been established between LIV positivity and any radiologic findings. The MRI appearances of LVI resemble in-situ ductal carcinoma, but these two entities could be differentiated by an immunohistochemical examination [16]. Van Goethem et al. [17] claimed that perilesional findings observed in the mass lesion might arise from in-situ component positivity, although Cheon et al. [18] ruled out this possibility by excluding patients with an in-situ component when creating their patient groups, and assumed that perilesional findings arose from the tumor itself, suggesting that peritumoral edema could be related to LVI in patients with lymph node-negative breast cancer. In our series, patients with in-situ component positivity were not excluded, and there were 31 patients (67.4%) with in-situ cancer that accompanied invasive cancer. No significant relationship was found between the probability of observing peritumoral and diffuse edema in these patients. In contrast to the literature, the present study found a significant relationship between in-situ positivity and prepectoral edema, which was attributed to insufficient randomization; there was only one patient with in-situ component positivity and prepectoral edema.

Beside this, no relationship was identified between prepectoral edema and the parameters that were evaluated in our study. However, in a study with 589 patients, Uematsu et al. [8] showed that prepectoral edema was associated with LVI, mass size, presence of in-situ carcinoma, and axillary lymph node status, and that the finding of edema had 12% sensitivity and 100% specificity to indicate LVI positivity. In our patient group, five (10.9%) patients had prepectoral edema, and of these, two patients had luminal A cancer, two patients had luminal B, and one patient had triple-negative breast cancer. We attribute this finding to the small number of patients with prepectoral edema.

Bae et al.'s study, which was about pretreatment MR imaging features of triple-negative breast cancer, concluded that peritumoral edema was observed in triple-negative cancers more commonly and it provided information about the patient's response to chemotherapy [19]. In our study, we observed no relationship between edema and tumor subtype. Also, receptor positivity is not related with all three edema types. Peritumoral edema is found specific to invasive ductal cancer because ILC does not often give rise to edema due to its growth pattern [20]. No edema was identified in two patients with ILC in our study group.

A significant relationship was found between the presence of peritumoral edema and Ki-67, as one of the prognostic markers in breast cancer (p=0.009; p<0.01). Edema was not observed in tumors with Ki-67 values of less than 15, whereas the prevalence of edema was higher in tumors with a Ki-67 value of between 15 and 60. The likelihood of observing edema was significantly lower in six patients (four triple-negative, two luminal B) with Ki-67 values greater than 60, which we attributed to the rapid growth of the mass lesion, and the subsequent lack of sufficient time for the development of edema prior to diagnosis. There is a paucity of data in the literature related to this subject. The relationship between tumor size and edema was also studied in the literature, although it has been reported that edema is rarely observed in tumors larger than 10 cm [21]. The only exception to this finding was a patient with a tumor larger than 10 cm with mucinous cancer with a diameter of 16 cm, who also had peritumoral edema. In our patient group, there were no patients with ductal or lobular cancers with a diameter larger than 10 cm.

Diffuse edema in breast cancer is observed in cases of inflammatory cancer. Increased skin thickness is observed in inflammatory breast cancer, with or without accompanying mass lesions. Patients with diffuse edema in our study were not evaluated for skin thickness radiologically and clinically. There may have been patients with inflammatory cancer in our study group. We found that the presence of diffuse edema was

significantly higher in patients with large tumors sizes. No relationship with other clinicopathologic parameters was found.

Limitations

The main limitation of the present study is related to the small number of patients in the sample, and the evaluation of edema was based on visual assessment rather than quantitative values. But we should mention that the power of our study sample in predicting peritumoral edema presence of lymphovascular invasion is more than 80%.

Conclusion

Peritumoral edema observed during preoperative breast MRI can provide information about histopathologic findings, particularly about LVI. Our study shows that MRI sign of edema could give early and/or additive information about the prognosis. Still detailed further studies are needed in this field.

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Research article
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Is ultrasound guided syringe-free method more efficient for saphenous vein catheterization? A prospective randomized controlled study

Safen ven kateterizasyonu için ultrason eşliğinde şırınga içermeyen yöntem daha verimli midir? Prospektif randomize kontrollü bir çalışma

Gözen Öksüz [1], Erdinç Eroğlu [2]

[1] Department of Anesthesia and Reanimation, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey
[2] Cardiovascular Surgery, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey

ORCID ID of the authors
GÖ: 0000-0001-5197-8031
EE: 0000-0003-1419-2157

Corresponding author / Sorumlu yazar:
Gözen Öksüz
Address / Adres: Kahramanmaraş Sütçü İmam Üniversitesi Tıp Fakültesi, Anestezi ve Reanimasyon Anabilim Dalı, Kahramanmaraş, Türkiye
E-mail: gozencoskun@gmail.com

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Abstract

Aim: Syringe-free is a novel technique without making blood aspiration with a syringe and by pushing forward the guide wire after verifying that the needle is inside the vein. In this study, we aimed to compare the vein intervention time between the ultrasound-guided syringe-free technique and the ultrasound-guided technique requiring syringe and aspiration procedures (classic technique), and also the success and complication rates of the first application.

Methods: A prospective randomized controlled study was designed to compare ultrasound-guided syringe-free and ultrasound-guided classic technique in patients performed saphenous vein catheterization between June 2018 and September 2018. Demographic data, the period passed until a successful catheterization, the time for the needle to enter to the vein and the needle intervention number and complications are recorded.

Results: 75 patient were enrolled in the study. There were no differences between demographical data in the patients ($p>0.05$). Vein puncture time were similar in each group ($p=0.750$). In the ultrasound-guided syringe-free group the catheterization time is determined to be significantly shorter ($p=0.003$). In the syringe-free method, it is determined that the successful catheterization number is higher at first try, but the difference is not determined to be significant ($p=0.370$). In both groups, central venous catheter-related complications were not observed during or after the procedure.

Conclusion: In conclusion, an ultrasound-guided syringe-free approach can a decrease the duration of saphenous vein catheterization and allows the operator to perform the whole procedure with ultrasound guidance without interruptions. This method can be used as an advantageous and practical method for experienced operators.

Keywords: Syringe-free, Ultrasound guided, Catheterization

Öz

Amaç: Şırınga ve aspirasyon içermeyen teknik yeni bir tekniktir. Kılavuz tel, kateter iğnesine yerleştirilir ve ultrason probu uzunlamasına veya oblik eksende yerleştirilmiş olarak şırınga ile kan aspirasyonu yapılmadan ve iğnenin damar içinde olduğu görüldükten sonra kılavuz tel ilerletilmesi yapılarak gerçekleştirilir. Bu çalışmada, uzun eksende ultrason eşliğinde uygulanan şırıngasız teknik ile ultrason eşliğinde şırınga ve aspirasyon yapılan tekniği damar girişim süresini, kateterizasyon süresini ve birinci uygulamada başarı ve komplikasyon oranlarını karşılaştırmayı amaçladık.

Yöntemler: Bu randomize kontrollü prospektif çalışma Haziran 2018 ve Eylül 2018 tarihleri arasında safen ven kateterizasyonu uygulanan hastalarda ultrason eşliğinde şırınga içermeyen teknik ile ultrason eşliğinde klasik tekniği karşılaştırmak için tasarlanmıştır. Her iki grupta hastaların demografik bilgileri, başarılı kateterizasyona kadar geçen süre, iğnenin damar içine girme süresi ve iğne girişimi sayısı ve komplikasyonlar kayıt edildi.

Bulgular: 75 hasta çalışmaya alındı. Hastaların demografik özellikleri arasında fark bulunmadı ($p>0,05$). Her iki grupta damar içine girişim zamanı benzer bulundu ($p=0,750$). Şırıngasız yöntemde kateterizasyon süresi anlamlı olarak kısa bulundu ($p=0,003$). Şırıngasız yöntemde ilk denemede başarılı kateterizasyonun daha çok olduğu ama farkın anlamlı olmadığı görüldü ($p=0,370$). Her iki grupta, işlem süresi boyunca veya işlem sonrası dönemde santral venöz kateterle ilişkili komplikasyon görülmedi.

Sonuç: Sonuç olarak ultrason eşliğinde şırıngasız yöntem safen ven kateterizasyonu işleminin süresini kısaltabilir ve uygulayıcının bütün işlemi ultrason eşliğinde kesintisiz yapmasını sağlar. Tecrübeli uygulayıcılar için bu yöntem avantajlı ve pratik bir yöntem olarak kullanılabilir.

Anahtar kelimeler: Şırınga içermeyen, Ultrason eşliğinde, Kateterizasyon

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Introduction

Vein catheterization under the guidance of ultrasound is a significant part of the varicose vein treatment methods for VNUS closure, endovenous laser, foam sclerotherapy, and glue ablation [1,2]. The catheterization by ultrasound allows rapid improvement, better cosmetic results, and higher success rates [3]. Ultrasound-guided vein catheterization is an essential skill for modern phlebologists, anesthetists, and surgeons. Veins can be catheterized by using ultrasound on transverse (short) section, longitudinal (long) section and oblique section [4,5]. It is still argued on which axis the ultrasound-guided venous catheterization method and intervention is realized best [6,7]. In all these approaches, the blood aspiration with syringe is realized in order to verify the position of the vein. Recently a technique that doesn't include syringe and aspiration (syringe-free) is defined. The guide wire is placed on the catheter needle and the ultrasound probe is placed on longitudinal or oblique axis without making blood aspiration with a syringe and by pushing forward the guide wire after verifying that the needle is inside the vein [8,9].

In this study, we aimed to compare the vein intervention time between the ultrasound-guided syringe-free (USGSF) technique and the ultrasound-guided classic (USGC) technique requiring syringe and aspiration procedures and also the success and complication rates of the first application.

Materials and methods

This prospective and randomized study is started following the receipt of approval ethical committee (2018/08-23) and the patients' informed consents. 75 patients (ASA I-III, between 18-75 ages) who received catheterization because of endovenous laser, foam sclerotherapy and glue ablation are included in the study. The patients with a presence of skin infection, anatomical abnormalities, patients who are older than seventy-five and younger than eighteen and patients who refused to participate in the study are excluded. The patients are separated randomly into two groups following the sealed tender technique. The group who got a catheter placed on saphenous vein by using a syringe on the long axis following an ultrasound guidance, is named Group USGC (n=38) and the group who got a catheter placed on the saphenous vein following an ultrasound guidance but without using a syringe on the long axis, is named Group USGSF (n=37). The flowchart of the study is shown in figure 1.

All saphenous catheter placement procedures are realized by the same cardiovascular surgeon experienced in ultrasound-guided procedures, and all the procedures are realized by a single person. In each of the two groups, high-frequency linear US probe (LOGIQ e; GE Healtycare, Solingen, Germany) is used. The patients whose consents are received are monitored through ECG, noninvasive blood pressure and pulse oximeter as a standard. Following the sterilization of the catheter placement area with povidone-iodine, the ultrasound probe is covered with a sterilized casing. In all of the cases, the venous catheter (Certofix® Duo / Trio, Braun, Germany) is placed by using the seldinger technique. In the group including the use of the syringe, the ultrasound probe is placed on the medial knee region and long axis and the saphenous vein is displayed. Together with the ultrasound image, the procedure is continued by using the needle and negative aspiration. After the needle is displayed in the form of a dot in saphenous vein and the blood flow is observed following aspiration, the ultrasound probe is released in the sterile area while the needle is stabilized with one hand and the guide wire is placed with the other. The presence of the wire within the vein is confirmed via the ultrasound probe. In Group USGS, before the procedure, the guide wire is placed inside the needle. The ultrasound probe is placed on the medial knee region, and the saphenous vein is displayed on the long axis. (Figure 2).

When the tip of the needle (on which guide wire is adapted), is displayed in the form of a dot, the saphenous vein is continued to be scanned by the ultrasound, and the guide wire is moved forward. The presence of the wire within the vein is confirmed via the ultrasound probe. The success of the catheterization is determined as the confirmation of the guide wire by the ultrasound. If the guide wire could not be placed within 3 minutes for the defined approach, this intervention is determined as an unsuccessful catheterization. In each of the two groups, demographic data, the period passed until a successful catheterization, the time for the needle to enter to the vein (its determination as a dot during the ultrasound) and the needle intervention (needle passage) number and complications are recorded. Possible complications such as arterial puncture, hematoma and nerve injury are recorded. Also, patient specifications such as age (year), sex, height (cm), weight (kg) and hemodynamic data (systolic and diastolic blood pressure, primary central venous pressure measurement following the placement of the catheter) are recorded.

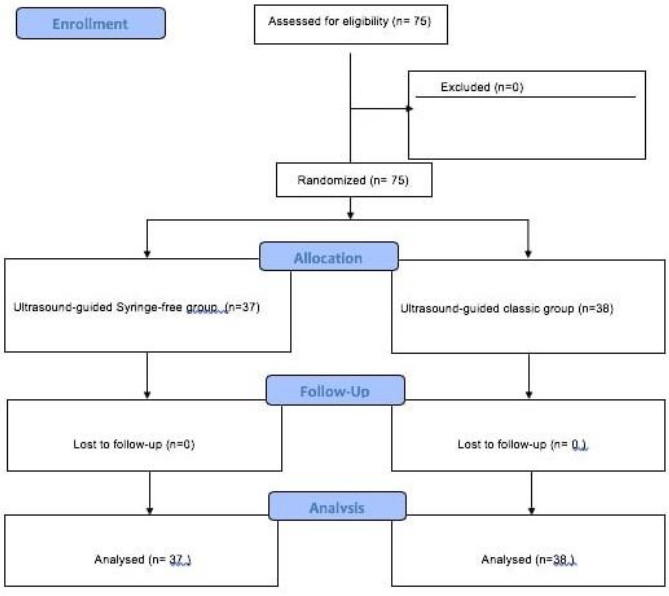

Figure 1: Flow chart

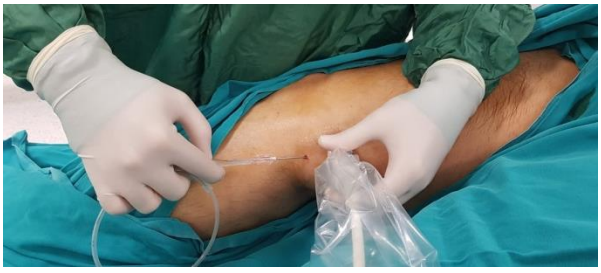

Figure 2: Ultrasound-guided syringe-free method

Results

75 patients who received an ultrasound-guided saphenous vein catheterization and who did not meet the exclusion criteria are included in the study. The patients separated randomly into 2 groups, being syringe-free and classic methods groups (Figure 1). When the demographical qualities of the patients are compared, the results are found to be similar in each group (Table 1). Vein puncture time were similar in each group. In the syringe-free method, the catheterization time is determined to be significantly shorter. In the syringe-free method, it is determined that the successful catheterization number is higher at first try, but the difference is not determined to be significant (Table 2). In each group, no complication is determined during the procedure (for example arterial puncture, hematoma) or after the procedure in relation to the central venous catheter (for example faulty catheter placement, catheter breaking).

Table 1: Demographic and clinical data

	USGSF (n=37)	USGC (n=38)	p
Age years	47.43 (12.67)	50.94 (11.11)	0.730
Weight kilo	78.59 (10.84)	77.44(13.55)	0.125
Height cm	168.75(7.5)	169.86 (9.38)	0.052
Sex Male/Female	18/19	20/18	0.836
Leg Side Right/Left	20/17	18/20(33.2)	0.812

USGSF: Ultrasound guided syringe free group, USGC: Ultrasound guided classic group *The Mann-Whitney U test was used for non-parametric variables. T-tests were used for normal continuous variables. Data are presented as mean and standard deviation (SD)

Table 2. Success rate and time

	USGSF (n=37)	USGC (n=38)	p
VPT	14(12-18)	14(12-21.5)	0.750
CT	56(50-60)	60(55-70)	0.003*
Attempt	26/9/2	23/8/6	0.370

USGSF: Ultrasound guided syhenge free group, USGC: Ultrasound guided classic group *The Mann-Whitney U test was used for non-parametric variables. CT: Catheterization Time VPT: Vascular Puncture Time Data are presented as median and IQR values (25%-75%) *Indicate p<0.05 when comparing groups IQR: Inter Quartile Range

Discussion

According to the conclusion of this study, the successful catheterization time is determined to be shorter when the syringe-free method is applied through an ultrasound-guided long axis approach. This study is the first study in the literature to realize an ultrasound-guided syringe-free method saphenous vein catheterization. Ultrasound-guided vein intervention methods have been compared and studied multiple times in the past [9,10]. There are studies that determined that long axis, short axis, and oblique axis approaches while applying an ultrasound-guided internal jugular venous catheterization don't provide different results within the context of success [11]. Even though it is reported that the primary intervention process takes a shorter period in short axis out of plane approach when compared to the long axis, this difference is not determined as significant [12]. The syringe-free method is firstly reported to be applied in internal jugular venous interventions by Matias et al. [8]. Whereas İnce et al. [13] compared the syringe-free approached applied on the oblique axis through ultrasound guidance and determined that this approach allows a shorter period for entering the vein and for catheterization. In the study that compares the classical and ultrasound-guided methods, the ultrasound-guided method is found much more successful as expected [14]. In this study, we aimed to research if the syringe-free method affects entering a vein and cannulation period and if a catheterization can be made successfully and in short time in saphenous vein catheterization through the syringe-free method, by realizing the catheterization through ultrasound guidance in each of the groups.

During the ultrasound-guided catheterization, sometimes it is difficult to aspirate while entering the needle. When the syringe-free approach is used, there is no need for blood aspiration. All of the needle and the needle tip can always be observed. The syringe-free technique allows us to display all of the procedures (needle, needle tip position, advancement of the guide wire) through the guidance of ultrasound and without any interruptions. In the method requiring aspiration with a needle, even though the needle tip is observed within the vein at the start, as we interrupt displaying in order to aspirate, the needle can move, and the tip of the needle can advance towards the other anatomical structures outside of the vein, or the repeat of the procedure can increase the complication ratio. In the catheterization result of Karakitsos et al. [15] that compared ultrasound and classical method, it is reported that the catheterization realized through ultrasound guidance caused fewer complications and is more secure. The long axis approach provides an advantage in following the guide wire [16]. In a study where the long and short axes are used together during an ultrasound-guided internal jugular vein catheterization and where this is compared with long and short axis approach, it is determined that the combined approach has a smaller vein wall puncture rate and that this provides an advantage in decreasing the complications [17]. In a study where the long axis and short axis approaches are compared, it is determined that the long axis approach caused fewer complications [18]. When the complications are compared in this study, it is determined that all two groups are similar and complications such as arterial puncture, hematoma, are not observed. It can be discussed that the complication risk can be decreased due to the fact that each of these two groups received a catheterization through ultrasound guidance and that the experience of the operator can be effective so as in all other medical processes. We consider that the fact that the surgeon who realized all catheterizations is experienced in procedures guided by the ultrasound increased the success rate and decreased the complication rate in each of the two groups.

Even though this new method provides the operator advantages such as continuing to use the ultrasound during the intervention, it is acceptable that realizing catheterization without aspiration can be a harder and newer process for operators that are not experienced. The limitations of our study are the nonrealization of the procedure by operators with different experience levels and the non-application of the intervention on different veins. There is a need for expanded studies that include more patients in order to observe and compare complications.

In conclusion, an ultrasound-guided syringe-free approach can also decrease the duration of saphenous vein catheterization and allows the operator to perform the whole procedure with ultrasound guidance without interruptions. This method can be used as an advantageous and practical method for experienced operators.

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DiGeorge syndrome (Chromosome 22q11.2 deletion syndrome): A historical perspective with review of 66 patients

DiGeorge Sendromu (Kromozom 22q11.2 delesyon sendromu): Altmış altı hastanın incelendiği tarihsel perspektif

Gökçe Celep [1], Gönül Oğur [2], Nazlıhan Günal [3], Kemal Baysal [4]

[1] Department of Pediatrics, Amasya University, Faculty of Medicine, Amasya, Turkey
[2] Department of Pediatric Genetics, Ondokuz Mayıs University, Faculty of Medicine, Samsun, Turkey
[3] Department of Pediatric Cardiology, Medicana International Hospital, Ankara, Turkey
[4] Department of Pediatric Cardiology, Ondokuz Mayıs University, Faculty of Medicine, Samsun, Turkey

ORCID ID of the authors
GC: 0000-0001-6250-5096
GO: 0000-0002-9944-4423
NG: 0000-0003-4906-8180
KB: 0000-0001-8969-590X

Corresponding author / Sorumlu yazar:
Gökçe Celep
Address / Adres: Sabuncuoğlu Şerefeddin Eğitim ve Araştırma Hastanesi, Merkez, Amasya, Türkiye
E-mail: gokce4celep@yahoo.com

Ethics Committee Approval: This study is based on a thesis approved by the Council of Higher Education with the decision number YÖK NO: 175304 and formally approved by Ondokuz Mayıs University with the decision number: 19054817-929-E.29544 for data sharing.
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Abstract

Aim: Congenital heart defects (CHD) are the most common major birth defects in humans. Conotruncal cardiac defects (CCD) and aortic arch anomalies, the outflow tract anomalies of the heart, usually accompany dysmorphic syndromes. Di George Syndrome, deletion of 22q11.2, is one of the typical examples for this entity. Our study was designed to determine the frequency of 22q11.2 deletion in a retrospectively ascertained sample of patients with conotruncal cardiac defects and structural cardiac defects accompanying other clinical findings of 22q11.2 deletion syndrome.

Methods: A total of 66 patients (4 days-16.6 years; mean 38 months), 56 followed with the diagnosis of conotruncal cardiac defects and 10 having congenital cardiac defects other than conotruncal abnormalities participated to our study . All patients underwent karyotype and Fluorescence in Situ Hybridization (FISH) analysis for 22q11.2 deletion. After the detection of the deletion a follow up protocol was formed for the patients

Results: Five of all patients were found to have the deletion positive (7.6%). Four of them had conotruncal cardiac defects. All patients having 22q11.2 deletion had at least one abnormality of the syndrome other than cardiac problems. Facial dysmorphism and growth retardation were the most common features .Cognitive disability, feeding problems, hypocalcemia, psychiatric problems, immunity differences were the other associated problems. Parental evaluation yielded one mother to be a deletion carrier.

Conclusion: We suggest that 22q11.2 deletion must be explored in all newborns with selective conotruncal cardiac defects and with non- conotruncal cardiac defects accompanying the other anomalies of the syndrome. All deletion positive patients must be evaluated for the accompanying features of the syndrome with genetic counselling.

Keywords: 22q11.2 deletion, Conotruncal anomalies, Fluorescence in Situ Hybridization

Öz

Amaç: Doğumsal kalp hastalıkları insanlarda en sık görülen konjenital anomalilerdir. Kalbin çıkış yolu anomalileri olan konotrunkal kalp hastalıkları ve aort arkı anomalileri genellikle dismorfik sendromlara eşlik eder. 22q11.2 delesyon sendromu bu klinik durumun tipik örneklerindendir. Bu çalışma konotrunkal kalp anomalileri ve 22q11. 2 delesyon sendromunun diğer klinik bulgularının eşlik ettiği doğumsal kalp hastalıklarında 22q11.2 delesyon sıklığını araştırmak amacıyla planlanmıştır.

Yöntem: Yaşları 4 gün ile 16.6 yaş arasında değişen 56 konotrunkal kalp anomalili, 10 yapısal kalp anomalisi ile sendromun diğer klinik bulgularının eşlik ettiği 66 hasta çalışmaya katıldı. Tüm hastalara karyotip analizi uygulandı, Floresan in situ hibridizasyon yöntemiyle delesyon tarandı. Pozitif saptanan hastalar için klinik izlem protokolü oluşturuldu.

Bulgular: Hastaların %7.6 (n=5) delesyon saptandı. Dördü konotrunkal kalp anomalileri grubundandı. Tüm hastalarda kalp anomalisine ek olarak sendromun diğer klinik bulgularından en az biri mevcuttu. Fasiyal dismorfizm ve gelişme geriliği en sık saptanan klinik sorunlardı. Kognitif yetersizlik, beslenme sorunları, hipokalsemi, psikiyatrik sorunlar, bağışıklık sisteminde değişiklikler saptanan diğer klinik bulgulardı. Ebeveyn değerlendirmesi sonucunda bir annede de delesyon pozitifliği saptandı.

Sonuç: Tüm seçilmiş konotrunkal kalp anomalisi olan olgularda ve sendromun diğer anomalilerinin saptandığı kalp anomalili olgularda 22q11.2 delesyonun taranması gerektiği düşünülmektedir. Delesyon pozitifliği bulunan tüm olgular diğer anomaliler açısından da değerlendirilmeli ve genetik danışma sağlanmalıdır.

Anahtar kelimeler: 22q11.2 delesyonu, konotrunkal anomaliler, Floresan in situ hibridizasyon

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Introduction

Congenital heart defects (CHD) are the most common major birth defects in humans [1]. Identifiable genetic etiologies are reported to be as high as 40% in syndromic CHD, including single gene disorders and chromosomal anomalies [1,2]. Conotruncal cardiac defects (CCD) and aortic arch anomalies, the outflow tract anomalies of the heart, may be presented as isolated cases, but usually accompany dysmorphic syndromes. Di George Syndrome, deletion of 22q11.2, is one of the most common human micro deletion syndromes and a typical example for this entity [3,4]. Genes located at the 22q11.2 locus lead to the embryonic development of the third and fourth pharyngeal arches yielding to the formation of cardiac outflow tract, great arteries, parathyroid glands, thymus, mid-face features derived from these neural crest originated arches. In spite of advanced diagnostic techniques such as multiplex ligation-dependent probe amplification (MLPA) and chromosomal microarray studies Fluorescence in Situ Hybridization (FISH) is still the most common and practical method used for screening this micro deletion syndrome [5,6].

Chromosome 22q11.2 deletion is presented in a wide spectrum of clinical features. Its frequency is 2.8-5% congenital heart defects [7,8]. In conotruncal defects this rate is reported as 10-19.4% in different studies [7,9]. Double outlet right ventricle (DORV), Tetralogy of Fallot (TOF), aortico-pulmonary window, truncus arteriosus (TA), abnormal conotruncal cushion defect, transposition of great arteries (TGA), branchial arch defects, interrupted aortic arch (IAA), double arcus aorta, sub-arterial ventricular septum defect (VSD) and right arcus aorta, the outflow tract malformations of the heart, are classified as "conotruncal cardiac defects" by Clark in 1986 [10]. A wide spectrum of clinical findings other than congenital heart defects, such as dysmorphic faces (ocular hypertelorism, bulbous nasal tip, lowset and posteriorly rotated ears), cleft palate, hypocalcaemia, T-cell mediated immune deficiency and velopharyngeal insufficiency accompany the 22q11.2 deletion syndrome. Learning difficulties, speech and feeding problems, psychiatric disorders are also common. Musculoskeletal and renal defects are less recognized clinical findings [4]. The deletion occurs as a de novo in 93% of the patients, but can be inherited in autosomal dominant fashion, that's why genetic counselling is very important for the affected families [4]. There is no genotype and phenotype correlation within the clinical features even among the same family members [4].

This study was designed to determine the frequency of 22q11.2 deletion in a sample of patients, having conotruncal cardiac defects or other congenital cardiac defects with the extra cardiac features of 22q11.2 deletion. We also aimed to form a follow up guide for evaluating the patients and their families to provide genetic counselling.

Materials and methods

This study was performed in Pediatric Genetics and Pediatric Cardiology departments of a tertiary health care center. A total of 66 patients having congenital cardiac defects were evaluated. Patients with conotruncal anomalies were the major patient group. Conotruncal cardiac defects were determined as TOF, TA, DORV, TGA, aortic arch anomalies, based on Clark's pathogenetic classification [10]. Patients with non- conotruncal cardiac anomalies enrolled to the study if they have at least one of the following features of 22q11.2 deletion syndrome: facial dysmorphism, laryngomalaise, cleft palate, hypocalcaemia, esophageal atresia, tracheoesophagial fistula, immune deficiency and neurodevelopmental delay. Two dimensional echocardiography was performed by two experienced pediatric cardiologists to define the cardiac anatomy of each patient.

For routine cytogenetic analysis, 1-3 ml of peripheral venous blood sample with sterile injectors containing 0.2 ml heparin was obtained from each patient. Conventional chromosomal analyses were performed in the Pediatric Genetic Diagnostic Laboratories to obtain chromosome plaques. Slide preparation of chromosome plaques were prepared by Giemsa-Trypsine method (GTG-taping) for the evaluation under light microscope and karyotype images were evaluated with the Olympus BX51 microscope-linked 3.9 version Applied Imaging Automatic Image Analysis System.

Slide preparations for FISH study were carried out by standard methods and hybridization fluid with probe mixture were prepared for each case. After spreading the mixture onto the slides in dark room conditions; a cover slip over the probe was fixed with protective glue for denaturation and hybridization. Fluorescence signals were examined with an x100 immersion lens on an Olympus BX 51 fluorescence microscope, which had a filter compatible with fluorescein isothiocyanate (FITC), tetramethyl rhodamine isothiocyanate (TRITC) and 4, 6-Diamidino-2-phenylindole dihydrochloride hydrate (DAPI). Signals related to DGCR were screened in at least 100 interphase nuclei and 10 metaphase chromosomes. In our kit, the TUPLE1 signals were red with Cy3 and the control region (ARSA-Arylsulfatase 22q13.3) was green with FITC. By using a 'double / triple band pass' filter in the fluorescence microscope we expected to observe two red-two green signals in the interphase nuclei and metaphases in non-deleted cases, whereas two green-one red signals in deleted ones [11,12]. FISH analyses were carried out with locus specific 'Di George/VCFS (TUPLE1, ARSA control) double color region specific probe' [Vysis Inc., Downers Grove, IL.]

For the patients having 22q11.2 deletion, physical examination, imagining and laboratory studies were performed again to find out other accompanying clinical features of the syndrome with regard to Tobias' suggestions [13]: Hypocalcaemia, thyroid dysfunctions, blood cell counts, velopharyngeal insufficiency, neuromotor and neuropsychiatric development delay, immunity problems, renal abnormalities (Table 1).

Finally parents of the affected patients underwent karyotype and FISH analyses. Genetic consultation was also performed for the future. Informed consent was obtained from the parents of all participants.

Table 1: The follow up protocol of the deletion positive patients

Evaluation topics	Parameters	Methods
Endocrinological Examination	Serum calcium, parathormone levels Free T4, TSH levels	Venous blood sample
Otorhinolaryngological Evaluation	Morphology	Routine examinations
	Audition	Auditory and autoaucustic tests
	Velopharyngeal insufficiency	Video nasal pharyngoscopy
Developmental and psychiatric evaluation		Child psychiatry consultation
Hematologic and Immunologic Evaluation	Leukocyte count Absolute lymphocyte count Thrombocytes Mean platelet volume	Complete blood count
	Leukocyte distribution Platelet morphology	Peripheral smears
	Thrombocyte function	Bleeding time by Ivy method
	Lymphocyte subgroups (CD3, CD4, CD8, CD56, CD19)	Flow cytometer
	Immunoglobulin levels	IgA, Ig G, IgM, IgE
Visceral anomalies		Abdominal ultrasonography
Genetic counselling	Karyotype analysis FISH analyses	Medical Genetics consultation

Results

Totally 66 patients aged between 4/365 days and 16. 5 years; 38 (57.6%) male and 28 (42.5%) females enrolled to the study. Fifty-six (84.8%) patients had a conotruncal anomaly and 10 (15.2%) had a non-conotruncal congenital cardiac anomaly. The features of both patient groups are summarized in Table 2 and Table 3.

Table 2: Conotruncal cardiac defects of the patients

Defect Type	n	%
Tetralogy of Fallot	34	51.5
Double outlet right ventricle	4	6
Transposition of Great Arteries	9	13.5
Truncus arteriosus	4	6
Aorticopulmonary window	1	1.5
Double arcus aorta	2	3
Atrioventricular septal defect with aortic arch anomaly	2	3

Table 3: Clinical features of non-conotruncal cardiac defect patients

	ASD	VSD	Pulmonary stenosis	Hypoplastic left heart	ASD +VSD
Facial dysmorphism	2			1	
Laryngomalacia	1				
Neurodevelopmental delay			1		
Cleft palate		1			
EA+TEF		1			
Facial dysmorpism+ EA+TEF+ Hypocalcemia		1			1
Facial dysmorpism+ Neurodevelopmental delay+Hypocalcemia			1		

ASD: Atrial septal defect, VSD: Ventricular septal defect, EA: Esophageal atresia, TEF: Tracheoesophageal fistula

All patients underwent karyotype analysis and except one patient all results were normal (Figure 1 and Figure 2).

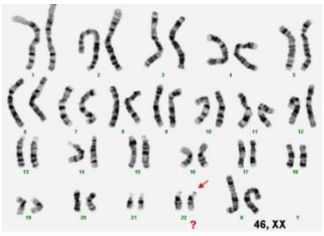

Figure 1: The karyotype of patient 3 (46,XX; Normal)

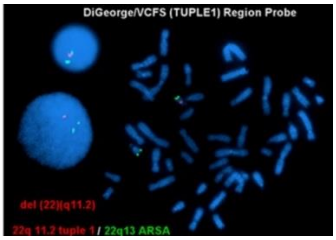

Figure 2: FISH analyses of patient 3, TUPLE1 signals were marked red with Cy3 (Cyanine dye) whereas the control region (ARSA-Arylsulfatase 22q13.3) was marked green with Fluorescein isothiocyanate (FITC). The observation of two red and two green signals was expected in interphase nuclei and metaphases in patients without deletion at the Fluorescence microscope by using a 'double/triple band pass' filter whereas the aim was to observe two green and one red signal in patients with deletion.

One of the CCD group patients had an unbalanced translocation with the karyotype 45, XY, der (7) t (7:22) (p22; q11.2),-22 (Figure 3 and Figure 4).

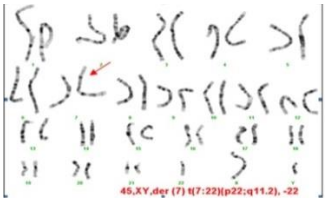

Figure 3: The karyotype of patient 4; unbalanced translocation of Chromosome 7 and Chromosome 22 resulting with the deletion of 22q11.2 region

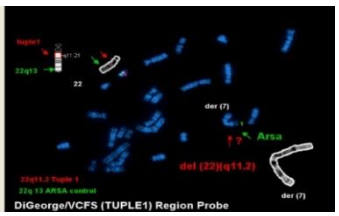

Figure 4: The FISH application of patient 4

22q11.2 deletion was detected by applying FISH method to all patients and five were found to have the deletion (7.6%). Four of the patients with deletion were from the CCD group, 3 with TOF and one with TA. All of these deletion positive patients had at least one accompanying clinical feature of 22q11.2 deletion syndrome. One patient with deletion was from the non- conotruncal cardiac defect group (10%). She had perimembranous VSD, atrial septum defect (ASD), hypocalcaemia, esophagus atresia – tracheaoesophagial fistula and facial dysmorphism.

Clinical findings other than cardiac defects of the deletion positive patients were evaluated prospectively (Table 4).

Table 4: The clinical features of 22q11.2 deletion syndrome patients

	Age Gender	Cardiac defect	Extracardiac problems	Family history
Patient 1	7/12 months Male	TOF	-Facial dysmorphism -Mildly decreased PTH with normocalcemia -Decreased CD4/CD8 without lymphopenia -Motor retardation (Denver test)	Mother, with facial dysmorphism and nasophonia, 46,XX; del 22q11.2(+)
Patient 2	3/12 months Female	TOF	-Facial dysmorphism -Hypocalcemia -Growth retardation -Reverse peristaltism in esophagus -Exitus before further evaluation because of pneumonia	None
Patient 3	6 years Female	TA	-Facial dysmorphism -Growth retardation -Neurodevelopmental delay -Selective mutism -Gastroesophageal reflux -Relative increase in CD 56; Mild increase in CD4/ CD8, no lymphopenia -Anorexia	None
Patient 4	4/365 days Female	VSD +ASD	-Facial dysmorphism -Prematurity (32 weeks), -Esophageal atresia, trachea-esophageal fistula -Hypoparathyroidism with hypocalcemia - Increase in CD 56	None
Patient 5	5/365 days Male	Tetralogy of Fallot	-Facial dysmorphism -Growth retardation -Karyotype:(45,XY, der(7)t(7:22)(p22;q11.2?),-22.;unbalanced translocation -Exitus before further evaluation	None

We weren't able to check all features in every patient although we had planned according to our follow up protocol because of survival problems. All patients had facial dysmorphism, feeding problems. Two presented hypocalcaemia. None had cleft palate or abnormal audition. One patient had communication problems and slight cognitive disability, diagnosed as 'selective mutism'. Platelet counts were within normal ranges. Thyroid functions (free T4 and TSH) in all patients were within normal ranges. Three patients could be tested for cellular immunity with CD markers. None had lymphopenia; but natural killer cell expression was increased in two patients. Immune globulin (Ig) levels could be detected in three patients and the results were compatible with age (references for laboratory evaluations [14,15]).

Family examinations of the five patients were revealed and one mother had the deletion positive (20%). She had mild

facial dysmorphism and nasophonia. The other four patients were assumed to have deletions de novo. All cases and their families were guided to the Department of Medical Genetics for genetic counselling.

Discussion

In this study the frequency 22q11.2 deletion in conotruncal and non-conotruncal cardiac defects was tested via FISH in 66 children and the frequency of the deletion was detected as 7.6% (n=5). Neither of the deletion positive patients had isolated cardiac defect, but at least one extracardiac feature of the syndrome.

FISH is still the most common method used for screening syndromes having common pathogenesis which emerges due to the loss of genetic material in the 11th region of the longer arm of the 22nd chromosome with famous names: DiGeorge Syndrome, Velocardiofacial Syndrome, Shprintzen Syndrome, Facial Syndrome with Conotruncal Cardiac Anomaly and 'CATCH 22' [4,16]. The genetic material loss by deletion and haploinsufficiency increase the variety of clinical findings and cause different phenotypes in generations within the same family [4,17]. A mother or father with no clinical signs or slight facial dysmorphism and mild velopharyngeal insufficiency, as it is the case in this study, may give birth to a baby with a severe cardiac defect [18]. In 93% of the cases, the deletion emerges 'de novo' or may be inherited in autosomal dominant manner in 6-25% of the patients [4]. In this study, compatible with the literature, one patient (20%) had maternal-originated deletion [18]. On this basis, detailed genetic counselling must be provided to the family and prenatal diagnosis possibilities must be explained well.

Seventy-five percent of the patients with 22q11.2 deletion have cardiac anomalies; most of these defects are conotruncal defects or aortic arch anomalies [19]. Among these, TOF and IAA are the most frequent ones (27-62.3%; 14-53%, respectively). Transposition of great arteries is rare [19,20]. Non-conotruncal structural cardiac anomalies are also reported, deletions may be involved in 5% of all newborns with cardiac defects [21,22]. The rate is higher in syndromic cases and patients with conotruncal cardiac anomaly. In patients having conotruncal anomalies, the frequency of deletion was reported as 2.8-4.2% [7,23]. In this study group all deletion positive patients had cardiac anomaly (7.6%; n=5). The number of patients with deletion was few, but distribution of cardiac defects was similar to the literature data, three of five had TOF, one TA, one VSD+ASD. Deletion was detected in three (8.8%) of 34 TOF patients one of four TA cases (25%). As one of the limitations of this study, the overall number of deletion positive patients was lower when compared with the literature. One reason for this could be that the number of patients with truncus arteriosus and interrupted aortic arch, which often accompany 22q11.2 deletion syndrome, was relatively low or none in this study.

Typical facial outlook is one of the prominent features of the syndrome. Upward-sloped eyebrows; short palpebral fissures; small, less convoluted, low set, posteriorly rotated ears, bulbous nose and nasal root, hypoplastic nasal wings, small mouth, micrognathia, flattening in facial mid- line structures, malar hypoplasia are characteristic findings; nevertheless they become obvious within years [5,24-26]. The findings may vary according to race and ethnicity [7]. In this study, all patients with deletion had the characteristic facial outlook of the syndrome. This situation once again emphasizes the importance of inspection in clinical evaluation.

Forty-nine (60%) of 22q11.2 the deletion positive patients display parathyroid dysfunction and temporary hypocalcaemia during infancy [27]. These patients have a tendency to arrhythmias due to cardiac anomalies that's why monitorization of serum calcium levels is recommended. Also, mineral density of the bones should be followed and early osteoporosis should be prevented. Hypothyroidism is another reported endocrinological problem [19]. In this study, hypocalcaemia was detected in two patients during neonatal period and early infancy. Thyroid functions were within normal ranges in all patients.

Eighty percent of the patients with 22q11.2 deletion display immune deficiency at varying levels [28]. T-cell count and antigenic markers must be evaluated. In this study group, no critical lymphopenia was detected and CD3 cell counts were within normal ranges with mild variations in CD4/ CD8 ratio. Early diagnosis of this problem is important because of vaccination schedule. Live vaccines are contraindicated in cellular immunity deficiencies and must be postponed until the T cell count and functions are improved [29]. Relative increase in CD56 (natural killer cells) was observed in two patients. T cell dysfunction with cardiac defects causes severe infections and necessity of intensive care unit hospitalization yielding to high healthcare costs [30]. All patients in this study experienced severe infections and hospitalized. Deletion can also cause variations in humoral immunity and tendency to severe infections may increase because of decreased antibody response [5]. Since low Ig A levels are closely related with transfusion reactions, caution is required for these patients as they are at high risk of blood and blood products exposure for various reasons. Ig levels of just three patients could be tested in this study and results were normal, compatible with age.

Palatal anomalies are frequent in patients with 22q11 deletion. Bifid uvula could be an important finding for sub-mucosal cleft palate, which can be observed by detailed physical examination [31]. Eighty percent of patients with cleft palate have velopharyngeal insufficiency. This situation, which is presented by nasophonia, articulation defects, poor feeding and nasal regurgitation, may be overlooked until the individuals begin to speak. In these cases, speech is delayed for various reasons; the problem can be diagnosed early by nasal pharyngeal endoscopy, video fluoroscopy or functional magnetic resonance imaging (MRI) so that speech therapies can begin earlier [31]. Since adenoid hypoplasia would increase velopharyngeal insufficiency, it is recommended that adenoidectomy should be avoided for these patients [5]. No palatal anomalies were detected in this study group. Also, due to patient incompatibility, only one patient could be evaluated for velopharyngeal insufficiency and pharyngeal functions were found normal with video nasal endoscopy. A study from Iran showed that 3.97% of patients with palatal problems had 22q11.2 deletion [32].

Deletion 22q11 patients may have thrombocyte dysfunction mimicking Bernard Soulier Syndrome. Since serious

bleeding may occur during surgical and invasive practices, assessment of these patients before such processes is recommended [33]. No critical thrombocytopenia, mean platelet volume (MPV) anomaly and thrombocyte dysfunction with Ivy method was observed in this group. A study in the literature suggests that the examination of 22q11 deletion is useful for those individuals who have both congenital cardiac disorders and MPV > 10fl [34].

Though it does not attract much attention, poor feeding is one of the most frequent problems. Functional problems of the gastrointestinal system such as motility disorders and anorexia are common. Due to the nasopharyngeal regurgitation caused by velopharyngeal insufficiency, the swallowing of liquid food is more difficult [5]. Poor feeding was a common problem for the affected patients of this group.

Many patients with 22q11 deletion syndrome have slight to moderate cognitive disability and require special education. The incidence of autism, attention deficit-hyperactivity syndrome, anxiety disorders, depression and obsessive-compulsive disorders are frequent [35]. Moreover, 20-30% of these patients may apply with schizophrenia or schizoid-affective disorders in adulthood [36,37]. This situation, which is often overlooked by families, causes socialization problems in these children. Supporting the child with psychiatric counselling and family education may be the solution of many problems. Similarly, one patient in this study group displayed shyness and affection disorder as well as slight cognitive disability. She could communicate only with her mother and was diagnosed with 'selective mutism' by Child Psychiatry.

In this study all cases with deletion had extracardiac clinical features of the syndrome. Particularly facial dysmorphism was accompanied by cardiac anomalies. Similarly, Khositseth et al. [24] reported that cardiac anomalies are accompanied by other clinical findings in cases with deletion. Frequency of 22q11.2 deletion in children with conotruncal heart defects was reported as 30% in another study from Turkey and the explanation of this high rate was that all patients had other dysmorphic findings of the syndrome [25]. On this basis, in routine clinical practice, examination of 22q11 deletion in all rare conotruncal anomalies such as interrupted aortic arch and truncus arteriosus is offered but for other congenital heart defects it is suggested when one of the accompanying features of the syndrome is detected.

The age of diagnose for the syndrome varies from center to center. In one study, 210 patients with 22q11 deletion were examined retrospectively and the age of diagnose for 34% of them was before one year old. Cardiac defects are the most remarkable findings for diagnosis [38]. In this study, cardiac anomalies were the key feature of the evaluation and all patients except one six year old girl were diagnosed during the neonatal period or early infancy.

In differential diagnosis, 4q deletion, unbalanced translocations or genetic arrangements related to the 22nd chromosome, 5q11.2 deletion and 10p deletion must be considered. Maternal diabetes mellitus, fetal exposure to alcohol and retinoic acid derivatives, maternal folate insufficiency may also result in similar clinic syndromes [39,40].

One of the limitations of this study is the non-exploration of the precise size of the deletion, which could have helped in establishing a genotype-to-phenotype correlation better. This study was designed for screening the deletion. Also all patients could not be evaluated for every clinical feature of the syndrome because of short survival. There is no gained new knowledge about this well-known syndrome with this study, but all clinical features are reviewed for general practitioners to provide a systematic follow up protocol for their patients and organize the treatment in a better way.

In conclusion clinical presentation of deletion 22q11 syndrome can be extremely variable. Various organ systems may be involved. For early intervention and management, early recognition of the deletion is important. The immediate performance of 22q11.2 screening for selective conotruncal anomalies (TA, IAA) via FISH analysis in addition to chromosome analysis is recommended as the severity of the cardiac anomaly shortens survive of the patients. It is clear that the rate of detection of the deletion increases if the test is applied to patients who have at least one other sign of the syndrome in addition to conotruncal anomaly. However this may cause some isolated cases with deletion to be under diagnosed, but selection is necessary for cost effectiveness. Concerning non-conotruncal cardiac anomalies, application of the test seems to be appropriate if at least two accompanying signs of the syndrome (facial dysmorphism, cleft palate, velopharyngeal insufficiency, hypocalcemia, cellular immune deficiency, speech and behavioral disorders) are present. The evaluation of the patients' parents is essential to determine the hereditary cases and for genetic counselling to provide further benefits with the chance of prenatal diagnosis.

Clinical follow-up of the 22q11.2 deletion positive patients must be carried out by a multidisciplinary teamwork [13, 39] (Table 1). Risks such as hypocalcaemia, immunity, vascular anomalies and platelet dysfunctions must be taken into consideration before surgical operations. Required modifications in diet and vaccinations must be in consideration. As some patients have tendency to severe, recurrent infections due to immune insufficiency, the treatment of infections should not be delayed. Besides; motor, behavior, speech developmental processes must be closely followed. For those patients who have speech problems and behavioral disorders, psychiatric counselling must be requested and families must be supported in this regard. An improved life quality for the patients and their families would be the success of a well-organized teamwork.

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The value of magnetic resonance imaging in diagnosing meniscal tears: A retrospective cohort study

Menisküs yırtıklarının tanısında manyetik rezonans görüntülemenin tanısal değeri: Retrospektif kohort çalışma

Almıla Coşkun Bilge [1], Nil Tokgöz [1], Hakan Dur [2], Murat Uçar [1]

[1] Gazi University Faculty of Medicine, Department of Radiology, Ankara, Turkey
[2] Gazi University Faculty of Medicine, Department of Orthopaedic Surgery, Ankara, Turkey

ORCID ID of the authors
ACB: 0000-0002-0371-4194
NT: 0000-0003-2812-1528
HD: 0000-0001-5535-0911
MU: 0000-0003-2650-0065

Corresponding author / Sorumlu yazar:
Almıla Coşkun Bilge
Address / Adres: Gazi Üniversitesi Tıp Fakültesi Radyoloji Bölümü, 06500 Beşevler, Ankara, Türkiye
E-mail: almilacoskun@gmail.com

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Abstract

Aim: Diagnostic arthroscopy is an invasive and an expensive method using for the diagnosis of meniscal tears. The aim of this study was to determine the value of knee magnetic resonance imaging in the diagnosis of meniscal tears and its role in the prevention of unnecessary diagnostic arthroscopy.

Methods: A total of 105 patients who underwent knee magnetic resonance imaging and arthroscopy due to meniscus injury were included in the study. Fifty-nine patients were examined using a 1.5 Tesla magnetic resonance scanner and 46 were examined using a 3.0 Tesla magnetic resonance scanner. Magnetic resonance imaging findings were evaluated retrospectively in workstations by two radiologists experienced in musculoskeletal magnetic resonance imaging. Meniscal tears were reported as anterior horn tear, corpus tear or posterior horn tear. Meniscal tears were classified by using surgical classification. Each patient's magnetic resonance images were evaluated with a consensus and compared with the arthroscopic diagnosis.

Results: Meniscal tears were detected in 96 out of 106 knees on arthroscopy. By using arthroscopy as the gold standard for diagnosis of meniscal tears, the sensitivity, specificity, and accuracy values of the magnetic resonance imaging evaluation were found as 85.71% (95% CI: 77.84-91.61), 93% (95% CI: 86.11-97.14) and 89.15% (95% CI: 84.17-93), respectively. These values of magnetic resonance imaging were found high in the diagnosis of meniscal tears.

Conclusions: Magnetic resonance imaging is an effective imaging method in the diagnosis of meniscal tears. Although the resolution of 3.0 Tesla magnetic resonance imaging is higher, 1.5 Tesla magnetic resonance imaging is sufficient in routine meniscus tear diagnosis.

Keywords: Magnetic resonance imaging, Arthroscopy, Meniscus

Öz

Amaç: Tanısal artroskopi, menisküs yırtıklarının tanısında kullanılan invaziv ve pahalı bir yöntemdir. Çalışmamızın amacı; diz manyetik rezonans görüntülemenin, menisküs yırtıklarının tanısında tanısal değerini ve gereksiz tanısal artroskopinin önlenmesindeki rolünü belirlemektir.

Yöntemler: Çalışmaya, menisküs yaralanması nedeniyle diz manyetik rezonans görüntüleme ve artroskopi yapılan toplam 105 hasta dahil edildi. 59 hasta 1,5 Tesla manyetik rezonans tarayıcı kullanarak, 46 hasta ise 3,0 Tesla manyetik rezonans tarayıcı kullanılarak incelendi.

Manyetik rezonans görüntüleme bulguları, kas iskelet sistemi manyetik rezonans görüntülemede deneyimli iki radyolog tarafından iş istasyonlarında retrospektif olarak değerlendirildi. Menisküs yırtıkları; ön boynuz, gövde veya arka boynuz yırtıkları olarak raporlandırıldı. Menisküs yırtıkları, cerrahi sınıflama kullanılarak sınıflandırıldı. Her hastanın manyetik rezonans görüntüleri, değerlendirilip fikir birliği sağlandı ve artroskopi tanısı ile karşılaştırıldı.

Bulgular: Artroskopide, 106 dizin 96'sında menisküs yırtığı tespit edildi. Menisküs yırtığı tanısında, altın standart olarak artroskopi kullanılarak, manyetik rezonans görüntülemenin duyarlılık, özgüllük ve doğruluk değerleri sırasıyla; %85,71 (%95 CI: 77,84-91,61), %93 (%95 CI: 86,11-97,14) ve %89,15 (%95 CI: 84,17-93) bulundu. Menisküs yırtığı tanısında manyetik rezonans görüntülemenin tanısal değerleri yüksek bulundu.

Sonuçlar: Manyetik rezonans görüntüleme, menisküs yırtığı tanısında etkili bir görüntüleme yöntemidir. 3,0 Tesla manyetik rezonans görüntülemede imajların çözünürlüğü daha yüksek olsa da, rutin menisküs yırtığı tanısında 1,5 Tesla manyetik rezonans görüntüleme yeterlidir.

Anahtar kelimeler: Manyetik rezonans görüntüleme, Artroskopi, Menisküs

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Introduction

Magnetic resonance imaging (MRI) plays an important role in the evaluation of musculoskeletal diseases. MRI has been used successfully for imaging of knee joints since Reicher et al. [1] explained meniscal anatomy in detail in 1985 and they began to use MRI for the diagnosis of knee joint pathologies. MRI is a non-invasive diagnostic method. MRI enables observation of intra-articular and extra-articular structures of the knee joint concurrently [2].

There are many studies depicting the accuracy of MRI in meniscal pathologies by using arthroscopy as the gold standard. In most studies, arthroscopy was performed in different hospitals or by different surgeons, and there were no prospective protocols used to report the arthroscopic results. In our study, a protocol was designed previously for arthroscopic findings, and the same orthopedic team performed the arthroscopy in all cases.

The aim of our study was to determine the value of knee MRI in the diagnosis of meniscal tears and to evaluate the reasons behind false-positive and false-negative MRI findings.

Materials and methods

Study population

Our institutional review board approved the study (approval number: 2010-009). Between June 2010 and June 2011, knee MRI of 114 patients who underwent arthroscopy by the same team of orthopedists were included in the study. Nine patients with previous knee surgery were excluded from the study. The final study group therefore involved 105 patients (63 females and 42 males) with a mean age of 49.53 (range, 19-76) years. The time intervals between symptom onset and arthroscopic surgery, and between MRI and arthroscopic surgery were recorded. The history of trauma was also noted.

Arthroscopic evaluation

In the evaluation of arthroscopic findings, a protocol was designed previously by consensus of the radiologists and orthopedists performing the study.

MRI technique

Fifty-nine (56.1%) patients were examined using a 1.5 T MRI scanner (Signa Excite; GE Healthcare, Wisconsin, USA), and 46 (43.8%) were examined using a 3.0 T MRI scanner (Verio VB17; Siemens Healthineers, Erlangen, Germany). A QD extremity coil was used in the 1.5 T MR scanner and an 8-channel knee coil was used in the 3.0 T MRI scanner. Knees were imaged in the neutral position through putting them in extension. On the 1.5 T MRI scanner, gradient recalled echo (GRE) T2-weighted (T2*W) sequences in the axial plane were obtained, fast spin echo (FSE) T2-weighted (T2W) and fat suppressed proton density-weighted (PDW) sequences in the sagittal plane, and T1W and FSE fat suppressed T2W sequences in the coronal plane. The sequence parameters used in 1.5 T MRI are shown in Table 1. On the 3.0 T MRI scanner, turbo spin echo (TSE) fat suppressed PDW sequences in the axial plane were obtained, TSE T2W and fat suppressed PDW sequences in the sagittal plane, T1W and TSE fat suppressed T2W sequences in the coronal plane. The sequence parameters used in 3.0 T MRI are shown in Table 2. On both 1.5 T and 3.0 T MRI, the total durations of examination were between ten and fifteen minutes.

Table 1: Sequence parameters used in 1.5 Tesla MRI

Parameters	Axial GRE T2W*	Sagittal Fat Sat FSE-PDW	Sagittal FSE- T2W	Coronal Fat Sat FSE-T2W	Coronal FSE- T1W
Slice Thickness (mm)	4	4	4	4	4
Number of slices	20	20	20	16	16
Slice gap (mm)	1	1	1	1	1
Matrix	320×192	288×192	320×192	256×160	288×192
TR (ms)	485	2600	4500	3825	375
TE (ms)	15	22	85	85	15
Average (NEX)	1	2	3	3	1
FOV (cm)	18	18	18	16	16

MRI: magnetic resonance imaging, W: weighted, GRE: gradient recalled echo, Sat: saturation, FSE: fast spin echo, PD: proton density, mm: millimeter, TR: repetition time, ms: millisecond, TE: time to echo, NEX: number of excitations, FOV: field of view, cm: centimeter

Table 2: Sequence parameters used in 3.0 Tesla MRI

Parameters	Axial Fat Sat TSE-PDW	Sagittal Fat Sat TSE-PDW	Sagittal TSE-T2W	Coronal Fat Sat TSE-T2W	Coronal TSE- T1W
Slice Thickness (mm)	3	3	3	3	3
Number of slices	25	25	25	25	25
Slice gap (mm)	0.3	0.6	0.6	0.3	0.3
Matrix	384×326	384×288	448×336	448×358	384×288
TR (ms)	2730	3800	4000	4230	550
TE (ms)	34	34	90	86	17
Average (NEX)	2	2	1	2	1
FOV (cm)	16	16	16	16	16

MRI: magnetic resonance imaging, Sat: saturation, TSE: turbo spin echo, PD: proton density, W: weighted, mm: millimeter, TR: repetition time, ms: millisecond, TE: time to echo, NEX: number of excitations, FOV: field of view, cm: centimeter.

Analysis of MRI imaging

MRI images were evaluated retrospectively on two workstations (Advantage V 4.1; GE Healthcare, Wisconsin, USA and Siemens satellite console; Siemens Healthineers, Erlangen, Germany) by two radiologists who had five and sixteen years' experience in musculoskeletal imaging, respectively. The radiologists were blinded to the arthroscopy findings. Each patient was evaluated through a consensus between these two radiologists.

The presence of intrameniscal signal increase related to one joint surface or free margin in two or more sequential images or both on coronal and sagittal images, or the presence of an abnormal meniscal morphology in the absence of meniscal surgery was evaluated as definite meniscal tear on MRI. Meniscal tears were defined as anterior horn, corpus or posterior horn tears according to their locations. On both MRI and arthroscopy, surgical classification was used, and meniscal tears were classified as radial, flap, horizontal, longitudinal, bucket-handle and complex tears.

Statistical analysis

Data analysis was performed using the SPSS 20.0 package program (IBM Corp.). The median, minimum, and maximum values of age, time interval between symptom onset and arthroscopic examination, and time interval between MRI and arthroscopic examination were calculated. Based on the arthroscopic findings, the diagnostic performance of MRI in the discrimination of patients with and without meniscal tears was evaluated using sensitivity, selectivity, and accuracy rates with a confidence interval (CI) of 95%. We also compared the diagnostic performance of 1.5 Tesla (T) and 3.0 Tesla (T) MRI in detecting meniscal tears in our study. Pearson's Chi-square test or Fisher's exact test was used to compare the sensitivity,

specificity, and accuracy. An overall p value of less than 0.05 was considered to show statistical significance.

Results

Of 105 patients included in the study, 63 (60%) were females and 42 (40%) were males. Our study included 106 knees because both knees of one patient were included in the study. The mean age of the patients was 49.53 (range, 19-76) years. The duration from symptom onset and arthroscopic examination was between one day and 120 days (mean: 30.77 days). The duration from MRI and arthroscopic examination varied between three days and 365 days (mean: 56.52 days). Imaging was performed using a 1.5 T MRI device in 59 (56.1%) patients and with a 3.0 T MRI device in 46 (43.8%). There was history of trauma in 40 (38%) of the 105 patients.

According to data obtained from arthroscopy reports of the participants, meniscal tear was detected in 96 (90.5%) out of 106 knees. In arthroscopy, 61 (63.5%) of 96 knees with tears were detected in the medial meniscus, 19 (19.7%) in the lateral meniscus, and 16 (16.6%) in both lateral and medial menisci.

False-positive findings

According to the MRI findings, there were seven false-positive findings. Three were misdiagnosed as complex tears in the anterior or posterior horn of the lateral meniscus. Three patients had incorrect diagnoses of horizontal tears that extended to the inferior or superior surface of the posterior horn of the medial meniscus. The other case was misdiagnosed as a horizontal tear in the body and posterior horn of the lateral meniscus. Four false-positive findings were acquired in 1.5 T MRI. Three false-positive findings were acquired in 3.0 T MRI.

False-negative findings

According to MRI findings, there were 16 false-negative findings in which ten were in the medial meniscus, and six were in the lateral meniscus. All of the false-negative findings except two cases involved the body or posterior horns of the medial and lateral menisci. Two cases were in the anterior horn of the lateral meniscus. Of the 16 false-negative findings, six were complex, four were radial, five were horizontal tears, and one was a longitudinal tear. Ten false-negative findings were acquired in 1.5 T MRI. Six false-negative findings were acquired in 3.0 T MRI.

The diagnostic performance of MRI for the detection of patients with meniscal tears using arthroscopy as the gold standard is shown in Table 3. A comparison of diagnostic performance of MRI in detecting medial and lateral meniscal tears is shown in Table 4. A comparison of diagnostic performance of 1.5 T and 3.0 T MRI in detecting meniscal tears is shown in Table 5.

Table 3: Diagnostic performance of MRI for detection of the patients with meniscal tears by using arthroscopy as a gold standard

	Values (95% CI)
Sensitivity	85.71% (77.84-91.61)
Specificity	93% (86.11-97.14)
Accuracy	89.15% (84.17-93)

MRI: magnetic resonance imaging, CI: confidence interval.

Table 4: Comparison of diagnostic performance of MRI in detecting medial and lateral meniscal tears

	Medial Meniscus (95% CI)	Lateral Meniscus (95% CI)	p
Sensitivity	87.01% (77.41-93.59)	82.86% (66.35-93.44)	0.560
Specificity	89.66% (72.65-97.81)	94.37% (86.20-98.44)	0.410
Accuracy	87.74% (79.94-93.31)	90.57% (83.33-95.38)	0.508

MRI: magnetic resonance imaging, CI: confidence interval.

Table 5: Comparison of diagnostic performance of 1.5 Tesla and 3.0 Tesla MRI in detecting meniscal tears

	1.5 T MRI (95% CI)	3.0 T MRI (95% CI)	p
Sensitivity	84.62% (73.52-92.37)	87.23% (74.26-95.17)	0.696
Specificity	92.45% (81.79-97.91)	93.62% (82.46-98.66)	0.999
Accuracy	88.14% (80.90-93.36)	90.43% (82.60-95.53)	0.594

MRI: magnetic resonance imaging, CI, confidence interval.

Discussion

The use of MRI in the diagnosis of meniscal tears has become daily routine practice. The accuracy of MRI in the diagnosis of meniscal tears has been reported widely in the literature [3,4]. A meta-analysis including 19 prospective studies reported that the sensitivity and specificity of MRI and arthroscopy in the diagnosis of meniscal tears were 89% (95% CI: 83-94) and 88% (95% CI: 82-93), respectively, for medial meniscal tears, and 78% (95% CI: 66-87) and 95% (95% CI: 91-97), respectively, for lateral meniscal tears [5]. In our study, the diagnostic accuracy of MRI was found to be similar to the literature. As in some studies in the literature, the sensitivity of MRI in the diagnosis of meniscus tears in the lateral meniscus was found slightly lower than that of the medial meniscus in our study [5–9]. However, this result was not statistically significant (p = 0.560). In several studies, the reasons for this result were thought to be the complex anatomy of the point joining the anterior cruciate ligament (ACL) with the lateral meniscus, the presence of ACL tears, magic angle phenomenon, and insufficient imaging of the posterior horn of the lateral meniscus on MRI due to pulsation artifact [6,7,9].

In our study, similar to studies in the literature, the specificity of MRI was found to be high in the diagnosis of meniscal tears at 89.66% (95% CI: 72.65-97.81) and 94.37% (95% CI: 86.20-98.44) for medial and lateral meniscal tears, respectively. Therefore, it was put forward that MRI detected patients without meniscal tears with high accuracy. According to the results of our study, it may be suggested that arthroscopy is unnecessary in cases in which meniscal tears are not detected on MRI. It was reported that the use of MRI could be prevented in 51% of diagnostic arthroscopic procedures [10]. Another study revealed that pre-operative knee MRI examinations precluded the need for surgery in 42% of patients [11]. However, the clinical findings of patients are of great importance. Arthroscopy must be performed in cases with high clinical suspicion for meniscal tears because MRI cannot detect small tears in the free margins of the meniscus [12].

The spatial resolution of images obtained with 3.0 T MRI was higher than those obtained with 1.5 T MRI. However, there was no statistically significant difference in the diagnostic performance regarding meniscus tears between 1.5 T and 3.0 T MRI in our study. The diagnostic performance rates of 1.5 T and 3.0 T MRI in terms of meniscus tears in the literature are compatible with our study [13–15]. Schoth et al. [16] showed that 3.0 T MRI provided better visibility of the meniscus and ligaments as compared with 1.5 T MRI. However, meniscus lesions were not investigated in this study with arthroscopic correlation. In the study of Wong et al., meniscal lesions were better visualized with 3.0 T than with 1.5 T, but the difference in diagnostic performances was not statistically significant [17]. In the retrospective study of Grossman et al., there was no significant difference in the efficacy of 1.5 T and 3.0 T MRI in

terms of meniscus tears. The authors suggested that the reason for this was the easy detectability of meniscus tears [13]. According to a meta-analysis by Smith et al., there is no evidence that the diagnostic efficacy of 3.0 T MRI is superior to that of 1.5 T, although 3.0 T MRI has perfect diagnostic ability to detect meniscus injuries [18]. Van Dyck et al. [19] performed their prospective study with 1.5 T and 3.0 T MRI in the same patients for diagnosing meniscal tears. This study showed that a routine 3.0 T knee MRI protocol did not significantly improve diagnostic performance for evaluating menisci pathology in symptomatic patients compared with a similar 1.5 T protocol. They suggested that image quality and diagnostic accuracy were not only based on magnetic field strength. Other factors, such as imaging planes, sequence type, parameter settings, and coil technology took an equally important role in the diagnostic quality of MRI examinations. The prospective study of Nouri et al. showed that 3.0 T MRI of the knee does not improve diagnosis accuracy compared with 1.5T MRI for detecting meniscal lesions [20].

In our study, there were seven false-positive findings. Three were misdiagnosed as complex tears in the anterior or posterior horn of lateral meniscus. Other cases were misdiagnosed as horizontal tears in the body and posterior horn of the lateral meniscus. Complex tears in the anterior horn of the lateral meniscus were seen at arthroscopy as degeneration (Figures 1a and 1b). On sagittal images, a linear band of lateral meniscus and anterior transverse ligament, occasionally simulate an oblique meniscal tear (Figure 1b) [21-23]. We may have exaggerated the degeneration of meniscus as a tear due to the transverse ligament. Complex tears in the posterior horn of the lateral meniscus and horizontal tears in the body and posterior horn of lateral meniscus can be misdiagnosed on MRI due to several anatomic structures or artifacts [21,24,25]. Three of the false-positive horizontal tears on MRI were documented as degeneration at arthroscopy, in our study. The orthopedists were often unable to directly visualize the inferior surface of medial menisci. These areas of the menisci could only be evaluated indirectly with a probe. This might be a reason for false-positive findings in horizontal tears of the medial meniscus that extend to the inferior surface [6,17,26]. In addition, some anatomic variations such as a fissured appearance of meniscus posterior roots, which looks like a meniscus tear in MRI, may cause misinterpretation [21].

In our study, there were 16 false-negative findings, ten of which were in the medial meniscus, and six were in the lateral meniscus. All of the false-negative findings except two cases involved the body or posterior horns of the medial and lateral menisci. The two cases were in the anterior horn of the lateral meniscus. Posterior horn tears can be missed on MRI due to several anatomic structures or artifacts. Common anatomic structures including the popliteomeniscal fascicles, meniscofemoral and meniscomeniscal ligaments can prevent visualizing meniscal tears on MRI. Truncation and arterial pulsation artifacts may complicate diagnosis of meniscal tears by causing streaks in MRI images (Figure 2a). The magic angle effect commonly occurs within the posterior horn of the lateral meniscus and it causes amorphous increased signal intensity that does not extend to the articular surface on MRI [21,24,25]. Of the false-negative findings, six were complex tears, four were radial, five were horizontal, and one was a longitudinal tear. The complex and horizontal tears appeared as meniscal degeneration signals on MRI. We interpreted the diffuse signal as degeneration because it did not extend to the surface area of the meniscus (Figures 2a and 2b). Due to the wide fibrillation of the degenerated meniscus articular surface, it may sometimes be difficult to detect the contact of the internal signal to the meniscus surface. It is difficult to differentiate a meniscal tear from fraying of the meniscus [21,27].

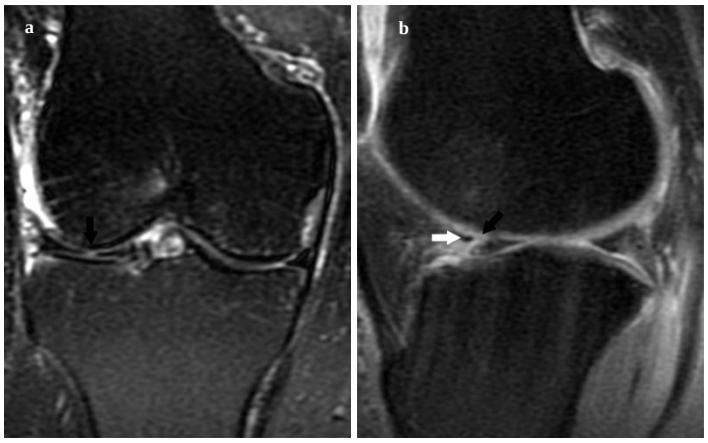

Figure 1. a, b: Coronal T2W Fat Sat 1.5 T MRI image shows a vertical tear in the lateral meniscus anterior horn (arrow, a). Sagittal PDW Fat Sat 1.5 T MRI image demonstrates an oblique tear (black arrow, b) adjacent to the transverse ligament (white arrow, b) in lateral meniscus anterior horn.

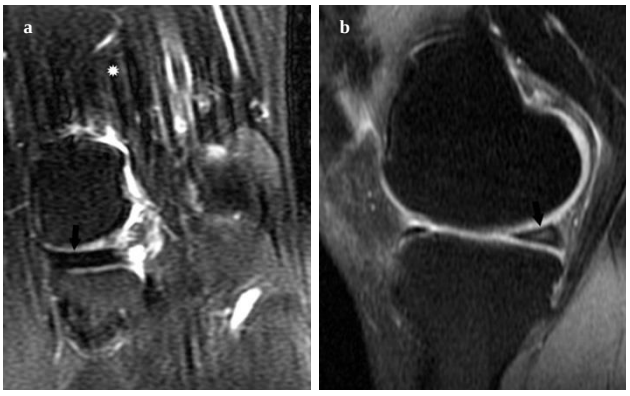

Figure 2. a, b: Coronal T2W Fat Sat 1.5 T MRI image shows linear signal did not extend to any of the surface area of the meniscus in medial meniscus posterior horn (arrow, a) and pulsation artefacts (star, a). Sagittal PDW Fat Sat 1.5 T MRI image demonstrates diffuse signal extended to no surface area of meniscus in medial meniscus posterior horn (arrow, b).

However, the orthopedists detected five horizontal tears and six complex tears in the posterior horn of the medial meniscus at the arthroscopy. We found that the interval of MRI and arthroscopy of these patients was long. The MRI and arthroscopy interval of horizontal tears was between 30 and 150 days. In this time interval, patients may experience trauma or overuse. This may lead to progression of the meniscus pathology and a false-negative diagnosis [25,28,29]. The radial tears and longitudinal tear in our study were very small in size. Radial and longitudinal tears may not be visualized clearly on coronal and sagittal MRI images because of the oblique orientation and smallness in size [21,22,30]. We did not evaluate them as a tear (Figures 3a and 3b, Figures 4a-4c).

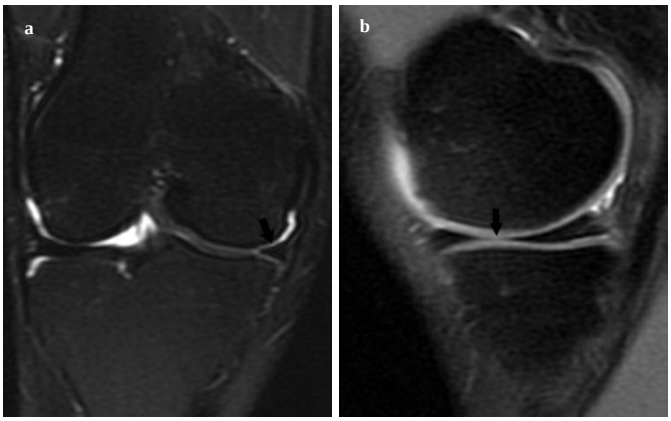

Figure 3. a, b: Coronal T2W Fat Sat 1.5 T MRI image shows the normal triangle shape of the medial meniscus and no signal at the tip of the free edge of medial meniscus body (arrow, a) Sagittal PDW Fat Sat 1.5 T MRI image shows a very small signal at the free edge of the medial meniscus body in only a single section (arrow, b).

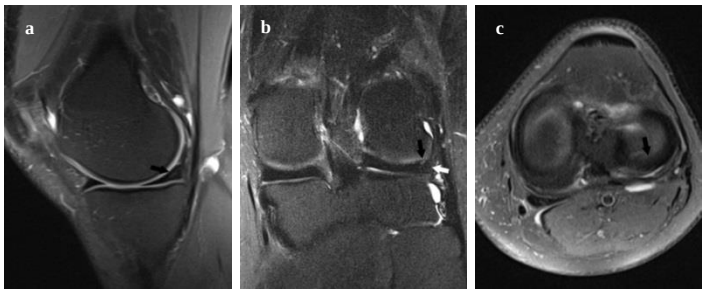

Figure 4. a-c: Sagittal PDW Fat Sat 3.0 T MRI image shows diffuse signal extended to no surface area of lateral meniscus posterior horn (arrow, a). Coronal T2W Fat Sat 3.0 T MRI image shows very small extrameniscal signal adjacent to lateral meniscus posterior horn (black arrow, b) due to the effusion between the popliteus muscle tendon (white arrow, b) and meniscus. There is no signal in lateral meniscus posterior horn in axial PDW Fat Sat 3.0 T MRI image (arrow, c).

In the literature, the accuracy of arthroscopy was reported as between 90% and 95% in the diagnosis of meniscal tears [31]. Therefore, arthroscopy was accepted as the gold standard method in the diagnosis of meniscus tears [32]. On the other hand, compared with arthroscopy, MRI shows the anatomy of the meniscus and other structures of the knee joint better [33]. The posterior horn of the medial meniscus and roots, particularly in the inferior part of the medial meniscus, cannot be clearly evaluated on arthroscopy [26]. The diagnostic sensitivity of arthroscopy depends on the clinical experience of the physician. Therefore, arthroscopy was reported as an insufficient diagnostic method in the evaluation of meniscal tears in the study of Kijowski et al. [6]. Arthroscopy is both an invasive and an expensive diagnostic method. Arthroscopy has surgical risks, including saphenous and peroneal nerve injures, deep infections, superficial infections, vascular injuries, and pulmonary embolism [34,35]. Arthroscopy is not usually needed in cases in which meniscal tears are not observed on MRI due to the high sensitivity of MRI in the diagnosis of meniscal tears. Therefore, MRI prevents unnecessary arthroscopic surgeries and the morbidity associated with arthroscopy. MRI also shows other pathologies that may lead to knee pain. The high diagnostic performance rate of MRI in our study compared with arthroscopy also demonstrates the importance of MRI the assessment of meniscal tears. MRI plays an important role in the diagnosis of knee pathologies, particularly meniscal tears [32].

Our study is a retrospective study, but we had MRI findings and we recorded them before looking at arthroscopy findings. Therefore, bias of the radiologists was prevented. After the arthroscopic evaluation, the radiologists and the orthopedists compared the MRI findings with those of arthroscopy. Another advantage of our study is that we used the same terminology for the evaluation of arthroscopy and MRI findings [31]. The use of a common terminology for imaging meniscal tears by orthopedists and radiologists' can potentially improve the interpretation of meniscal tears [36]. There are some limitations to our study that should be addressed. One of these limitations is the evaluation of MRI images of patients by orthopedists before arthroscopy. This may cause orthopedists to be biased. The second limitation is the long time interval from MRI to arthroscopy, which is between three days and 365 (mean: 56.52) days. This situation is likely to cause inconsistencies between MRI and arthroscopy findings. The third limitation is the relatively small-sized study population.

Conclusion

Although arthroscopy is accepted as the gold standard, MRI has been shown to be quite effective in the diagnosis of meniscus tears. Due to the high specificity value of MRI, arthroscopic surgery should not be performed in cases in which meniscal tears have not been observed on MRI examination. Besides, although the resolution of 3.0 T MRI is higher, we found no superiority over 1.5 T MRI in the diagnosis of meniscal tears. Based on our study's results, 1.5 T MRI can be considered sufficient in the routine diagnosis meniscus tears. Further prospective studies with a large number of patients should be performed to evaluate the sensitivity and specificity of MRI in the diagnosis of meniscus pathologies.

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Portal vein variation and thrombosis in right lobe living donor liver transplantation

Canlı vericili sağ lob karaciğer naklinde portal ven varyasyonları ve trombüsleri

Gökhan Ertuğrul [1]

[1] **Hepatobiliary Surgery and Organ Transplantation Center, Medipol University Faculty of Medicine, Istanbul, Turkey**

ORCID ID of the author(s)
GE: 0000-0002-8351-4220

Corresponding author / Sorumlu yazar:
Gökhan Ertuğrul
Address / Adres: Medipol Üniversitesi Tıp Fakültesi, Hepatobilier Cerrahisi ve Organ Nakli Merkezi, TEM Avrupa Otoyolu Göztepe Çıkışı No: 1, 34214, Bağcılar, İstanbul, Türkiye
E-mail: mdgertugrul@gmail.com

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Informed Consent: The author stated that the written consent was obtained from the patients presented with radiological images in the study.
Hasta Onamı: Yazar çalışmada radyolojik görüntüleri sunulan hastalardan yazılı onam alındığını ifade etmiştir.

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Abstract

Aim: The only definitive treatment of end stage liver disease is liver transplantation. In countries where cadaveric liver transplants are limited, living donor liver transplantation is performed. However, the presence of a variation in the portal vein of the donor, or a thrombus in the portal vein of the recipient, requires specific consideration. In this study, both of these potential limitations to living donor liver transplantation were evaluated.

Patients: We designed a retrospective cohort study. From April 2014 to December 2017 we retrospectively evaluated 129 patients who underwent right lobe living donor liver transplantation in Organ Transplantation Center, Medipol University Faculty of Medicine, Istanbul, Turkey.

Results: Nine (7%) of the patients underwent portal venous reconstruction due to either portal vein variation or portal vein thrombosis. In six patients (67%) reconstruction was performed due to the presence of a double PV in the right lobe graft. In three (33%) patients, a thrombus in the PV necessitated a reconstruction. Early postoperative morbidity occurred in one patient (11.1%) and mortality in one patient (11.1%).

Conclusions: In this study, we found portal vein reconstructions using safely frozen iliac vein grafts.

Keywords: Right lobe living donor liver transplantation, Portal vein variation, Portal vein thrombosis, Portal vein reconstruction

Öz

Amaç: Son dönem karaciğer hastalığının kesin tek tedavi yöntemi karaciğer naklidir. Kadavra karaciğer naklinin sınırlı olduğu ülkelerde, canlı donör karaciğer nakli yapılır. Bununla birlikte, donörün portal veninde bir varyasyonun veya alıcının portal veninde bir trombüsün varlığı özel bir dikkat gerektirir. Bu çalışmada, canlı vericili karaciğer nakli için bu potansiyel sınırlamaların her ikisi de değerlendirildi.

Yöntemler: Retrospektif kohort çalışma planlandı. Nisan 2014 - Aralık 2017 tarihleri arasında Medipol Üniversitesi Tıp Fakültesi, Organ Nakli Merkezi'nde sağ lob canlı vericili karaciğer nakli yapılan 129 hastayı retrospektif olarak değerlendirdik.

Bulgular: Hastaların dokuzuna (%7) portal ven varyasyonu veya portal ven trombüsünden dolayı portal venöz rekonstrüksiyon uygulandı. Altı hastada (%67) sağ lob greftinde çift portal ven açıklığının olması nedeniyle rekonstrüksiyon yapıldı. Üç hastada (%33) portal vende trombüs nedeniyle rekonstrüksiyon yapıldı. Bir hastada (%11,1) ameliyat sonrası morbidite ve bir hastada (%11,1) mortalite görüldü.

Sonuçlar: Bu çalışmada, dondurulmuş iliak ven greftlerinin portal ven rekonstrüksiyonları için güvenli bir şekilde kullanılabileceği saptanmıştır.

Anahtar kelimeler: Canlı vericili sağ lob karaciğer nakli, Portal ven varyasyonu, Portal ven trombüsü, Portal ven rekonstrüksiyonu

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Introduction

Currently, the only treatment for end stage liver disease is liver transplantation. In countries where cadaveric liver transplants are limited, living donor liver transplantation (LDLT) is performed. The first such procedure using the right hepatic lobe was reported in 1994 [1]. Since then, right lobe LDLT has become standard practice in adult patients. However, thrombus in the portal vein (PV) of the transplant recipient and anatomic variation in the PV of the donor are crucial determinants of the surgical strategy in right lobe LDLT.

If, in the recipient, a thrombus in the PV has led to an area of venous deterioration, anastomosis should be completed using a vein graft. In the presence of an anatomic variation in the PV of the donor, the anastomosis is also completed using a vein graft and does not pose any risk to the donor [1,2].

In this study evaluated portal venous reconstructions using frozen iliac vein grafts in right lobe LDLTs.

Materials and methods

Patients

From April 2014 to December 2017 we retrospectively evaluated 129 patients who underwent right lobe living donor liver transplantation in our center.

Triphasic abdominal computed tomography (CT) of the vascularity was performed preoperatively to evaluate the relevant vascular structures. Retrospective review of these examinations and the operative notes were used to determine the number of PV reconstructions and the indications for the procedure.

Liver transplantation recipients were classified according to the Yerdel classification [2] for the evaluation of a thrombus in the PV, and graft donors according to the Cheng classification [3] of variations in the PV of the right lobe (Figure 1, 2).

Yerdel classification [2];

- Grade 1: Minimally or partially thrombosed PV, in which the thrombus is mild or at most confined to <50% of the vessel lumen with or without minimal extension into the superior mesenteric vein (SMV)
- Grade 2: >50% occlusion of the PV, including total occlusion, with or without minimal extension into the SMV
- Grade 3: Complete thrombosis of both the PV and the proximal SMV but an open distal SMV
- Grade 4: Complete thrombosis of the PV as well as the proximal and distal SMVs

The Cheng classification [3] of PV configurations is as follows;

- Type I: A short right common neck formed by the right anterior branch and the posterior branch (normal)
- Type II: Early division of the anterior and posterior sectoral branches, trifurcation
- Type III: Independent posterior sectoral branching from the main trunk
- Type IV: Anterior sectoral branching from the left PV and unclassified types

Reconstruction of the PV was performed in all right lobe grafts. Portal system Doppler ultrasonography was performed once a day for the first postoperative week to evaluate anastomosis of the portal venous system. The portal venous pattern was assessed using Doppler ultrasonography during the monthly follow-ups conducted during the first postoperative year.

Iliac vein grafts removed from cadavers and stored at −80°C in RPMI 1640 medium (Life Technologies Inc., Gaithersburg, MD, USA) were used in the reconstructions.

Surgical procedure

Patients with anatomic variation or thrombus in the portal venous system underwent a reconstructive surgical procedure. For portal vein reconstruction, iliac vein grafts from cadaveric donors were used.

The receiving patient with portal vein thrombus was first cleared of the portal vein thrombus. The damaged portal vein part was expelled. The frozen iliac vein was used to lengthen the graft portal vein, and the graft portal vein was implanted using 6/0 prolene sutures.

Patients with graft-type II portal vein variation were treated by cutting the two portal vein sidewalls, using a side-by-side 6/0 prolene suture with a single lumen. The frozen iliac vein graft, cut into the perimeter of this single lumen, was stitched using a 6/0 prolene suture. A circumscribed elongated graft portal vein was achieved.

Y-shaped frozen iliac vein grafts were used in patients with graft-type III portal vein variability. Two portal vein openings in the graft were implanted and anastomosed using y-shaped iliac vein 6/0 prolene sutures (Figure 3).

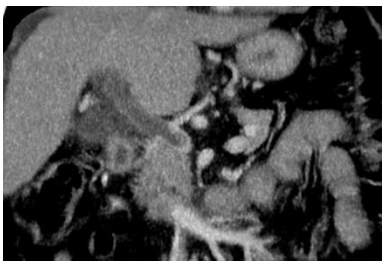

Figure 1: Portal vein thrombosis

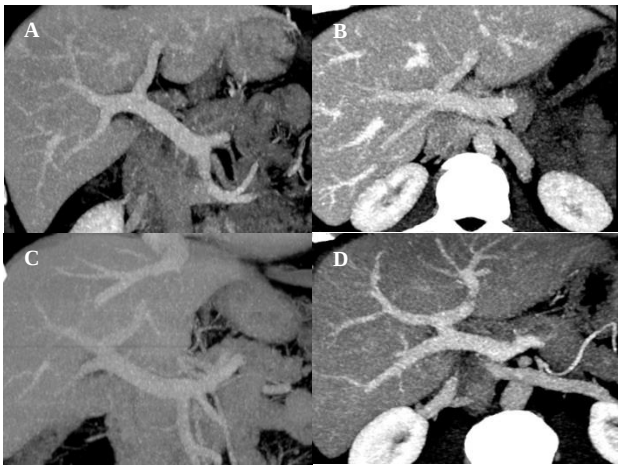

Figure 2: Portal vein variation, A: Type I (normal), B: Type II variation, C: Type III variation, D: Type IV variation

Results

From April 2014 to December 2017 we retrospectively evaluated 129 patients who underwent right lobe living donor liver transplantation in our center. Portal vein reconstruction was performed in nine (7%) patients (seven male and two female) due to an anatomic variation in the PV of the donor, or a thrombus in the PV of the recipient. Patients had a mean age of 32.3 (22–64) years. The indications for liver transplantation are

Hepatitis B virus in four (44.5%) patients, Hepatitis C virus in two (22.2%) patients, non-alcoholic steatohepatitis in two (22.2%) patients and ethanol in one (11.1%) patient (Table 1).

In 6 patients (67%) reconstruction was performed due to the presence of a double PV in the right lobe graft. In three (33%) patients, a thrombus in the PV necessitated a reconstruction (Table 2).

Table 1: Indications for right lobe living donor liver transplantation

	n	%
Hepatitis B	4	44.5
Hepatitis C	2	22.2
Non-alcoholic steatohepatitis	2	22.2
Ethanol	1	11.1
Total	9	100

Table 2: Indications for portal vein reconstruction

	n	%
Portal VeinVariations	6	66.7
Portal VeinThrombus	3	33.3
Total	9	100

According to the Yerdel classification [2], the PV thrombosis was grade 2 in all three (33.3%) patients. After clearance of the thrombus, the damaged PV segment was excised and the anastomosis completed by reconstruction using a frozen iliac vein graft.

According to the Cheng classification [3], two (33.3%) of the variations in the PV of the right lobe liver graft were type II and four (66.7 %) were type III. For the type II variations, a collar was made using frozen iliac vein (Figure 2). Reconstruction of the type III variation was performed using a y-shaped frozen iliac vein graft (Figure 3).

Early PV thrombosis developed in one (11.1%) patient, and the patient treated by surgical thrombectomy. One (11.1%) patient died due to sepsis. The mean follow-up time was 22.9 (0.5– 44) months. The overall survival rates of the patients were 88.9%.

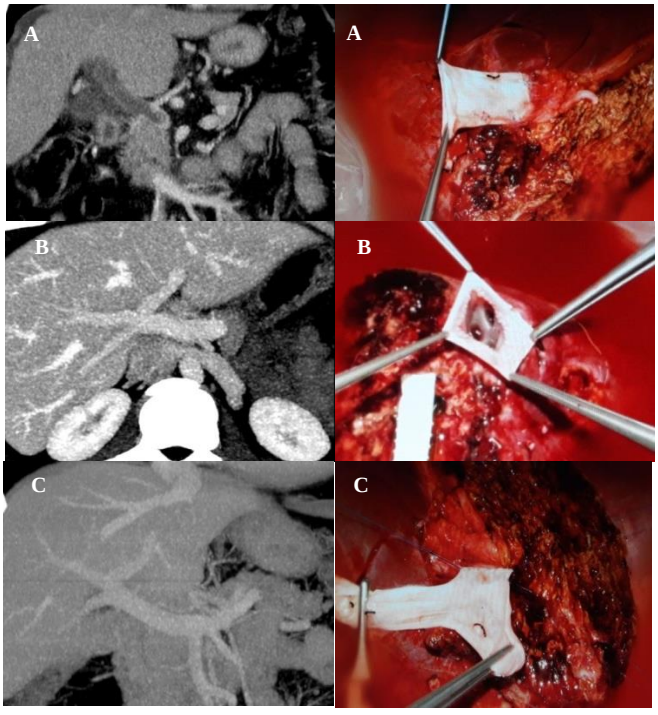

Figure 3: Portal veins reconstructions, A: Portal vein thrombus and reconstruction, B: Type II portal vein variation and reconstruction, C: Type III portal vein variation and reconstruction

Discussion

In this study, we evaluated portal vein reconstruction using frozen iliac vein grafts in right lobe LDLTs.

End stage liver disease is treatment by liver transplantation worldwide. In countries where cadavers are rare, LDLT is performed. Since the first report of right lobe LDLT in 1994 [1], it has served as the standard treatment in nearly all adult LDLT patients.

Careful assessment of the recipient and donor before LDLT is essential. During the surgical preparations, triphasic abdominal CT is performed to evaluate the PV of both the recipient and the donor. Triphasic abdominal CT is standard practice, including in our center, and is used to determine the branching features of the PV and to detect a thrombus within the vein. Individuals with severe anatomic variations, such as type IV, are not considered as donors, as the risk of serious complications is high.

PV thrombosis is a common complication of end-stage liver disease. The underlying cause is often cirrhosis (1–26% of patients), which is particularly prevalent among patients with hepatocellular carcinoma (35%) [4-7]. Although the pathogenesis of PV thrombosis against a background of cirrhosis is not well understood, abnormal portal blood flow due to portal hypertension, periportal lymphangitis, and fibrosis are probable contributing factors, as are decreases in the levels of coagulation factors such as protein C, protein S and antithrombin3, all of which are synthesized in the liver [8].

For many years, a thrombus in the PV was a relative, and in some cases an absolute, contraindication to LDLT. However, following the report of Shaw et al. [9] in 1985, and with advances in thrombectomy and graft interposition as well as acquired experience in LDLT, many patients with a PV thrombosis are candidates for this type of transplantation. Nonetheless, this complication may increase postoperative morbidity and mortality. In our series of LDLT patients, a PV thrombosis was present in 3 patients (2.3%) with who had developed end-stage liver disease. After clearance of the thrombus, the involved PV segment was removed and the anastomosis completed using frozen iliac vein graft.

The incidence of portal vein variations is between 5 % and 35 % in deferent series [10-13]. All of these variations were double PVs of right lobe liver grafts and reconstruction was carried out using Y-grafts [14,15].

Possible variation in the anatomy of the PV needs to be well examined in the preoperative period due to the potential risk to the donor and the greater likelihood of complications in the recipient. Patients receiving a graft with a variant PV need close follow up after surgery, especially in transplants with type III branching, because of the need for a double portal anastomosis. The use of frozen vascular grafts is becoming the standard treatment protocol and has allowed LDLT even with double PV grafts. With a larger pool of donors, surgery for a greater number of patients has thus become possible. However, in these cases, extensive surgical and institutional experience with this type of graft is extremely important [15].

Morbidity after LDLT in a recipient with preoperative PV thrombosis is extremely rare (1–2%) [16]. In our series, PV thrombosis resulted in the early morbidity of 1 (11.1%) patient who underwent PV reconstruction and patient was treatment with surgical thrombectomy.

The PV in the right lobe of a liver transplant mediates portal flow. Manipulations of the length of the PV to reduce tension in the anastomosis site may lead to a reduced portal flow, after stasis and thrombus or even graft loss or death. Suzuki et al. [17] reported that a PV diameter of <3.5 mm was a risk factor for portal venous occlusion. Kanazawa et al. [18] and Moon et al. [19] determined that a PV diameter <4 mm and <5 mm, respectively, increased the rate of PV complications, mainly thrombus. Thus, patients at high risk of PV complications should be regularly evaluated with PV Doppler ultrasonography. In our center Portal system Doppler ultrasonography were performed once a day for the first postoperative week to evaluate anastomosis of the portal venous system. The portal venous pattern was assessed using Doppler ultrasonography during the monthly follow-ups conducted during the first postoperative year.

In our study one (11.1%) patient died, due to sepsis. The mean follow-up time was 22.9 (0.5–44) months. The overall survival rates of the patients were 88.9%, respectively.

Conclusion

In this study, we found portal venous reconstructions using safely frozen iliac vein grafts in right lobe LDLTs involving a portal vein variation or portal vein thrombosis.

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Does hydroxyprogesterone caproate injection alter second trimester screening markers and neonatal outcomes?

Hidroksiprogesteron kaproat enjeksiyonu, ikinci trimester tarama belirteçlerini ve yenidoğan sonuçlarını değiştirir mi?

Yusuf Madendağ [1], İlknur Çöl Madendağ [2]

[1] Department of Obstetrics and Gynecology, Erciyes University Medicine Faculty, Kayseri, Turkey
[2] Department of Obstetrics and Gynecology, Health Sciences University Kayseri City Hospital, Kayseri, Turkey

ORCID ID of the author(s)
YM: 0000-0002-7622-2991
İÇM: 0000-0001-6700-2236

Corresponding author / Sorumlu yazar:
Yusuf Madendağ
Address / Adres: Erciyes Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Kayseri, Türkiye
E-mail: yusufmadendag@gmail.com

Ethics Committee Approval: Erciyes University, Medical Faculty, clinical research Ethics Committee approved this study (13.10.2017, 2017/475).
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Abstract

Aim: In the second trimester, biochemically evaluating maternal serum markers such as alpha-fetoprotein (AFP), unconjugated estriol (uE3), and human chorionic gonadotropin (hCG) may be performed as prenatal screening for neural tube defects (NTDs) and fetal aneuploidy and anomalies. We evaluated whether supplementation of 17-hydroxyprogesteronecaproate (17OHPC) in the second trimester can effect these markers. In addition, we evaluated pregnancy outcomes in pregnant women using 17OHPC.

Methods: This case control study included 1275 pregnant women between December 2014 and March 2018. The progesterone (study) group included women with a previous preterm birth and cervical length >25 mm. The control group included healthy pregnant women with a cervical length >25 mm and no previous preterm birth. Maternal age, body mass index (BMI) at the time of screening, gestational age at the time of screening, levels of maternal serum AFP, uE3, and hCG, fetal sex, fetal birth weight, Apgar score 5th minute <7, and admission to the neonatal intensive care unit (NICU) were evaluated.

Results: There was no statistically significant difference for maternal age, BMI, gestational age, fetal sex, fetal birth weight, Apgar score 5th minute <7, and admission to the NICU. The mean maternal serum uE3 and AFP levels were significantly less in the study group than in control group (P=0.008 and P=0.046, respectively). However, the mean maternal serum hCG levels were significantly higher in the study (P=0.033).

Conclusions: Second trimester screening tests for fetal aneuploidy and NTDs can give incorrect results in pregnant women using 17OHPC. These incorrect results may cause misdiagnosis and over-management. New threshold values for these markers in pregnant women using 17OHPC should be identified.

Keywords: 17-hydroxyprogesterone caproate, Prenatal screening tests, Progesterone therapy, Preterm delivery

Öz

Amaç: İkinci trimesterde, alfa-fetoprotein (AFP), konjuge olmayan estriol (uE3) ve insan koryonik gonadotropin (hCG) gibi maternal serum markırlarını biyokimyasal olarak değerlendirerek; nöral tüp defekti (NTD) ve bazı fetal anöploidi taraması yapılabilmektedir. İkinci trimesterde düşük tedavisi için 17-hidroksiprogesteron kaproat (17OHPC) takviyesinin bu markerleri etkileyip etkilemediğini değerlendirmek. Ayrıca, gebelerde 17OHPC kullanımının gebelik sonuçlarına etkisini değerlendirmektir.

Yöntemler: Bu retrospektif çalışma Aralık 2014 ile Mart 2018 arasında 1275 gebe içermekteydi. Annelik yaşı, tarama sırasındaki vücut kitle indeksi (VKİ), tarama sırasındaki gebelik yaşı, maternal serum AFP, uE3 ve hCG düzeyleri, fetal cinsiyet, fetal doğum ağırlığı, Apgar skoru 5. dakika <7 ve yenidoğan yoğun bakım ünitesine (NICU) giriş değerlendirildi.

Bulgular: Anne yaşı, VKİ, gebelik yaşı, fetal cinsiyet, fetal doğum ağırlığı, Apgar skoru 5. dakika <7 ve NICU'ya kabul edilmesinde istatistiksel olarak anlamlı bir fark yoktu. Ortalama maternal serum uE3 ve AFP düzeyleri progesteron grubunda kontrol grubuna göre anlamlı derecede düşüktü (sırasıyla p=0,008, p=0,046). Bununla birlikte, ortalama maternal serum hCG düzeyleri progesteron grubunda kontrol grubundan anlamlı derecede yüksekti (p=0,033).

Sonuçlar: Fetal anöploidi ve NTD'ler için yapılan ikinci trimester tarama testleri, 17OHPC kullanan hamile kadınlarda yanlış sonuçlar verebilir. Bu yanlış sonuçlar yanlış tanı ve aşırı yönetime neden olabilir. 17OHPC kullanan gebelerde bu belirteçler için yeni eşik değerleri tanımlanmalıdır.

Anahtar kelimeler: 17-hidroksiprogesteron-kaproat, Doğum öncesi tarama testleri, Progesteron tedavisi, Erken doğum

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Introduction

Preterm birth, which is defined as delivery prior to 37 weeks of gestation, accounts for over 85 percent of all perinatal morbidity and mortality. It is unsuccessful to postpone acute preterm labor, so protective strategies such as progesterone therapy are used by many clinics. Progesterone has an important role in maintaining pregnancy by protecting fetal membrane explants from apoptosis. Hence, progesterone therapy may decrease the rate of preterm birth or premature membrane rupture [1,2]. In addition, it maintains uterine serenity in the second and third trimesters [3].

The Food and Drug Administration (FDA, USA) approved 17-hydroxyprogesterone caproate (17OHPC) to reduce the risk of recurrent preterm birth in women with a singleton pregnancy and a history of prior spontaneous preterm delivery [4]. According to recent randomized trials, 17OHPC should start in the second trimester and continue until 37 weeks of gestation for maximum effect [5,6].

In the second trimester, biochemically evaluating maternal serum markers such as alpha-fetoprotein (AFP), unconjugated estriol (uE3), and human chorionic gonadotropin (hCG) may be performed as prenatal screening for neural tube defects (NTDs) [7] and some fetal aneuploidy and anomalies [8]. For example, elevated maternal serum AFP levels may indicate a fetal abnormality such as NTDs, abdominal wall defects, congenital nephrosis, or some tumors related to elevated AFP [9].

We evaluated whether supplementation of 17OHPC in the second trimester can affect the serum markers AFP, uE3, and hCG. In addition, we evaluated pregnancy outcomes in pregnant women using 17OHPC.

Materials and methods

This case control study, which was approved by the Institutional Ethics Committee, was performed in the Health Sciences University Kayseri Training and Research Hospital between December 2014 and March 2018. In total, 1275 pregnant Caucasian women were included in the study. Demographic characteristics such as maternal age, body mass index (BMI), gestational age, fetal birth weight, Apgar score 5th minute <7 and fetal gender were obtained from the hospital database. In addition, admission to the neonatal intensive care unit (NICU) and levels of maternal serum AFP, uE3, and hCG were evaluated.

All pregnant women included in this study were examined in our hospital from the first visit to delivery. All participants received a second trimester triple test for fetal aneuploidy and NTDs between the 16th and 19th weeks of gestation. Women with high-risk pregnancy factors such as multiple pregnancy, hypertension, body mass index >30 kg/m^2, diabetes mellitus, fetal growth retardation, miscarriages, fetal aneuploidy, endocrine diseases, chronic liver disease, using other medications, and tobacco were excluded from this study. All patients used folic acid, iron, or multivitamin preparations.

For measurement of hCG, AFP and uE3 levels in maternal serum samples, ImmuliteOne® system kits (Siemens Medical Solutions Diagnostics Limited, United Kingdom), which are based on the chemiluminescence method, were used with the Immulite 2000 device (Diagnostic Products Corporation, ABD). The values were recorded as the multiple of the median (MoM). Values were adjusted for age, weight, and gestational week. The second trimester triple test was calculated using the PRISCA 4.0 (Prenatal Risk Calculator, TYPOLOG Software/GmBH, Hamburg, Germany).

The progesterone (study) group included women with a previous preterm birth and cervical length >25 mm [5,6]. In our clinic, we apply 250 mg 17OHPC intramuscularly after the 16th week of gestation and continue weekly until the 37th week of gestation [6]. Patients with a cervical length ≤25 mm were excluded from this study because we use natural progesterone vaginally [5]. The control group included healthy pregnant women with a cervical length >25 mm and no previous preterm birth.

Statistical analysis

The Kolmogorov-Smirnov test was used for testing the normality of the data, and the variance homogeneity was assessed with the Levene test. Values were stated as mean ± standard deviation or median (25th percentile–75th percentile). Parametric comparisons were performed using a t-test, and nonparametric comparisons were performed using the Mann–Whitney U test. Minitab 16 (Minitab Inc.; State College, PA, USA) was used for all comparisons, and results were considered statistically significant when the P value was less than 0.05.

Results

This study consisted of 1275 pregnant women with 1115 in the control group and 160 in the progesterone group. Comparisons of maternal characteristics are shown in Table 1. There was no statistically significant difference between groups in terms of maternal characteristics such as age, gravidity, BMI, and gestational week at the examination time. Comparisons of biochemical parameters are shown in Table 2.

Table 1: Comparisons of maternal characteristics

	Progesterone group (n: 160)	Control group (n: 1115)	p
Maternal Age (years)	26.31 ± 6.14	26.73 ± 6.00	0.453
Maternal BMI (kg/m^2)	24.7 (23.7-28.9)	24.9 (23.5-28.6)	0.513
Gravidity	2 (2-3)	2 (2-3)	0.841
Gestational week at screening	17 (16-17)	16 (16-17)	0.278

Values are expressed as mean ± standard deviation or median (25th percentile–75th percentile). BMI: body mass index

Table 2: Comparison of biochemical parameters

	Progesterone group (n: 160)	Control group (n: 1115)	p
uE3 (ng/ml)	0.57 ± 0.26	0.72 ± 0.36	0.008
uE3 MoM	0.71 (0.55-0.92)	0.77 (0.62-0.98)	0.216
AFP(lU/ml)	31.0 ± 12.0	36.3 ± 23.5	0.046
AFP MoM	0.82 (0.61-1.08)	0.90 (0.69-1.12)	0.435
hCG (mlU/ml)	23698 (16733-31766)	18993 (13073-26303)	0.033
hCG MoM	0.98 (0.81 -1.29)	0.84 (0.60-1.11)	0.029

Values are expressed as mean ± standard deviation or median (25th percentile–75th percentile). uE3: unconjugated estriol, AFP: alpha-fetoprotein, hCG: human chorionic gonadotropin, MoM: multiple of the median

The mean maternal serum uE3 and AFP levels were significantly less in the progesterone group than in the control group (p=0.008 and p=0.046, respectively). However, the mean maternal serum hCG levels were significantly higher in the progesterone group than the control group. In addition, the MoM values of these biochemical parameters were evaluated. The median (25th percentile–75th percentile) uE3 MoM value was 0.71 (0.55-0.92) in the progesterone group whereas it was 0.77 (0.62-0.98) in the control group (p=0.216). The median (25th

percentile–75th percentile) AFP MoM value was 0.82 (0.61-1.08) in the progesterone group and 0.90 (0.69-1.12) in the control group (p=0.435). However, the median (25th percentile–75th percentile) hCG MoM value was statistically higher in the progesterone group than the control group [the median (25th percentile–75th percentile) values were 0.98 (0.81-1.29) and 0.84 (0.60-1.11), respectively, p=0.029].

Neonatal outcome and fetal characteristics were evaluated (Table 3). No significant differences for fetal birth weight, fetal gender, Apgar score 5th minute <7, and admission to the NICU were found.

Table 3: Comparison of fetal characteristics and neonatal outcomes

	Progesterone group (n: 160)	Control group (n: 1115)	p
Fetal gender	Male: 78 (48.7%)	Male: 555 (49.8%)	NS
	Female: 82 (51.2%)	Female: 560 (50.2%)	NS
Fetal birth-weight (g)	3120 ± 440	3130 ± 380	0.919
Apgar 5th minute <7	5 (3.1%)	31 (2.7%)	0.761
Admission to NICU	7 (4.5%)	47 (4.2%)	0.401

Values are expressed as mean ± standard deviation or n (%). NS: not significant, NICU: neonatal intensive care unit

Discussion

Maternal serum AFP, uE3, and hCG are markers of second trimester screening tests for fetal aneuploidy and NTDs. In this study, we evaluated whether using 17OHPC affected these markers. In order to increase the power of the study, homogeneous groups were selected. For maternal characteristics such as maternal age, BMI, gravidity, and gestational weeks at the time of screening, there was no significant difference between groups.

hCG, which is synthesized from trophoblasts, is a glycoprotein hormone. The secretion amount is proportional to the amount of trophoblastic tissue [10]. In the present study, we found that 17OHPC could increase maternal serum hCG levels. Both serum hCG levels and hCG MoM values were higher in the progesterone group than control group. Progesterone may increase placental volume [11]. Hence, increased trophoblastic tissue can increase production of hCG. Seventy percent of hCG is metabolized in the liver and 30% of hCG is metabolized in the kidneys [12]. However, progesterone may slow the metabolism of hCG in the liver. The effect of 17OHPC on hCG levels may be important for clinical use of hCG as a biochemical marker. Increased serum hCG levels may unfavorably affect second trimester screening tests for fetal aneuploidy. There is no similar study evaluating the effect of 17OHPC on maternal serum hCG level in the literature.

AFP, which is synthesized from the yolk sac, gastrointestinal tract, and fetal liver, is a glycoprotein macromolecule. It binds the estradiol hormone in the normal fetus. The AFP level rises until the 32nd gestational week, and then falls rapidly towards birth. The level increases in multiple pregnancies, open neural tube defects, and abdominal wall defects. The levels of AFP can fall in pregnant women with Down syndrome and trisomy 18 [7]. It can also be used as a tumor marker in adults. Although high-quality second-trimester fetal anatomy ultrasonography is suggested, maternal serum AFP should be performed to improve detection of NTDs when optimal images of the fetal spine or intracranial anatomy cannot be acquired (e.g. absence of high-quality ultrasound device, fetal position, or maternal obesity) [13]. In this study, we found serum AFP levels were lower in the progesterone group than in the control group. No similar studies evaluate the effect of 17OHPC on maternal serum AFP. 17OHPC may decrease production of AFP in the fetal liver. The effect of 17OHPC on AFP levels may be important for the clinical use of AFP as a biochemical marker. Decreased serum AFP levels may unfavorably affect the success of second trimester screening tests for NTD and fetal aneuploidy.

uE3 is one of the three major estrogens produced in the human body. Because uE3 production occurs in the placenta and fetus, levels increase significantly in pregnancy. Non-pregnant women, post-menopausal women, and men have similar levels. The fetal adrenal cortex-derived dehydroepiandrostenedione-sulfate (DHEA-S) is converted to 16-hydroxydehydroepiandrostenedione-sulfate (16α-OH-DHEA-S) in the fetal liver. DHEA-S and 16α-OH-DHEA-S are converted into estradiol-17α (E2) and estriol (E3) in the placenta. Shortly after E3 is produced, it is metabolized to the conjugate form in the maternal liver [14]. The active form of unconjugated estriol (uE3) accounts for 9% of total E3 in circulation. A decrease in the level of uE3 may indicate problems with fetal development. In this study, we found that serum uE3 levels were lower in the progesterone group than in the control group. Effect of 17OHPC on uE3 levels may be important for clinical use of uE3 as a biochemical marker. Decreased serum uE3 levels may unfavorably affect the success of second trimester screening tests for fetal aneuploidy. 17OHPC may negatively affect production of estriol in the fetal adrenal gland and liver as well as the placenta. Another study assessed the effect of 17OHPC on maternal salivary E3 levels. Klebanoff et al. [15] found significantly less salivary E3 levels in the progesterone group than in the control group.

We also investigated whether there was a difference in pregnancy outcomes. We did not find any positive or negative impact of 17OHPC use on neonatal outcomes such as fetal birth weight, Apgar score 5th minute <7, and admission to the NICU between study groups.

17OHPC, which is used to reduce the risk of recurrent preterm birth in women with a singleton pregnancy and a history of prior spontaneous preterm delivery, considerably alters serum markers such as AFP, uE3, and hCG. There was no previous study evaluating whether supplementation of 17OHPC in the second trimester affects these maternal serum markers in the literature. Hence, this is the first study. The limitation of this study is the nature of the retrospective. Another limitation is that we cannot evaluate long term effect of 17HPC on neonates.

Conclusion

We suggest that second trimester screening tests for fetal aneuploidy and NTDs might give incorrect results in pregnant women using 17OHPC. These incorrect results may cause misdiagnosis and over-management. Further research is needed and new threshold values for these markers in pregnant women using 17OHPC should be identified.

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The role of intravenous iron sucrose treatment in patients with iron deficiency anemia in pregnancy: A prospective controlled cohort study

Gebelikte demir eksikliği anemisi olan hastalarda intravenöz demir sükroz tedavisinin rolü: Prospektif kontrollü kohort çalışması

Mefkure Eraslan Şahin [1], İlknur Çöl Madendağ [2]

[1] Department of Obstetrics and Gynecology, Kayseri Pinarbasi Government Hospital, Kayseri, Turkey
[2] Department of Obstetrics and Gynecology, Health Sciences University, Kayseri Education and Research Hospital, Kayseri, Turkey

ORCID ID of the author(s)
MEŞ: 0000-0001-6484-9132
İÇM: 0000-0001-6700-2236

Corresponding author / Sorumlu yazar:
Mefkure Eraslan Şahin
Address / Adres: Gültepe Mahallesi, Aydoğdu Caddesi, Enplus Apart No3, Melikgazi, Kayseri, Türkiye
E-mail: mefkureee@hotmail.com

Ethics Committee Approval: This study approved by Ethics Committee of Cumhuriyet University (approval no:2018-1/13).
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Abstract

Aim: Iron deficiency anemia is the most common nutritional disorder in pregnancy and approximately 40% of all pregnant women are complicated with perinatal morbidity and mortality. In this work, the efficacy of intravenous iron sucrose and oral iron hydroxypolymaltose is compared in third-trimester pregnancies with iron deficiency anemia.

Methods: A prospective cohort study is planned. A total of 140 pregnant women were enrolled in the study in two groups. The first group consisted of patients who could not tolerate oral iron therapy and were treated with intravenous iron sucrose and the second group was composed of patients who used oral iron III hydroxy polymaltose for anemia treatment in third trimester.. The treatment effects of blood count parameters were compared between groups.

Results: Demographic and baseline characteristics were similar in both groups. Mean hemoglobin levels before treatment were 9.03±0.47 g/L in the intravenous treatment group and 8.82±0.39 g/L in the oral treatment group. 30 days after treatment, the mean hemoglobin levels were 10.7±0.55 g/L in the intravenous treatment group and 10.9±0.58 g/L in the oral treatment group. Before delivery, the mean hemoglobin levels were 11.38±0.56 g/L in the intravenous treatment group and 11.35±0.47 g/L in the oral treatment group. There was no significant difference between groups for hemoglobin levels before treatment, 30 days after treatment, and before delivery (p=0.355, p=0.513, and p=0.975, respectively). The mean mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) levels were not statistically different between groups before treatment, 30 days after treatment, and before delivery.

Conclusions: Intravenous administration of iron sucrose is an alternative to blood transfusion for the treatment of pregnant women with iron deficiency anemia during the third trimester.

Keywords: Iron sucrose, Iron deficiency anemia, Third-trimester pregnancy

Öz

Amaç: Demir eksikliği anemisi gebelikte en sık görülen beslenme bozukluğudur ve tüm gebelerin yaklaşık% 40'ı anemi nedeni ile perinatal morbidite ve mortalite ile komplikedir. Bu çalışmada, demir eksikliği anemisi olan üçüncü trimester gebeliklerde intravenöz demir sukroz ve oral demir hidroksipolizmaltozun etkinliği karşılaştırıldı.

Yöntemler: Prospektif bir kohort çalışması planlandı. Çalışmaya iki grupta toplam 140 hamile kadın alındı. Birinci grup oral demir tedavisini tolere edemeyen ve intravenöz demir sukroz ile tedavi edilen ve ikinci grup üçüncü trimesterde anemi tedavisi için oral demir III hidroksi polmaltoz kullanan hastalardan oluşuyordu. Kan sayımı parametrelerinin tedavi etkileri. gruplar arasında karşılaştırıldı.

Bulgular: Demografik ve bazal özellikler her iki grupta da benzerdi. Tedavi öncesi ortalama hemoglobin düzeyleri intravenöz tedavi grubunda 9.03±0.47 g / L, oral tedavi grubunda 8.82±0.39 g / L idi. Tedaviden 30 gün sonra, ortalama hemoglobin düzeyleri intravenöz tedavi grubunda 10.7±0.55 g / L, oral tedavi grubunda 10.9±0.58 g / L idi. Doğum öncesi ortalama hemoglobin düzeyleri intravenöz tedavi grubunda 11.38±0.56 g / L, oral tedavi grubunda 11.35±0.47 g / L idi. Gruplar arasında hemoglobin düzeyleri açısından tedaviden önce, tedaviden 30 gün sonra ve doğumdan önce anlamlı fark yoktu (sırasıyla p = 0.355, p = 0.513 ve p = 0.975). Ortalama korpüsküler hakim (MCV), ortalama korpüsküler hemoglobin (MCH) ve ortalama korpüsküler hemoglobin konsantrasyonu (MCHC) seviyeleri, tedaviden önce, tedaviden 30 gün sonra ve doğumdan önce gruplar arasında istatistiksel olarak farklı değildi.

Sonuçlar: İntravenöz demir sukroz uygulaması, üçüncü trimesterde demir eksikliği anemili gebelerin tedavisinde kan transfüzyonuna bir alternatiftir.

Anahtar kelimeler: Demir sukroz, Demir eksikliği anemisi, Üçüncü trimester gebelik

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Introduction

Iron deficiency anemia is the most common nutritional disorder worldwide and it is the most common form of anemia. Approximately 40% of all pregnancies are complicated by anemia, which causes increased perinatal morbidity and mortality, as well as low birth weight and preterm labor [1-3].

The increased requirement for iron in pregnancy can further aggravate the anemia if untreated. Recently, a range of oral, intramuscular, and intravenous iron formulations have been applied for the treatment of anemia [4]. Oral iron preparations are the first choice as they are efficacious, safe, and low cost. However, orally administered iron is poorly tolerated and associated with various gastrointestinal side effects (nausea, vomiting, abdominal pain, constipation, and diarrhea). Iron gluconate and iron dextran preparations are traditionally used for intravenous iron therapy, but their application is limited by high rates of side effects. Iron sucrose is the most recently developed intravenous iron preparation; it is increasingly used owing to its efficacy, safety, and good side-effect profile, making it one of the first options in patients who cannot tolerate oral iron preparations [4-6].

In the present study, the efficacy of intravenous iron sucrose and oral iron hydroxy polymaltose was compared for the treatment of women with iron deficiency anemia in third-trimester pregnancies.

Materials and methods

The present study was conducted at Sivas Şarkışla Government Hospital in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Cumhuriyet University (approval no:2018-1/13).

The study included pregnant women between the ages of 18 and 35, between 30 and 34 gestational weeks, with a single gestation, with iron deficiency anemia. The study was composed of two groups. The first group (IV group) consisted of patients who could not tolerate oral iron therapy and were treated with intravenous iron sucrose (Venofer, Abdi İbrahim İlaç Sanayi, Turkey). The second group (Oral group) was composed of patients who used oral iron III hydroxy polymaltose (Ferrum Hausmann Fort, Abdi İbrahim İlaç Sanayi, Turkey) for at least 4weeks. Anemia was defined as having a hemoglobin level of 70–110 g/L and patients known to have hemoglobinopathy, a history of allergic reactions, or systemic disease were excluded from the study.

For oral iron therapy, the patients were administered two100-mg elemental iron III hydroxy polymaltose tablets per day. The dose of intravenous iron sucrose used in this study was calculated as kg (target Hb-present Hb) × 0.24 + 500mg. The dose was diluted to 200mg and given on consecutive days to not exceed 600mg per week [5-8].

Demographic characteristics such as maternal age, gravida body mass index (BMI), gestational age at initiation of treatment, and gestational age at delivery were recorded. The mean mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) levels were measured before the treatment, 30 days after treatment, and before delivery, and the groups were compared.

Statistical analysis

The Shapiro–Wilk test was used to test the normality of the data. Levene's test was used to test the variance homogeneity. Values are expressed as mean±standard deviation (SD), median (25–75th percentile), or n (%). Parametric comparisons were made using a t-test or a z-test, and nonparametric comparisons were made using the Mann–Whitney U test. All comparisons were made using PASW Statistics ver. 18 (SPSS Inc., Chicago, IL, USA). A p value of <0.05 was considered statistically significant.

Results

Of the 140 pregnant women enrolled in the study, 100 received oral treatment (oral group) and 40 received intravenous treatment (IV group). Their demographic and obstetric characteristics were compared and the details are presented in Table 1. Maternal age (p=0.537), gravida (p=0.753), BMI (p=0.944), gestational age at initiation of treatment (p=0.740), and gestational age at delivery (p=0.870) were similar in both groups.

Maternal blood count values were compared and are shown in Table 2. The mean hemoglobin levels before treatment were 9.03±0.47 g/L in the IV group and 8.82±0.39 g/L in the oral group. 30 days after treatment, the mean Hb levels were 10.7±0.55 g/L in the IV group and 10.9±0.58 g/L in the oral group. Before delivery, the mean Hb levels were 11.38±0.56 g/L in the IV group and 11.35±0.47 g/L in the oral group. There was no significant difference in Hb levels between groups before treatment, 30 days after treatment, and before delivery (p=0.355, p=0.513, and p=0.975), respectively). The mean MCV, MCH, and MCHC levels were not statistically different between groups before treatment, 30 days after treatment, and before delivery, as illustrated in Table 2.

Table 1: Comparison of maternal characteristics between groups

	IV group (n=40)	Oral group (n=100)	p
Maternal age (years)	25.44±5.49	25.78±2.82	0.537
Gravida	2.09±1.01	2.10±1.04	0.753
BMI (kg/m^2)	26.90 (26.20–27.75)	27.05 (26.10–27.95)	0.944
Gestational age at initiation of treatment (weeks)	32.4±1.4	32.6±1.3	0.740
Gestational age at delivery (weeks)	39.3±0.7	39.4±0.4	0.870

Values are expressed as mean±standard deviation (SD)

Table 2: Comparison of maternal blood count values between groups

	IV group (n=40)	Oral group (n=100)	p
Hb (g/L) Before treatment	9.03±0.47	8.82±0.39	0.355
After treatment 30 days	10.7±0.55	10.9±0.58	0.513
Before delivery	11.38±0.56	11.35±0.47	0.975
MCV Before treatment	85.35±1.91	85.73±1.70	0.342
After treatment 30 days	88.23±1.86	88.62±1.64	0.410
Before delivery	90.23±3.34	91.38±2.42	0.110
MCH Before treatment	25.73±1.11	25.70±1.01	0.611
After treatment 30 days	28.33±0.93	28.49±0.97	0.986
Before delivery	29.02±1.00	29.00±1.04	0.721
MCHC Before treatment	30.70±0.87	30.57±0.83	0.391
After treatment 30 days	32.29±1.63	32.73±0.84	0.349
Before delivery	32.96±1.77	33.19±1.18	0.735

Values are expressed as mean±standard deviation (SD), median (25–75th percentile), or n (%), Hb: hemoglobin, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration

Discussion

In routine clinical practice, all clinicians encounter anemic pregnant women who cannot tolerate oral iron or who do not benefit from oral treatment. It is well documented that the babies of mothers with moderate to severe anemia have significantly lower levels of serum ferritin in their cord blood, indicating that they have insufficient iron stores [9]. Moreover, increased levels of preterm births, stillbirths, babies that are small for their gestational age, and mortality have been observed in babies born to anemic mothers [10]. It was recently reported from a study of 130 women with severe anemia that 69.2% of the mothers experienced preterm deliveries and 24.6% of babies born had lower birth weights than would be expected [11]. The goal of this study was to compare the efficacy of intravenous iron sucrose and oral iron hydroxy polymaltose in third-trimester pregnancies with iron deficiency anemia.

The main aim of anemia treatment in pregnancy is to restore hemoglobin to normal levels at the time of giving birth to avoid complications such as preterm births, stillbirths, babies that are small for their gestational age, and mortality, and to reduce the risk associated with blood transfusions. Various treatment options are available to increase hemoglobin levels, but the fastest and most reliable should be selected. Typically, oral administration of iron was believed to be a convenient, safe, and low-cost method of treatment. However, its efficacy is significantly hampered by gastrointestinal side effects, including nausea, vomiting, diarrhea, and constipation. In addition, oral administration of iron is associated with poor adsorption and a long time (months) is needed to replenish iron stores and restore hemoglobin levels [12]. Intravenous iron dextran can be used, but it leads to severe anaphylactic reactions, including sudden cardiovascular collapse, respiratory failure, and loss of life, in 0.1 to 2% of patients. Furthermore, adverse effects were reported by 30% of patients treated with iron dextran, including fever, arthritis, and urticarial [4]. Intramuscular administration of iron in the form of an iron–sorbitol citric acid complex has various side effects, including a metallic taste on the tongue, nausea, vomiting, and pain at the site of injection [13]. Other parenteral iron preparations are available in the form of ferric gluconate and ferric citrate, but they have been reported to cause severe and extended necrosis of the liver [14,15].

Our results showed that maternal serum Hb levels in pregnant women treated with IV iron sucrose and oral iron III hydroxy polymaltose were similar after 30 days and before delivery. There are now multiple reports in the literature on treatment of iron deficiency anemia in pregnancy using parenteral iron therapy, demonstrating similar or faster increases in hemoglobin levels and improved restoration of iron stores versus oral iron therapy, particularly for IV iron sucrose [4,16-21]. The positive outcomes with iron sucrose are attributed to it being a polynuclear iron complex that is analogous to ferritin, which is well tolerated and with a low level of antigenicity. It can be used for erythropoiesis within 5 min of infusion. Moreover, since it is stored in reticuloendothelial rather than parenchymal cells, it has a 68–97% utilization rate after 2–4 weeks [22]. When compared to iron dextran, the main advantage of iron sucrose is that no test dose is required before administration. There is a low level of adverse reactions to iron sucrose (0.002%) reported in the literature [23] and no adverse reactions or any other major side effects were observed during this study. However, the sample size in this study was not sufficient to statistically confirm the safety of iron sucrose.

Blood transfusions can be used to treat moderate and severe anemia in the third trimester of pregnancy. However, blood transfusion is associated with severe side effects, including, febrile and hemolytic reactions, infections anaphylactic shock, alloimmunization, and graft versus host disease [20]. In a meta-analysis of 75 clinical trials and 72 studies, treatment with IV iron preparations was associated with increased hemoglobin concentrations and it reduced the need for red blood cell transfusions (risk ratio: 0.74, 95% confidence interval: 0.62–0.88) [24]. Intravenous administration of iron sucrose may reduce the need for blood transfusions because it rapidly restores hemoglobin to normal levels. Therefore, IV iron sucrose can be considered as an alternative to oral iron treatment, thus reducing the need for blood transfusions, in the treatment of pregnant women with moderate iron deficiency anemia during the third trimester.

There are some limitations of our study. The small number of patients is the most important limitation of the study.

Conclusion

Intravenous administration of iron sucrose is a viable alternative to oral administration of iron III hydroxy polymaltose for the treatment of pregnant women with moderate iron deficiency anemia during the third trimester, which may help to reduce the need for risky blood transfusions.

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Research article
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Efficacy of foam sclerotherapy accompanied by near infrared light and duplex ultrasonography in treatment of symptomatic recurrent varicose veins: A retrospective cohort study

Semptomatik rekürren varis varislerinin tedavisinde near infrared ışık ve dubleks ultrasonografi eşliğinde köpük skleroterapinin etkinliği: Retrospektif kohort çalışma

Nail Kahraman [1], Deniz Demir [1]

[1] Bursa Yüksek Ihtisas Training and Research Hospital, Department of Cardiovasculary Surgery, Bursa, Turkey

ORCID ID of the author(s)
NK: 0000-0001-9343-0947
DD: 0000-0003-2169-7647

Corresponding author / Sorumlu yazar:
Nail Kahraman
Address / Adres: Bursa Yüksek Ihtisas Eğitim ve Araştırma Hastanesi, Kalp Damar Cerrahisi Kliniği, Bursa, Türkiye
E-mail: nailkahraman1979@gmail.com

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Abstract

Aim: The recurrence of Great Saphenous Vein (GSV) and that of Small Saphenous Vein (SSV) is a common, costly and complex challenge which is related with technically insufficient surgery or insufficient endovenous ablation and neovascularization. The purpose of this study is to assess the efficacy and the reliability of the foam sclerotherapy with Near Infrared (NIR) Light and/or Duplex Ultrasonography (DUS) in the treatment of the symptomatic Recurrent Varicose Veins (RVV).

Methods: One hundred sixty four patients (181 legs) who had been treated between April 2014 and May 2017 have been studied retrospectively. The demographic data of the patients, DUS findings, Clinical, Etiologic, Anatomic and Pathophysiologic (CEAP) classification, peri-operative data and follow-up examinations were recorded.

Results: The mean age our patients were 44.79±12.57 and 76 of them were females. It was detected that RVV in 145 extremities were developed after the open surgery (GSV ligation, GSVstripping, SSV ligation and phlebectomy) and that RVV in 36 extremities were developed after endovenous ablation (Radiofrequency ablation, Laser ablation). The reflux pathologies which led to RVV were evaluated in four groups such as incompetent saphenofemoral junction (SFJ) ±neovascularization in 114 patients, reflux from incompetent perforator / reflux from pelvic vein in 17 patients, incompetent SFJ ±neovascularization in 15 patients and combined causes in 35 patients. The stages of the patients were detected as C2 for 24 patients, as C3 for 91 patients, as C4 for 45 patients, as C5 for 16 patients and C6 for five extremities. Total occlusion was developed occurred in 172 extremities in the sixth-month control following the treatment. No major complication was seen during the follow-up.

Conclusions: Tactical and technical errors, the progression of the diseases, neovascularization may lead to RVV. The redo open surgery is more difficult compared to primary surgery. Besides, the neurovascular injury and the infection incidence of the redo surgery may be higher compared to primary surgery. Nowadays, open surgery, endovenous ablation, sclerotherapy, mechanochemical ablation (N-butyl-cyanoacrylate) may be performed in the treatment of the RVV. According to our experiences, we suggest that when foam sclerotherapy is applied in companion with NIR light and/or DUS it is a reliable, effective and cheaper treatment option that may be considered an alternative to other treatments in the convenient patients for the treatment of RVV.

Keywords: Recurrent varicose vein, Near infrared light, Foam sclerotherapy, Duplex ultrasonography

Öz

Amaç: Büyük safen ven (GSV) ve Small Safen ven (SSV) rekürrensi teknik olarak yetersiz cerrahi ya da yetersiz endovenöz ablasyon ve neovaskülarizasyona bağlı olarak yaygın, maliyetli ve karmaşık bir sorundur. Bu çalışmanın amacı semptomatik rekürren variköz venlerin(RVV) tedavisinde Near Infrared light (NIR) ve/veya Dublex Ultrasonografi (DUS) eşliğinde köpük skleroterapinin etkinliğini ve güvenliğini değerlendirmektir.

Yöntemler: Kliniğimizde nisan 2014- Mayıs 2017 yılları arasında semptomatik RVV nedeniyle köpük skleroterapi ile tedavi edilen 164 hasta (181 bacak) retrospektif olarak incelendi. Hastaların demografik verileri, DUS tarama bulguları, CEAP sınıflaması, perioperatif veriler ve takip muayeneleri kaydedildi.

Bulgular: Hastalarımızın yaş ortalaması 44.79±12.57 ve 76 (%46.3) 'i kadındı. 145 ektremitedeki RVV'ler açık cerrahi (GSV ligasyon, GSV striping, SSV ligasyon ve flebektomi) sonrası, 36 ekstremiteki RVV'lerin endovenöz ablasyon (Radyofreakans ablasyon, Lazer ablasyon) sonrası geliştiği tespit edilmiştir. RVV sebeb olan reflü patolojilerini incompetent safenofemoral junction (SFJ) ± neovascularizasyon 114 hasta, reflux from incompetent perforator / reflux from pelvic vein 17 hasta, Incompetent safeno popliteal junction (SPJ) ± neovascularizasyon 15 hasta ve combine sebebler 35 hasta olmak üzere 4 grupta değerlendirildi. Hastaların CEAP evreleri C2: 24 ekstremite, C3: 91 ekstremite, C4: 45 ekstremite, C5: 16 ekstremite, C6: 5 ekstremite olarak tespit edildi. Tedavi sonrası 6. ay kontrolünde total oklüzyon 172 (95.02 %) ekstremitede gerçekleşti. Takip süresi boyunca majör komplikasyon görülmedi.

Sonuçlar: RVV'lere taktiksel ve tekniksel hatalar, hastalığın ilerlemesi, neovaskülarizasyon sebeb olabilir. Yeniden açık ameliyatı primer cerrahiye göre daha zordur. Ayrıca redo cerrahinin nörovasküler yaralanma ve enfeksiyon insidansı da primer cerrahiye göre daha yüksek olabilir. Günümüzde RVV tedavisinde açık cerrahi, endovenöz ablasyon, skleroterapi, mekanokimyasal ablasyon(N-Butil Siyanoakrilat) yapılabilir. Deneyimlerimize göre köpük skleroterapi NIR light ve/veya DUS eşliğinde uygulandığında RVV'lerin tedavisi için uygun hastalarda diğer tedavilere alternatif olarak düşünülebilecek güvenli, etkili ve ucuz bir tedavi seçeneneği olduğunu düşünüyoruz.

Anahtar kelimeler: Recurrent varis, Near infrared ışık, Köpük skleroterapi, Duplex ultrason

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Introduction

The recurrence of the varicose veins following the varicose vein surgery is a sophisticated and costly challenge which is commonly seen. Despite the improvements in the pre-operative assessment and in the treatment methods, the recurrence following the varicose vein surgery takes place in 15% to 65% of the cases [1]. The causes such as neovascularization, technical errors done in the varice treatment and the progression of the diseases may count for the emergence of the RVV [2].

Although new endovascular treatment techniques are used, the repetition of the varices after the treatment persists to be a challenge. The advocates of the endovascular intervention claim that while neovascularization reveals commonly following the open surgery, the appearance of the neovascularization is rare following the endovascular treatments [3,4]. Regardless of which method is used in varicose vein treatment, it is a known fact that recurrent varices occur in many patients. This situation is disturbing the patients either in terms of quality of life or due to the cosmetic reasons. Many medical and surgical methods are used in the treatment of the RVV. RVV treatment is more difficult compared to technically primarily performed varice treatment procedure [5]. Thus, we used foam sclerotherapy method with 1% to 2% polidocanol which is less invasive compared to surgery in the companion NIR light (Accuavein® AV400, USA) and/or Duplex ultrasonography (DUS) in the symptomatic RVV treatment. The main purpose of our study is to assess the efficacy and the results of the method that we used in the RVV treatment.

Materials and methods

This study was performed in the Varice Treatment Center of the Cardiovascular Surgery Department of the Bursa High Specialized Hospital between April 2014 and May 2017. After the approval of the Ethics Committee from the local committee, work started. Varice treatment procedures were established in the outpatient clinic conditions by a single surgeon. The study is retrospective cohort study

The study is retrospective and monocentric and is performed in a single center. 164 patients (181 legs) who were treated by means of foam sclerotherapy due to the symptomatic RVV were investigated retrospectively. The demographic data of the patient DUS Scanning Findings, CEAP (Clinic, Etiologic, Anatomic, and Patophysiologic) classification, peri-operative data and follow-up examinations were recorded.

Preoperative DUS assessment

The deep and superficial venous system of the patients who had complaints due to the recurrent varices were evaluated with detail preoperatively by means of DUS (SonoSite Titan, SonoSite Ltd, Hitchin, UK) and the venous pathologies causing the recurrence were marked with a permanent pen on the patient. The DUS assessment was begun with GSV. The existence of flow for more than one second in the GSV and SSV segment causing recurrence was considered as significant in terms of reflux. Furthermore, GSV which was important in terms of recurrence was studied in the collateral vessels to which it was flowing. The perforating veins which had diameter greater than 3.5 centimeters and which had demonstrated retrograde flow longer than 0.5 seconds were considered as pathological perforating veins. It was recorded in terms of venous variations by performing detailed DUS.

Evaluation via preoperative NIR light

The examination was done while the patient was standing and while NIR light was in the hand of the surgeon. NIR instrument presents the instantaneous image of the venous vessels one to three millimeters below the skin. The varices with deeper localization cannot be shown through this device. RVV were scanned by moving the NIR device in fashion that it will be in a fifteen to thirty-centimeter distance to the patient on the extremity (Figure 1A, 1B). Prior knowledge was obtained about the prevalence of RVV, about the diameter of RVV and its progression in the extremity.

Sclerotherapy procedure

1% to 2% Polidocanol (Aetoxysclerol®; Kreussler, Wiesbaden, Germany) was used as the sclerosing agent in the sclerotherapy. The foam was prepared by mixing the air and the sclerosing agent foam kit in one fourth ratios. Ten millimeter foam in average was used in each session. All interventions were established by the same surgeon while the legs of the patients were in forty five-degree elevation. The injection of the sclerosing agent was done by means of 25 gauge scalp vein set and in the companion of the NIR light (Accuavein® AV400, USA) inserted on a portable carrier (Figure 2A). Punction was done to varicose vein with the image provided by the NIR light device (Figure 2 B). The progression of the sclerosing drug along the varicose vein was followed while it was being injected (Figure 2C, 2D). Moreover, if the drug was extravased during the injection with NIR light, it was attempted to preclude the complications by terminating the procedure. In varicose veins with deeper localization in which NIR light device with deeper localization could not ensure venous image, foam sclerotherapy was in the companion of DUS. Compression bandage, calcium dobecilate (Modet® tablet, Berksam Pharmaceuticals A. S., Turkey), hirudin (Hirudoid® cream, Santa Farma, Turkey) form thrombophlebitis prophylaxis were administrated for two days following the procedure.

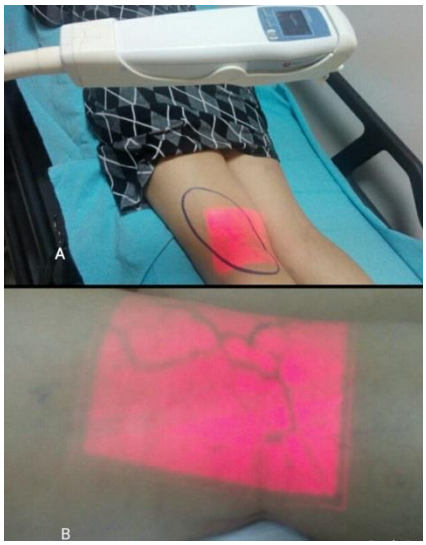

Figure 1: A: Evaluation of the patient with NIR light before sclerotherapy, B: NIR light appearance of varicose veins

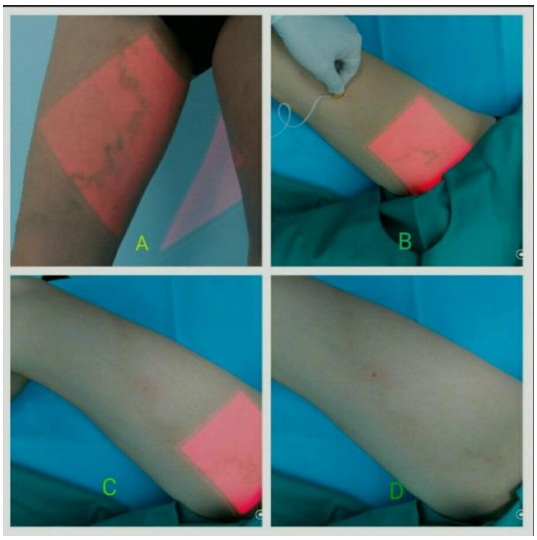

Figure 2: A: View of RVV with NIR light while patient standing, B: Foam sclerotherapy injection with NIR light in RVV, C: RVV disappeared as foam progresses in RVV, D: View of the leg treated with naked eye after foam sclerotherapy

Follow-up

Thrombophlebitis, pain, skin pigmentations, neurologic problems and skin ulcers of the patients after the patients were recorded. Minor complications belonging to the skin and major complications such as anaphylaxis, neurologic event occurring for the first month after the procedure were evaluated. RVV segments were evaluated in terms of the success of the procedure in the sixth month after the procedure. The RVV segment in which sclerotherapy with NIR light was applied was compressed by hand and the vein was assessed by patting. We evaluated the successful sclerotherapy as the absence of the blood motion in the RVV and unsuccessful sclerotherapy was accepted as the presence of the blood motion with compression and patting. Our second evaluation was tackled in terms of total occlusion of the target vein with DUS (there was no compression), partial occlusion (semi-compressible) and in terms of being patent (compressible). Sclerotherapy was continued until the complete occlusion of RVV was ensured and more than one session.

Results

Totally, 181 extremities in 164 were included into the study. 76 (46.3%) of the patients who had RVV and in which foam sclerotherapy was applied were females. The mean age of the patients was 44.79±12.5. The demographic and clinical characteristics of the cases are summarized in Table 1. The Clinical, Etiologic, Anatomic and Pathophysiologic (CEAP) stages of the patients were detected as 24 extremities for C2, 91 extremities as C3, 45 extremities for C4, 16 extremities for C5, five extremities for C6 (Table). The intervened causes of RVV were separated into four groups such as Incompetent Saphenofemoral Junction (SFJ) ± neovascularization (Anterior Accessory Saphenous Vein (AASV), Posterior Accessory Saphenous Vein (PASV) in 114 extremities (62.9 %), Reflux from incompetent perforator / Reflux from pelvic vein in 17 extremities (9.3%), Incompetent Saphenopopliteal Junction (SPJ) ± neovascularization in 15 extremities (8.2%) and Combined causes in 35 extremities (19.3%) extremities (Table 2).

In the sixth-month control of the RVV after the treatment with foam sclerotherapy total occlusion was detected in 172 extremities (95.0%), partial occlusion was detected in six (6) extremities (3.3%) and patent recurrent varice was detected in three extremities (1.7%) (Table 3).

After the treatment temporary edema was detected in 36 extremities (19.9%), local thrombophlebitis was detected in 18 extremities (9.9%), leg pain was detected in 14 extremities (7.7%), and hyperpigmentation in skin was detected in 25 extremities (13.8%) and skin necrosis was detected in two extremities (1.1%). No major complication such as death, deep vein thrombosis, anaphylaxis, neurologic complication was seen (Table 3).

Table 1: Baseline characteristics of patients

		n (%)
Number of patients		164
Number of patients (limbs)		181
Age median±SD		44.7±12.5
Gender	Female (%)	76 (46.3%)
	Male (%)	88(53.7%)
Clinical, Etiologic, Anatomic and Pathophysiologic (CEAP)	C2 of CEAP(number of lims)	24
	C3 of CEAP(number of lims)	91
	C4 of CEAP(number of lims)	45
	C5 of CEAP(number of lims)	16
	C6 of CEAP(number of lims)	5
Previous venous surgery (number of limbs)	GSV ligation	21
	GSV striping+ ligation	73
	SSV striping+ ligation	15
	GSV striping+ligation+perforating vein ligation	36
Endovenous intervention story (number of limbs)	Endovenous Laser Ablation (EVLA)	23
	Radiofrequency (RF)	10
	unknown	3

Table 2: Causes of recurrent varicose veins

	Number of Limbs n (%)
Incompetent saphenofemoral junction (SFJ)± neovascularization (Anterior Accessory Saphenous Vein (AASV), Posterior Accessory Saphenous Vein (PASV))	114(62.9)
Reflux from incompetent perforator / Reflux from pelvic vein	17(9.4)
Incompetent Saphenopopliteal Junction (SPJ) ± neovascularization	15(8.3)
Combined Causes	35(19.3)

Table 3: Intraoperative and postoperative data

		n (%)
Number of sessions of foam Sclerotherapy (Inter quartile Range(IQR))		1.9 (1-4)
Six months after treatment	complete occlusion Recurrent Varicose Veins	172 (95.0)
	partial occlusion Recurrent Varicose Veins	6 (3.3)
	patent Recurrent Varicose Veins	3 (1.7)
Complications after sclerotherapy	Skin necrosis	2(1.1)
	Local Thrombophlebitis	18(9.9)
	Hyperpigmentation	25(13.8)
	Localized pain	14(7.7)
	Deep vein thrombosis	0(0)
	Anaphylactic reaction	0(0)
	Neurological complications	0 (0)
	Temporary edema	36(19.9)

Discussion

Vena saphena magna begins from the anterior of the medial malleoli, it proceeds upwards in cruris and at the medial of the thigh and it terminates at SFJ in the inguinal region. Anterior Accessory Saphenous Vein (AASV) and Posterior Accessory Saphenous Vein (PASV) which are two primary collateral veins joint to GSV at the proximal of thigh. There are bicuspid venous valves in saphenous veins. Great Saphenous Vein may be duplicated as an anatomic variation. GSV which is the longest vein in human body is the vein in which the superficial venous problems are seen most commonly. The underlying cause of the majority of the venous problems observed in this vein is the venous valves which demonstrate function impairment [6].

The varices treatment is based on the treatment of the underlying superficial venous stasis (truncal reflux, axial reflux). Dilatation in truncal vein and the existence of reflux in DUS and the existence of the symptoms related with venous stasis in the

patient constitute the treatment indication. Regression in varices is expected with the disappearance of the superficial venous stasis. In order to eliminate the symptoms related with varices and the cosmetic problem completely sclerotherapy is usually applied either simultaneously with the treatment concerning the truncal reflux or in a separate session. Since the dilatation and stasis in the perforating veins arise mainly from the superficial venous stasis, treating the insufficiency of the varices and that of the superficial venous insufficiency regress indirectly the dilated perforating veins. In general, although the results of the surgical treatment resemble to those of thermal ablation, the complication ratios, post-operative pain, recovery time and recurrence ratios are higher in surgical treatment. In the recent guidelines, it is recommended to prefer radiofrequency or Laser ablation to surgery for the truncal reflux treatment [7]. Despite its advantages, surgical treatment may be required in cases that thermal ablation is unsuccessful, in cases that truncal vein is large in advanced level or tortuous or in cases that it is located very superficially.

The recurrence after the primary open surgery may be originated from the insufficient or wrong surgery depending on the variability of the GSV progress and on the variability of valvular anatomy. The vessel may be ligated wrongly or stripping may be done to the wrong vessel. New connections may be developed between the deeper veins and superficial veins depending on the progression of the disease. Neovascularization in the surgical procedure region may also cause recurrence [2]. In redo surgery, to reveal venous anatomy depending on the adherences and to repair surgically the pathology leading to varice is more difficult compared to primary surgery. Moreover, it brings along increased surgical complications such as paresthesia, bleeding, infection, wound traces [8-10].

In many studies, neovascularization has always been in the forefront as the most common cause after the surgery [11-13]. It is demonstrated in another study done after surgery that the recurrence of varicose veins are common. Furthermore, they have stated that some recurrences which do not depend on the neovascularization and on the progression of the disease through the examination (DUS) performed to reveal better the pathology of the disease before the surgery and through the surgical procedures [2].

In our RVV patient series, there were 181 with recurrence after varice surgery (Table 1). In the DUS scanning of these our patients, Incompetent SFJ ± neovascularization (Anterior Accessory Saphenous Vein (AASV), Posterior Accessory Saphenous Vein (PASV) was detected as the causes of the RVV in 114 extremities (62.9%), Reflux from incompetent perforator / Reflux from pelvic vein was detected as the causes of the RVV in 17 extremities (9.4%), Incompetent Saphenopopliteal Junction (SPJ) ± neovascularization was detected as the causes of the RVV in 15 extremities (8.3%) and Combined Causes were detected in 35 extremities (19.3%) (Table 2).

Although the interventions concerning the perforating veins are rarely applied, Pathological perforating veins leading to the recurrence in varices after the treatment of the truncal reflux or being adjacent to the venous ulcers (The patients with CEAP 5 to 6) should be treated selectively. As the general rule, perforating veins with diameter greater than 3.5 millimeters demonstrating retrograde longer than 0.5 seconds and being localized in the adjacency of the ulcer were referred as pathological perforating veins. In non-complicated varice patients (CEAP 2), selective perforating vein treatment is not recommended even perforating vein demonstrates insufficiency and dilatation [7]. In the Clinical, Etiologic, Anatomic and Pathophysiologic (CEAP) classification of the patients in our study, there was C2 in 24 extremities, there was C3 in 91 extremities, there was C4 in 16 extremities and there was C6 in five extremities. The most commonly used methods in the treatment of the perforating reflux are ligation or perforating vein, thermal ablation (Radiofrequency (RF) or Laser), sclerotherapy under DUS and SEPS (subfascial endoscopic perforator surgery). In a study in which superficial venous surgery combined with SEPS and with twelve-year follow-up neovascularization has been emphasized in the cause of the RVV. In this study, it was detected that incompetent lower leg perforating veins constituted 25% of the causes of the RVV and that neovascularization constituted 45% of the causes of the RVV. Although RVV has been detected in many patients through DUS, it has been revealed that long-term general results have been favorable impressively in the investigation. Besides, they have stated that open venous surgery which had been well-performed technically has successful results [14].

Endovenous Laser ablation (EVLA) is used in order to treat the varicose veins due to the reflux in the GSV and it is usually established without the ligation of Saphenofemoral Joint (SFJ) ligation [15]. No significant difference has been detected between the technic and clinic results of EVLA and RF ablation [16]. The occlusion success in the saphenous vein has been reported as over 90% in the first year and in almost 90% in the third to fifth years in both technics [6,7]. In another performed study, it has been stated that less complication has been developed in EVLA compared to open surgery. They submitted the cause of this as the use of DUS during the procedure. Since GSV can be seen along its course, the probability of occurring of recurrence depending on the insufficient surgery is lower [17].

In the SFJ ligation, external pudendal, superficial epigastric and epigastric circumflex iliac vein branches are ligated. However, in endovenous treatments, the intervention is performed into the GSV in the guidance of the with DUS via catheter from the five centimeters below the knee and the fiber tip of the LASER or RF is inserted in a fashion that it will remain 0.5 to 1 centimeters below the Saphenofemoral Joint (SFJ). Recurrences mainly being related with remaining open of the Anterior Accessory Saphenous Vein (AASV), Posterior Accessory Saphenous Vein (PASV) branches or being related with the progression of the disease may be related due to the errors depending on the performer during this procedure. In our study, RVV has been detected in 23 extremities after EVLA, in 10 extremities after the RF ablation and in three extremities after the unknown procedure (RF or EVLA). We suggest that this is due to the endovenous ablation which the accessory saphenous veins are not ligated in due form.

Theivacumar, et al. [4] have stated that recurrence after the surgery has been developed due to the neovascularization and mid-thigh perforator reflux in a study. Again in the same study,

they have emphasized that the recurrences after EVLA have arisen in Anterior Accessory Saphenous Vein (AASV) in three patients and from the mid-thigh perforator reflux. A successful GSV ablation depends not only on LASER Power and LASER wavelength and retraction ratio but also on the influential performance of the peri-venous tumescent anesthetic infiltration, on the effective application of the compression to the vein during the ablation with LASER and on the initiation of the procedure 0.5 to 1 centimeter below the Saphenous Femoral Joint (SFJ) [18]. The situation that proximal GSV does not occlude after the EVLA and/or early re-canalization have been reported as approximately 10%. In a conducted study, it has been shown that residue varices should be treated in 40% of the patients after the saphenous vein is treated [20]. In the treatment of the varices which do not regress or which demonstrate recurrence, both phlebotomy and sclerotherapy are among the accepted methods [7].

In sclerotherapy, as the liquid sclerosing agent may be directly injected, it can be injected in the form of foam by mixing with air. It is suggested that the application in the foam form ensures a more effective sclerotherapy by reducing the amount of drug and by increasing the contact duration. Since it will increase the success of the punction made telengiectasic and reticular veins which seem to observe, to use appropriate overhead light and illuminators during the sclerotherapy is extremely beneficial. DUS in sclerotherapy can be used during the treatment procedure in revealing the vascular pathology. The advantages of Ultrasound-guided foam sclerotherapy (UGFS) are being minimally invasive and return of the patients earlier to job. A disadvantage is the necessity for more than one session [21, 22]. The most commonly seen minor complications of sclerotherapy are pigmentations in the skin phlebitis, skin necrosis, reticular changes and recurrence. Major complications such as deep vein thrombosis, transient visual disturbance, stroke and transient ischemic attack are rarely seen [23]. In our study, sclerotherapy procedure was performed in the companion of NIR light and/or in the companion of DUS. With NIR light, varicose veins that cause subcutaneous RVV become visible. In addition the diffusion of the sclerozing drug within the vessel may be followed via NIR light. By this means, we suggest that this will be helpful in preventing the extravasation and injection into the deeper vein. When NIR light was insufficient in presenting the presence of varicose veins in overweight patients and in the presence of deep localized RVV, foam sclerotherapy was performed with DUS. Following the RVV foam sclerotherapy procedure, Skin necrosis complication was seen in two extremities (1.1%), Local Thrombophlebitis complication was seen in 18 extremities (9.9%), hyperpigmentation complication was seen in 25 extremities (13.8%), Localized pain was seen in 14 extremities (7.7%) and temporary edema complication was seen in 36 extremities (19.9%). Deep vein thrombosis, Anaphylactic reaction, Neurological complications were not developed in none of our patients (Table 3).

In a study evaluating 808 varicose patients treated with UGFS, the total occlusion of GSV was detected as 88% and the total occlusion rate of SSV was detected as 82%. As a result of this study, they stated that UGFS can be used effectively to treat varicose disease in outpatient clinic conditions without requiring for surgical intervention. Moreover, thy reported that the effectiveness ratios and the complication ratios were similar to those which were reported in other new treatments applied for varicose veins [24]. As a result of a meta-analysis in which the mean follow-up time of the patients was thirty two (32) months, the success of the UGFS total occlusion was 77% (69% to 84%) and the success of the open surgery was seventy eight percent (78%)(70% to 84%) [16]. In another study comparing surgical treatment and foam sclerotherapy, they stated that their effectivities were found similar as a result of five-year follow-up. However, they claimed that the superiority of the sclerotherapy is to be applicable several times [25]. In our study, in the sixth-month control after the treatment total occlusion was detected in 172 extremities (95.0%), partial occlusion was detected in six extremities (3.3%); patent recurrent varice was detected in three extremities (1.7%) (Table 3). We suggest that this higher success ratio is related with the performance of the procedure in the companion of the NIR light and DUS. Because we can follow with NIR light that RVV is completely filled with sclerosing agent and we can follow the course of the sclerosing agent within the RVV with a wide angle of vision. We suggest that this provides us either to apply an effective foam sclerotherapy or to protect our patient from many complications such as Deep Venous Thrombosis (DVT), skin necrosis.

This study has some limitations, including its retrospective design and small sample size.

Conclusion

Tactical and the technical errors in the management of RVV may lead to impairment of the diseases and to neovascularization. Redo open surgery is more difficult than the primary surgery. The incidence of neurovascular injury and that of the infection may also be higher compared to primary surgery. In the treatment of the RVV, open surgery, endovenous ablation (RF/EVLA), mechanochemical ablation (N-butyl-Cyanoacrilate) may be performed. The choice of RVV treatment should be tailored to each patient especially by taking into account factors such as the anatomy of the vessels, the requests of the patient, and the preferences of the surgeon. According to our experiences, we suggest that when it is applied in the companion of the NIR light and/or DUS, sclerotherapy may be considered as a safe, effective and cheaper treatment option alternatively to other treatments that can be applied in patients which are convenient for the RVV treatment.

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Carcinoid tumor of the small intestine: A case report

İnce bağırsakta karsinoid tümör: Olgu sunumu

Moussa Sylla [1], Pierlesky Elion Ossibi [1], Ismael Dandakoye Soumana [1], Somuah Tenkorang [2], Souiki Tarik [1], Imane Toughrai [1], Karim Ibn Majdoub Hassani [1], Khalid Mazaz [1]

[1] Department of Visceral Surgery B, Hassan II University Hospital, Fez, Morocco
[2] Departement of Urology, Hassan II University Hospital, Fez, Morocco

ORCID ID of the authors
MS: 0000-0002-5739-7382
PEO: 0000-0003-2716-4518
IDS: 0000-0003-2451-4199
ST: 0000-0001-5657-7253
ST: 0000-0002-2416-4355
IT: 0000-0003-0401-3012
KIMH: 0000-0002-0421-7296
KM: 0000-0001-7779-7802

Abstract
Carcinoid tumors are the second most common tumors of the small intestine after adenocarcinoma. These tumors are discovered either incidentally in the event of investigating non-specific digestive disorders notably in patients with Konig's syndrome. Diagnosis is confirmed through histopathology complemented with immunohistochemistry. Surgery is the only curative treatment and it is indicated upon decision by a multidisciplinary treatment team. We report a case of a 65-year-old woman with carcinoid tumor of the ileum.
Keywords: Carcinoid tumor, Ileum, Retractile mesenteritis, Surgery

Öz
Karsinoid tümörler adenokarsinom sonrası ince bağırsağın ikinci en yaygın tümörleridir. Bu tümörler, özellikle Konig sendromlu hastalarda spesifik olmayan sindirim bozukluklarını araştırırken tesadüfen keşfedilmiştir. Tanı immünohistokimya ile tamamlanan histopatoloji ile doğrulanır. Cerrahi tek küratif tedavidir ve çok disiplinli bir tedavi ekibinin kararıyla belirtilir. Biz ileumun karsinoid tümörü olan 65 yaşında bir kadın hastayı sunuyoruz.
Anahtar kelimeler: Karsinoid tümör, Ileum, Retraktil mezenterit, Cerrahi

Introduction

Carcinoid tumors are well differentiated neuroendocrine tumors. They are mostly derived from digestive tract, of non-pancreatic origin, developed at the expense of the enterochromaffin cells of the digestive tract. They are located in the gastrointestinal tract in 67% of cases and bronchial tubes in 25% of cases. They are the second most common tumor in the small intestine after adenocarcinoma. We report a case of a 65-year-old woman with carcinoid tumor of the ileum.

Case presentation

A 65 year old female patient with a history of cholecystectomy performed a year ago was admitted for periumbilical pain and hematochezia associated with konig's syndrome. Clinical examination found a patient with a satisfactory general condition, sensitivity in the right iliac fossa and a hard, painful and mobile mass (35mm large). Proctologic exams revealed an anterior large anal fissure which appeared recent in nature. Digital rectal exam was normal. Ileo-colonoscopy was normal. Abdominal computed tomography (CT) detected the presence of an endoluminal ileal mass in the right iliac fossa. This mass enhanced heterogeneously after contrast injection. It measured 30 x 26mm in diameter associated with multiple mesenteric lymph nodes (the largest of which was 18mm) containing calcifications, calcifications with retractile Mesenteritis (Figure 1).

Corresponding author / Sorumlu yazar:
Moussa Sylla
Address / Adres: Department of Visceral Surgery B, Hassan II University Hospital, Fez, Morocco
e-Mail: syllams86@yahoo.fr

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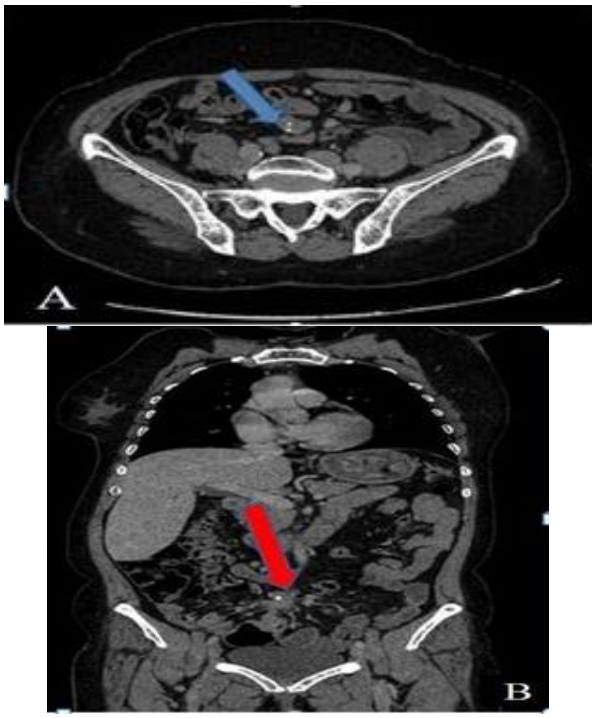

Figure 1: A: Axial abdominal computed tomography showing endoluminal ileal mass in the right iliac fossa, B: Axial image showing retractile mesenteritis

The patient's case was discussed by our multidisciplinary team of specialists who decided on surgery.

A 3 cm mass of the ileum located at 80 cm from the ileocecal valve was found during surgery. The mesentery of this portion of the ileum was retracted with the presence of multiple reactive lymph nodes. We preceded by performing resection the portion of the diseased ileum followed by termino-terminal anastomosis of healthy portions of the ileum (figure 2).

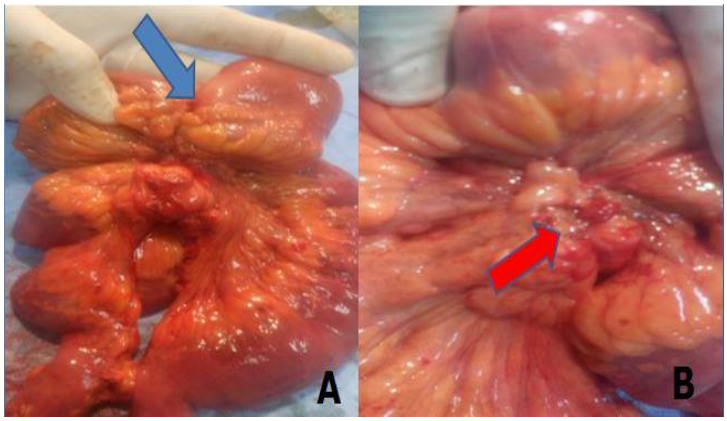

Figure 2: A: The surgical specimen showing the tumor, B: The surgical specimen showing the retractile mesenteritis

The postoperative course was unremarkable. Histopathological examination of the surgical specimen revealed a well differentiated pT4N1, Grade 2 neuroendocrine carcinoma (ENETS), infiltrating the ileal fat. This exam was complemented by Immunohistochemistry which revealed tumor cells expressing synaptophysin and chromogranin A; The Ki67 was estimated at 15%.

The patient's case was discussed again by the multidisciplinary team of specialists who decided on adjuvant chemotherapy. The patient was referred to the department of oncology for adjuvant chemotherapy.

Discussion

Carcinoid tumors are well differentiated neuroendocrine tumors. They develop mostly from enterochromaffin cells located in the gastrointestinal (GI) tract. They are located in The GI tract in 67% of cases and in the bronchial tubes in 25% of cases. Among its localizations in the GI tract, the small intestine represents 42%. It is the second most common tumor of the small intestine after adenocarcinoma [1], Carcinoid tumors are located in the rectum (27%), the stomach (8.7%), and the appendix (5%) [2]. Non carcinoid tumors can be associated with carcinoid tumors of the small intestine in 29% of cases. At the time of diagnosis, 12.9% of patients already have metastases [2].

These tumors of the small intestine are discovered either fortuitously in the event of investigating non-specific digestive disorders [3], or when symptoms such as abdominal mass, GI hemorrhage, mesenteric infarction or Konig's syndrome occur which was the case in our patient.

The confirmation of the carcinoid origin of the tumor is based on:

- Blood immunity test (Serotonin, chromogranins A, B or C, synaptophysin, Neuron Specific Enolase), 5-hydroxyindoleacetic acid urine test (5- HIAA) [4].
- Radiological imaging (ultrasound, CT, octreotide scan) [5]
- Histopathological and immunolabeling findings.

New less radiating radiological modalities such as hydro-MRI or PET-scan are being developed and evaluated [6]. All these examinations are not always necessary. In practice, at least one urine 5-HIAA should be performed during three consecutive days and an additional imaging should be performed by an octreotide scan. An upper GI fibroscopy should be performed if there is gastroduodenal involvement. A cardiac ultrasound should also be performed when there is a carcinoid syndrome. In the presence of hepatic metastases, hepatic MRI, chest CT scan should be performed. Biopsies should be discussed in order to assess the degree of tumor differentiation.

The treatment of carcinoid tumors has a dual purpose: firstly, to perform complete tumor excision or, if possible, to minimize tumor volume (maximum tumor cytoreduction), and secondly to undertake a symptomatic treatment based on somatostatin and its analogues (which has no proven anti-tumor effect but reduces the symptoms of carcinoid syndrome). Many forms of treatment can be undertaken (surgery, immunotherapy, arterial embolization of hepatic metastases). Hence, it is recommended to discuss the case by a multidisciplinary team of specialists (doctors, surgeons, oncologists and interventional radiologists) [7]. Treatment of non-metastatic forms is based on complete surgical excision in order to obtain negative margins (R0).This may be the only way to significantly improve the survival of patients at five years [2,8,9] .

In practice, intestinal resection combined with systematic mesenteric lymph node dissection should be performed, taking into account the incidence of lymph node invasion (40%) even in the case small primary tumors(<1 cm). The excision of mesenteric metastases may justify a colectomy in the case where e mesenteric vessels are affected.

If the tumor is unresectable, non-progressive and non-symptomatic, simple monitoring with regular multidisciplinary re-evaluation will be performed [10].

In the case of an unresectable and evolutive or symptomatic tumor, several attitudes are possible [10]: In case of isolated liver metastases, chemoembolization will be performed

(contraindicated if biliary prosthesis, cholestasis or biliodigestive anastomosis). If it proves to be effective, the possibility of surgical excision will be discussed again in a multidisciplinary setting.

If metastasis is hepatic and extrahepatic, chemotherapy, transient hepatic ischemia of one hour combined with alternate chemotherapy (carcinoid tumors being 90% vascularized by the hepatic artery), or interferon alpha can be discussed.

The combination of these different therapeutic modalities improves overall survival and in most cases the quality of life [11]. In all cases, the management of these patients must be "aggressive": Current chemotherapies make it possible to regress certain lesions considered previously unresectable. Therefore, regular discussions may be necessary to decide on the possibility of an excision which remains the only curative treatment.

The prognosis of carcinoid tumors of the small intestine is better than that of adenocarcinomas (given the low scalability of these lesions), with 67-75% survival at 5 years for resectable tumors and 50% survival at 5 years for unresectable tumors [10,12]. However, it is worse than rectal tumors (88% survival), tumors of the appendix (71%), and bronchopulmonary tumors (73.5%).

Conclusion

Carcinoid tumors of the small intestine are often small and relatively evolve slowly. Thus, these tumors are lately diagnosed. In a majority of cases, the diagnosis is suspected when there is a retractile mesenteritis or a rare carcinoid syndrome. Diagnosis is confirmed by the pathological examination. Surgery is the only curative treatment to date.

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Case report
Olgu sunumu

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The unexpected surgical emergency in a child with cystic fibrosis: An acute appendicitis with unusual presentation

Kistik fibrozlu bir çocukta beklenmedik cerrahi acil: Atipik sunumlu akut apandisit

Emrah Doğan [1], Alev Süzen [2], Marwa Mouline Doğan [3], Serkan Yaşar Çelik [4], Neşat Çullu [5]

[1] Mugla Sıtkı Kocman University Education and Research Hospital, Radiology, Mugla, Turkey
[2] Mugla Sıtkı Kocman University Education and Research Hospital, Pediatric Surgery, Mugla, Turkey
[3] Universite de Mohammed V, Department de Cardiologie, Rabat, Morocco
[4] Mugla Sıtkı Kocman University, Faculty of Medicine, Pathology, Mugla, Turkey
[5] Mugla Sıtkı Kocman University, Faculty of Medicine, Radiology, Mugla, Turkey

ORCID ID of the authors
ED: 0000-0002-9446-2294
AS: 0000-0002-0595-3308
MMD: 0000-0002-3401-895X
SYÇ: 0000-0001-6557-1451
NÇ: 0000-0002-5045-3919

Corresponding author / Sorumlu yazar:
Emrah Doğan
Address / Adres: Muğla Sıtkı Koçman Üniversitesi Eğitim ve Araştırma Hastanesi, Radyoloji Anabilim Dalı, Muğla, Türkiye
e-Mail: dr_e_dogan@hotmail.com

Informed Consent: The author stated that the written consent was obtained from the patient presented in the study.
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Abstract

Cystic fibrosis is an autosomal recessive disease characterized by structural and metabolic genetic dysfunction of the exocrine glands. Abdominal pain is the most common symptom in patients with cystic fibrosis within gastrointestinal symptoms. It is more commonly related to distal ileal obstruction syndrome. In patients with cystic fibrosis, the appendix is frequently distended due to an intense eosinophilic secretion but ironically, the incidence of acute appendicitis has been reported under the general population. Acute appendicitis in patients with cystic fibrosis commonly present with atypical symptoms. We present the case of cystic fibrosis with an acute appendicitis which had atypical radiologic and laboratory findings that were not compatible with the diagnosis. The diagnosis was made on the basis of clinical examination. As a result, it is of great importance to know that acute appendicitis in patients with cystic fibrosis can present with unusual clinical and radiological findings in order to avoid delayed diagnosis and related serious complications.

Keywords: Cystic fibrosis, Appendicitis, Pediatric age group

Öz

Kistik fibrozis ekzokrin glandların yapısal ve metabolik genetik disfonksiyonu ile karakterize otozomal resesif bir hastalıktır. Kistik fibrozisli hastalarda gastrointestinal semptomlar içerisinde ağrı en yaygın semptomdur ve genellikle distal ileal obstrüksiyon sendromuna bağlıdır. Kistik fibrozisli hastalarda apendiks yoğun bir eozinofilik sekresyondan dolayı sıklıkla distandüdür ancak ironik olarak akut apandisit insidansı genel popülasyondan daha düşüktür. Akut apandisit, kistik fibrozisli hastalarda sıklıkla atipik semptomlarla kendini gösterir. Bu yazıda atipik radyolojik bulguları olan kistik fibrozisli bir akut apandisit olgusu sunuldu ve laboratuvar bulguları, tanı ile uyumsuzdu. Hastada sadece defans ve rebound gibi klasik muayene bulguları mevcuttu ve bu temelde hasta tanı aldı. Sonuç olarak, geç tanıya bağlı ciddi komplikasyonları önlemek için, akut apandisitli kistik fibrozis hastalarının atipik klinik ve radyolojik bulgularla başvurabileceği akılda tutulmalıdır.

Anahtar kelimeler: Kistik fibrozis, Apandisit, Pediatrik yaş grubu

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease characterized by structural and metabolic genetic dysfunction of the exocrine glands. It is more common in the white population. Defects in the cystic fibrosis transmembrane regulator protein (CFRT) gene lead to impaired chlorine transportation of the epithelial cell in plasma membrane of organs such as the lung, pancreas, intestine, liver, epididymis and sweat glands. Lungs are the most affected organ [1]. When gastrointestinal system is affected, abdominal pain is the most common symptom in patients with CF and is frequently due to distal ileal obstruction syndrome (DIOS). Other conditions which are leading to lower abdominal pain in these patients are intussusception, volvulus, pancreatitis and fecaloma [2]. Acute appendicitis is a rare entity in CF [3]. This paper reports, with clinical and radiological findings, the case of a patient in the pediatric age group with acute appendicitis complicating CF.

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Case presentation

A 13-year-old patient was admitted to the public state hospital for abdominal pain and nausea. Simultaneously, chest and plain abdominal X-ray had been taken. Bilateral hilar and perihilar overload in chest X-ray were found. White blood cell (WBC) and biochemical tests were normal. There were insignificant several scattered gas shadows in the abdominal X-ray graphic and a levelling gas corresponding to fundus anatomical localization (Figure 1).

Defense and rebound were found during clinical examination, thus ultrasonography was requested. Ultrasonography revealed a distended appendix with loss of response to compression. No evidence of perforation with issue of fluid and free gas was observed. Patient was referred to university hospital for evaluation by a pediatric surgeon with an initial diagnosis of acute appendicitis.

During the interrogation, the notion of cystic fibrosis was found in the antecedents, diagnosed at the age of 2 months, followed regularly and treated with pancreatic enzymes, Proton Pump Inhibitor (PIP), vitamins and osteoporosis' medications.

Our findings were similar to those of the examinations made previously. Physical examination revealed a rebound and defense in the lower right quadrant. Hemogram and biochemistry tests were repeated and results were normal (WBC: 7600 / mm3, Hb: 15 g / dL, CRP: 1.3 mg / L). Fundus shadows were similar to those observed in the old abdominal radiography however in the medial part gas clarity of transverse colon had appeared. There was no fluid and air level but DIOS was suspected for the increase in gas shadows, the transverse colon shadow and the fact that WBC was low. Therefore, we decided to repeat the patient's ultrasonography.

The abdominal ultrasonography performed in our hospital showed an increased appendix diameter (6.5 mm) and a partial response to compression. Liquid, lymphadenopathy, perforation and abscess were not observed. In addition, the liver was granular and heterogeneous which raised the confusing question if there was a chronic liver parenchymal disease. Furthermore, splenic cranio-caudal dimension was 132 mm which was compatible with splenomegaly.

Finally, the decision of the operation was made on the basis of clinical and radiological findings. Appendectomy was done and no complications were observed. Patient was discharged on the 2nd day. Before preparing case report, the consent form was signed by family in 10.8.2018

Histopathology

The material of appendectomy consisted on 6 cm long, 1 cm wide and cross-section lumen-shaped tissue. The material was sampled into tissue cassettes after 10% formalin fixation. Following routine tissue formation, paraffin blocks were formed. 5 µm thick sections were taken from the blocks and stained with hematoxylin-eosin. The slides were examined by light microscope.

In the pathological sections; mucosa of the appendix was characterized by ulceration, lymphoid follicles (Figure 2) and acute inflammation (Figure 3) involving a large number of polynuclear leukocytes extended to the muscularis mucosa.

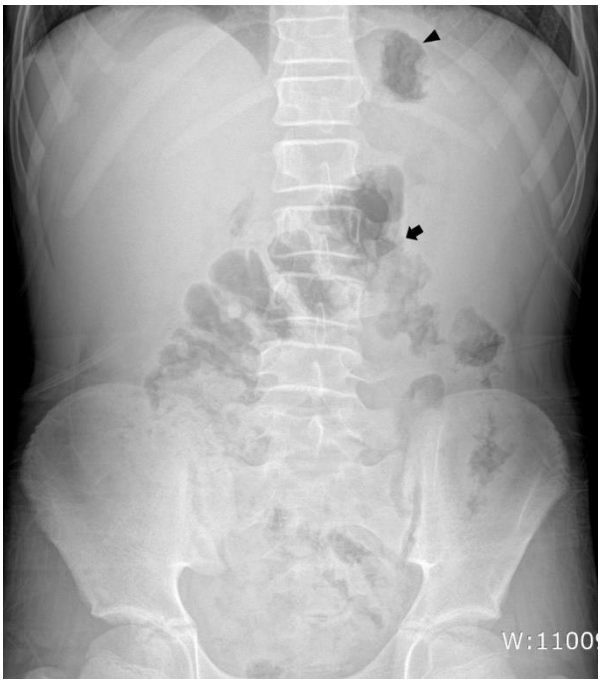

Figure 1: Arrow Head: Fundus gas, Short arrow: Increased gas shadows

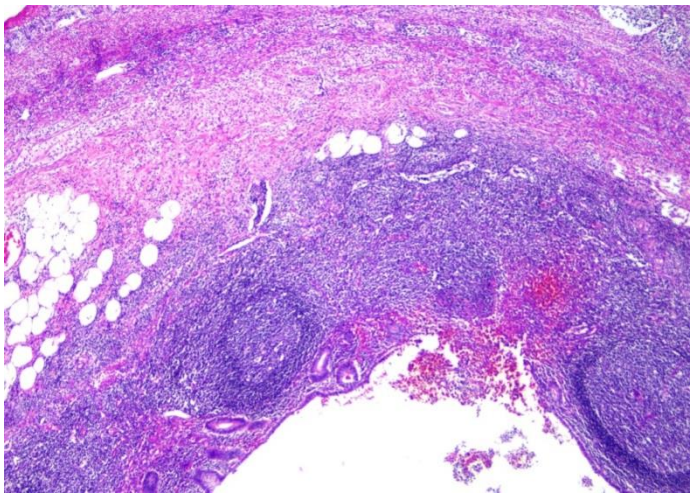

Figure 2: Ulceration and lymphoid follicles in the appendix mucosa. Hematoxylin-eosin (HE) x 40

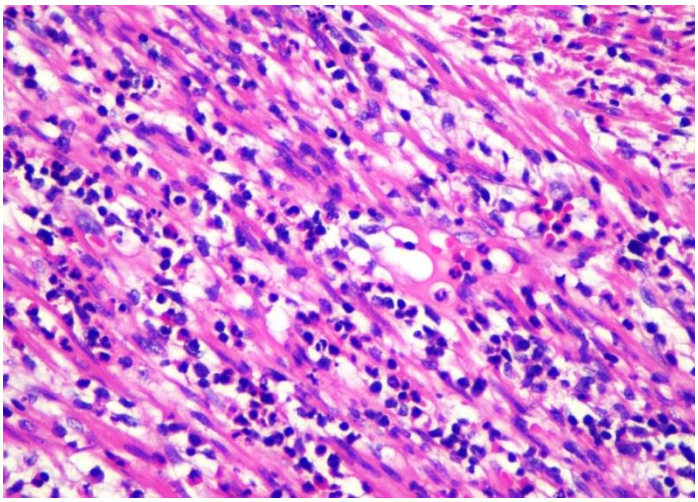

Figure 3: Acute inflammation involving a large number of polynuclear leukocytes in muscularis mucosa. Hematoxylin-eosin (HE) x 400

Discussion

The incidence of CF in Turkey is unknown. Given the prevalence in neighboring countries in Europe and the Mediterranean, it is thought to be about 20 000 CF patients in Turkey. The number of patients monitored at various centers in

Turkey is around 750-1000 [4]. The surplus of rare mutations increases the number of CF patients who are likely to come with atypical presentations [4,5]. It seems that more than 1000 mutations were associated with CF where localized in the long arm of the 7th chromosome in the CFTR gene that was found in 1989 [6]. Kilinc et al. [7] conducted a study of 83 CF patients, to determine CFTR mutations in our region (Aegean region). 36 different CFTR mutations were detected and these results indicate that Turkish population has the highest genetic heterogeneity among the studies reported so far.

In patients with CF, the appendix is frequently distended due to an intense eosinophilic secretion but ironically, the incidence of acute appendicitis has been reported under the general population [2]. In patients with CF, the incidence of appendicitis varies between 1 and 2% while in normal population rates are defined as 7% [5]. Authors attributed the low incidence of appendicitis to the protective effect of mucous secretion in the appendix in these patients. This theory has been described as a continuous distension of the appendix lumen, reducing the risk of acute appendicitis and luminal occlusion. Thus, acute appendicitis may be atypical. Symptoms may be confusing with DIOS and intussusception or the results may be masked by a prescribed antibiotic therapy to prevent pulmonary exacerbation [2]. Coughlin et al. reported 60% of the classical symptoms of appendicitis in the general population against only 45% in CF. As a result, perforation and abscess formation are higher in CF patients with acute appendicitis [8].

As mentioned above, patients with CF usually have an increased appendix diameter (>6 mm) due to an intense secretion without appendicitis. Therefore, the increase in appendix size is not a reliable finding in these patients [5]. Differentiating acute appendicitis from chronic distention of the appendix in CF patients is important for avoiding unnecessary appendectomy yet can be challenging [3,5]. It is important that the diagnosis should be supported by secondary signs of inflammation including tenderness, rebound and defense [9]. In our case, atypical radiology findings were blurred and the laboratory findings didn’t support the diagnosis. Therefore, the diagnosis was only made on the basis of clinical examination.

Conclusion

Distal ileal obstruction syndrome remains the most common cause of acute abdominal pain in CF patients and it could also mimic the symptoms of acute appendicitis. Turkey has a broad genetic spectrum for CF; therefore, we can more frequently face atypical expressions of acute appendicitis. The diagnosis of acute appendicitis and its complications in CF patients is difficult, despite the availability of modern laboratory and radiological techniques. It is of great importance to evaluate the clinical, laboratory and radiological findings together in CF patients with acute abdominal pain.

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Nodular sclerosing adenosis: Case report

Nodüler sklerozan adenosis: Olgu sunumu

Emrah Doğan [1], Leyla Tekin [2], Serkan Yaşar Çelik [2], Murat Polat [3], Marwa Mouline Doğan [4]

[1] Muğla Sıtkı Koçman University, Training and Research Hospital, Radiology Clinic, Muğla, Turkey
[2] Muğla Sıtkı Koçman University, Faculty of Medicine, Pathology Clinic, Muğla, Turkey
[3] Muğla Sıtkı Koçman University, Faculty of Medicine, Department of General Surgery, Muğla, Turkey
[4] Universite de Mohammed V, Department de Cardiology, Morocco

ORCID ID of the authors
ED: 0000-0002-9446-2294
LT: 0000-0003-1172-5536
SYÇ: 0000-0001-6557-1451
MP: 0000-0002-7430-8572
MMD: 000-0002-3401-895X

Abstract
Sclerosing adenosis (SA) is a benign proliferative type of breast disease affecting the acinar, myoepithelial and connective tissue in the terminal ductal lobular units. Sclerosing adenosis, which gives a nodular appearance on mammography and ultrasonography, is defined as nodular sclerosing adenosis (NSA). NSA is an atypical radiological presentation of SA. Such lesions may arouse suspicions about the reliability of the diagnosis when they receive a diagnosis of SA in the needle biopsies. Therefore, it should be kept in mind that SA may rarely be seen as a nodular mass.
Keywords: Nodular sclerosing adenosis, Breast, Ultrasonography, Mammography

Öz
Sklerozan adenozis (SA) terminal lobuler ünitte asiner, miyoepitelyal ve konnektif dokuyu etkileyen benign proliferatif tipte bir meme hastalığıdır. Mammografide ve ultrasonografide nodüler ve vizualize SA, nodüler sklerozan adenozis (NSA) olarak tanımlanır. NSA, SA'nın atipik bir radyolojik presentasyonudur. Bu tarz lezyonlar ince ve kalın iğne biyopsilerinde SA tanısı aldığında tanının güvenilirliği açısından kuşku uyandırabilir. SA'nın nadir olarak nodüler kitle şekilde görülebileceği akılda tutulmalıdır.
Anahtar kelimeler: Nodüler sklerozan adenozis, Meme, Ultrasonografi, Mammografi

Corresponding author / Sorumlu yazar:
Emrah Doğan
Address / Adres: Muğla Sıtkı Koçman Üniversitesi, Eğitim ve Araştırma Hastanesi, Radyoloji Kliniği, Muğla, Türkiye
e-Mail: dr_e_dogan@hotmail.com

Informed Consent: The author stated that the written consent was obtained from the patient presented in the study.
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Introduction

Sclerosing adenosis (SA) is a benign proliferative type of breast disease affecting the acinar, myoepithelial and connective tissue in the terminal ductal lobular units and a subtype of adenosis [1]. SA is a differential diagnosis that has a broad spectrum of shapes which can mimics a variety of breast lesions in ultrasound (USG) and mammography (MG), including even malignancy [2-4].

SA is defined as an adenosis tumor or a nodular sclerosing adenosis (NSA) when presented as a clinically palpable mass and as a nodular lesion in USG or MG [2]. The lesion without lobulation and without heterogeneity forming a well circumscribed mass is a very rare presentation at the age of perimenopause. This case is presented with histological and radiological findings in the purpose to emphasize this atypical presentation of SA.

Case presentation

A 45-year-old female patient admitted to the hospital with complaints of breast pain in right side. There was no family history about breast cancer and also any drug. The patient was in perimenopausal ages and her menstrual cycles was regular.

MG was performed with Giotto Tomo digital mammography device. Images were taken on craniocaudal (CC) and mediolateral (MLO) standard plans. The breast pattern was ACR type B. Partially superposed a nodular density was revealed on the upper-outer quadrant in the right breast (Figure 1).

USG was performed with Toshiba S 300 sonography device and used 14 MHz high resolution linear probe. A well-circumscribed, ovoid and uniform, hypoechogenic nodular mass was seen. The Mass dimension was 21x10 mm (Figure 2) No flow signal was seen in Doppler USG (Figure 3). The patient underwent a true-cut biopsy.

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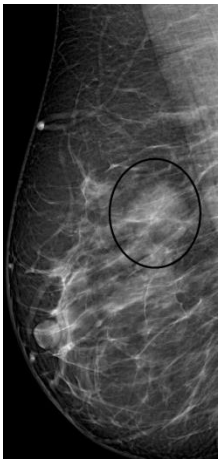

Figure 1: In MG, right superficial nodular opacity is observed in the right breast, which is seen in the upper outer

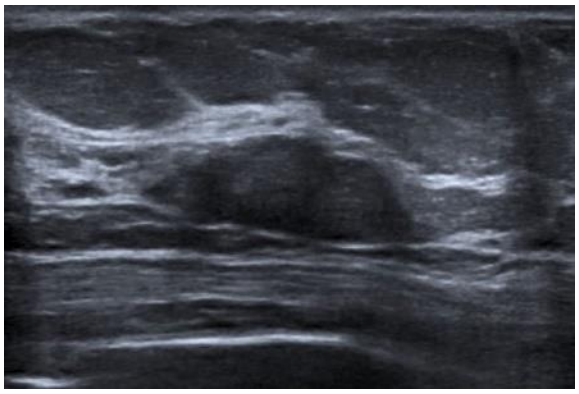

Figure 2: Well circumscribed, hypoechoic, solid lesion in ultrasonography

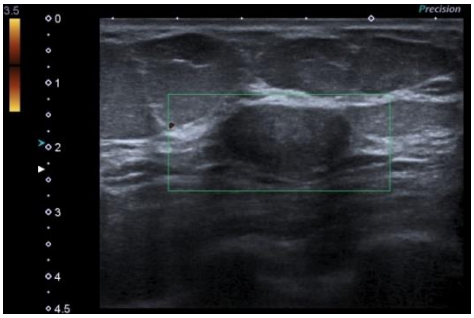

Figure 3: No flow signal in Doppler ultrasonography

Histopathology

The true-cut biopsy material consisted on 7 cream-colored tissues. The size of the biggest tissue was 1.2 cm while the smallest was 0.2 cm. Materials were sampled into tissue cassettes after 10% formalin fixation. Samples were transformed into paraffin blocks after routine tissue following. Sections of 5 µm thickness were taken from the blocks and stained with hematoxylin-eosin. The slides were examined by light microscope.

In the pathological sections, compression of the fibrous stroma was observed. The lesion consists of a benign and often flattened proliferation of epithelial cells surrounded by the myoepithelial cell layer, resulting in compression and structural damage in the glandular structures (Figure 4).

Immunohistochemically, CD10 staining was applied to the glands, suggesting that the myoepithelial layer was preserved (Figure 5). The lesion without cellular atypia was diagnosed as "Sclerosing Adenosis".

The patient fulfilled the consent form before writing this case report.

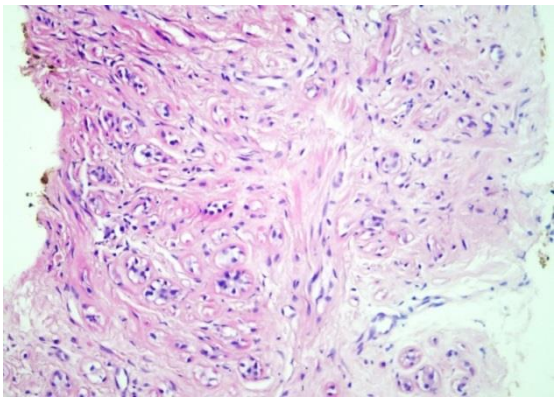

Figure 4: Proliferating gland structures with double row epithelium in the fibrotic stroma; Haematoxylin-eosin (HE) x 200

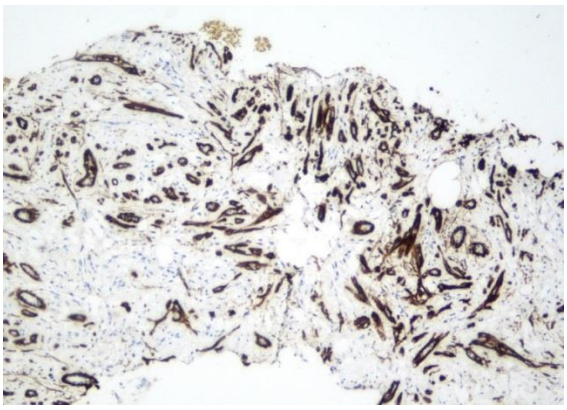

Figure 5: Immunohistochemically; stained gland structures, stained in fibrous stroma, stained positive by CD10 all around, preserved myoepithelial layer; CD10 x 200

Discussion

SA is a benign proliferative lesion of the breast gland found in 27.8% of benign biopsies and 3.1% of breast's post-mortem studies [4,5]. Haagensen described adenosis as a phenomenon of the menstrual phase of life. The formation of adenosis is related to the stimulation of breast tissues due to estrogen [6].

SA and NSA are subtypes of adenosis [4]. SA is more common in the perimenopausal age group [5] while NSA is usually seen in the 30-45 age range [7]. Information on the radiological features of NSA is very little. Only a few articles in the literature describe mammographic and sonographic findings of it [4].

In MG, SA can be seen as focal asymmetric opacity with distortion or microcalcifications while nodular mammographic image is rare [8]. When SA is percepted as a clinically palpable mass, it is usually detected only in mammography [2]. Paradoxically, when it is visualized in USG, it does not appear in MG [4]. Focal clusters or diffuse calcifications were reported in 50% of cases, thus it can mimic malignancy when calcifications are involved [6]. In fact, the relationship with malignancy is weak. Indeed, Jensen et al. [9] reported a 1.5-2-fold increase in malignancy risk.

Furthermore, SA is a difficult diagnosis among pathologists, because stromal sclerosis and elastosis can mimic infiltrating carcinoma [3].

Histologically, NSA is not different than SA. It is a complex lobulocentric lesion characterized by enlarged, distorted lobules containing duplicated and crowded acini (ductuli) whose luminal epithelial and myoepithelial components and basal membrane are however preserved. Stromal fibrosclerosis

involves at least half of the terminal duct lobular unit (TDLU), which is elongated, distorted and compressed by the sclerosis [10].

NSA is very rare condition. Gunhan-Bilgen et al. [4] evaluated 33,700 patients and only 43 patients were diagnosed as having sclerosing adenosis. Among these patients, only 1 patient was similar to our case with a well-defined nodular mass and in the same time visualized in USG.

In our case two important points should be highlighted. First one is that NSA was found in a patient at the perimenopausal age while it is commonly seen in younger patients. Second point is that all of the cases reported in the literature as having NSA had dimensions less than 2 cm while in our case it was more (2.2 cm).

Conclusion

NSA is an atypical radiological presentation of SA. If it is followed as a benign solid mass, it leads to confusion by showing dimensional and shape changes. Thus, when such lesions are diagnosed as sclerosing adenosis in needle biopsies, patients may undergo excisional biopsy because of radio-pathologic mismatch. Such radiological shape arouses suspicions about the reliability of SA's diagnosis by needle biopsies. Therefore, it should be kept in mind that it is rare but possible to see SA as a nodular mass.

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A rare cause of acute abdominal pain in a child: Giant sigmoid volvulus

Çocukta akut abdominal ağrının nadir bir nedeni: Dev sigmoid volvulus

Ayşe Selcan Koç [1], Zerrin Özçelik [2]

[1] Department of Radiology, University of Health Sciences - Adana Health Practices and Research Center, Adana, Turkey
[2] Specialist of Pediatric Surgery, Department of Pediatric Surgery, University of Health Sciences - Adana Health Practices and Research Center, Adana, Turkey

ORCID ID of the authors
ASK: 0000-0003-1973-0719
ZÖ: 0000-0003-3728-0846

Corresponding author / Sorumlu yazar:
Ayşe Selcan Koç
Address / Adres: Sağlık Bilimleri Üniversitesi, Radyoloji Anabilim Dalı - Adana Sağlık Uygulama ve Araştırma Merkezi, Adana, Türkiye
e-Mail: drayseselcankoc@gmail.com

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Hasta Onamı: Yazar çalışmada sunulan hastanın velisinden yazılı onam alındığını ifade etmiştir.

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Abstract

Sigmoid volvulus (SV) is a rare, but also life-threatening disease if not diagnosed earlier. SV appears as torsion of the sigmoid colon around its mesentery and causes necrosis, perforation, peritonitis and sepsis when obstruction and ischemia progresses in the colon segment. The important issue in SV to keep in mind is consideration of this rare condition during detailed examination of the history, physical examination and laboratory findings in the patient who refers because of some complaints such as abdominal pain, constipation and distention. This would allow planning the advanced radiological examinations and adequate treatment protocols to confirm the diagnosis.

Keywords: Sigmoid volvulus, Child, Abdominal pain

Öz

Sigmoid volvulus (SV) çocukluk çağında nadir görülen erken tanı konulmazsa hayatı tehdit edici bir hastalıktır. SV sigmoid kolonun kendi mezenter kökü etrafında dönmesi ile oluşup kolonik segmentteki obstrüksiyon ve iskemi ilerleyince nekroz, perforasyon, peritonit, sepsis gelişmesine neden olmaktadır. SV'de önemli olan karın ağrısı, konstipasyon, distansiyon gibi şikâyetlerle başvuran hastalarda ayrıntılı hikaye, fizik muayene ve laboratuvar bulgularının incelenmesinde hekimin bu tanıyı da akılda tutmasıdır. Böylece tanıyı doğrulayacak ileri radyolojik incelemelerin zaman kaybedilmeden planlanması ve uygun tedavi protokolü mümkün olacaktır.

Anahtar kelimeler: Sigmoid volvulus, Çocuk, Karın ağrısı

Introduction

Sigmoid volvulus (SV) is mechanical obstruction of the colon and very rare during childhood [1]. The most common cause is torsion of a long and mobile sigmoid colon around a narrow mesenteric root [1]. The most significant causes include cramp-like or blunt abdominal pain, distention as well as interruption of gas-stool passage [1]. However, clinical findings are not specific in every case and clinical suspicion is very important for the diagnosis. Abdominal X-ray graph and computed tomography are common imaging methods used for SV. Perforation and necrosis-induced morbidity as well as mortality decreases by early diagnosis.

Case presentation

A 10-year old boy who do not have any previous disease referred to our emergency service because of abdominal pain and exhaustion intermittently for 2 days. The patient had no fever, nausea and vomiting. In the physical examination, an epigastric distention was detected; however, no rebound and defense was present. The patient had not any gas-stool passage for 24 hours. The rectal examinations revealed that the rectum was completely empty and clean without any palpable mass or fullness. The laboratory findings were as follows; white blood cell count: $10.3x10^3$/mL, C-reactive protein: 0.5 mg/dL and other biochemical parameters and urine analysis were normal.

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In the Abdominal X-ray graph sharp air-fluid levels as well as dilatation and reverse U finding were detected in intestinal segments (Figure 1a). The identified findings were evaluated in favor of intestinal obstruction however patient relatives did not accept the treatment. After 6 hours from leaving the hospital, the patient was taken to our hospital again due to increased abdominal pain. Noticeable rebound and defense were detected in the abdomen; air-fluid leveling were more significant in the abdominal X-ray graph (Figure 1b); abdominal computed tomography was showed a significant dilatation at intestinal segments and torsion were detected (Figure 2 and 3).

The patient was taken laparotomy it was seen that sigmoid colon rotated 540 degrees around its mesentery and the effected segment showed dilatation and edema (Figure 4). The twisted part of the sigmoid colon appeared as longer and the cause of volvulus was considered as longer sigmoid colon and we performed sigmoid colon resection with primer anastomosis. There was not any ischemia and necrosis in the intestine segment. The patient was fed after 48 hours from the surgery. The patient was discharged at postoperative day 5 by suggesting a polyclinic control. There was not any significant finding during control visit. Written informed consent was obtained from the parents of the patients who participated in this study.

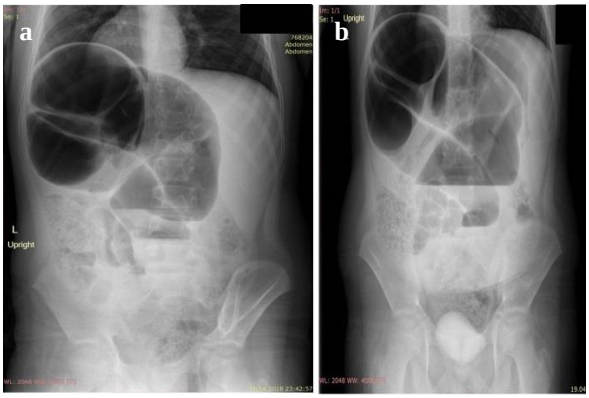

Figure 1: Abdominal X-ray demonstrating dilated colon segments, air fluid level, inverted "U" sign (a) First day of admission (b) Second day of admission.

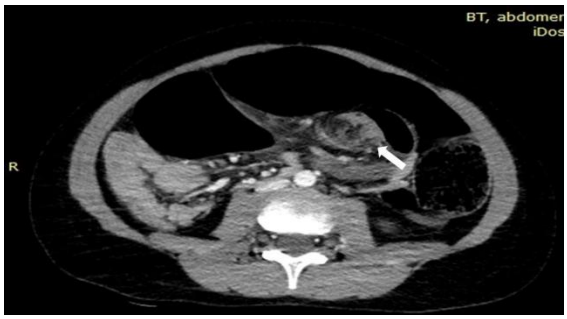

Figure 2: Axial abdominal CT image showing a distended gas-filled colonic loop and the whirlpool sign (twisting of the mesentery and vessels: arrow) suggestive of sigmoid volvulus.

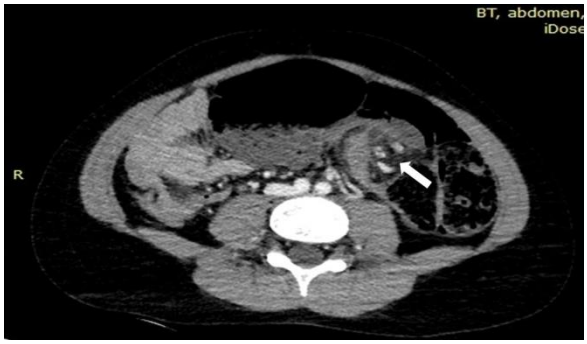

Figure 3: Axial abdominal CT image showing a distended gas-filled colonic loop and the whirlpool sign (twisting of the mesentery and vessels: arrow) suggestive of sigmoid volvulus.

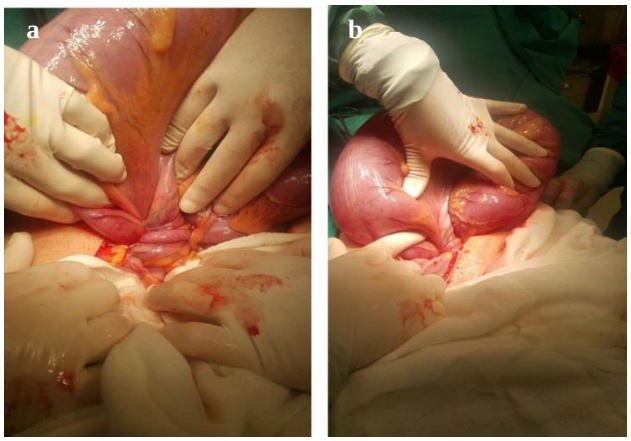

Figure 4: Intraoperative two different views (a and b) of sigmoid volvulus.

Discussion

SV is very rare in the children and may cause life threatening clinical manifestations. In the literature, Salas et al. [2] detected that the patients were usually between 7 and 12 years of age; the rate of male/female was 3.5/1. Volvulus is a pathological condition that appears as a result of anatomic torsion of the intestine around its narrow mesentery root [1]. Torsion may affect the intestinal supply; strangulation and gangrene may develop as a result. Development of volvulus requires a mobile colon which means a sufficient length of the colon mesentery for volvulus; mesenteries of the caecum and sigmoid colons were feasible for volvulus whereas other colon segments have low tendency [1].

Hirschsprung's disease, chronic constipation often play a predisposing role in development of SV, but other conditions like intestinal malrotation, anal stenosis, surgical adherence, prune belly syndrome, and mental retardation may also cause [1]. Our patient was a 10-year old boy and did not present any underlying significant pathology.

The important issue for diagnosis of SV is a detailed history, physical examination, laboratory tests as well as imaging methods. Severity of the symptoms is associated with degree of the torsion, strangulation and closed loop obstruction; the findings may vary between acute, subacute, chronic and persisting attacks. Major symptoms include cramp-like abdominal pain with sudden onset, increasing abdominal distention and loss of gas-stool discharge. Pain is usually diffuse; however, rarely blunt and localized [3]. Although nausea-vomiting also appears at the beginning, these usually develop following other symptoms. Such symptoms progresses rapidly in younger patients. Rectal examination may be completely normal or appear as red blood or in form of melena [4]. Dehydration, hematochezia, abdominal mass and fecaloid breath odor are other findings [4]. Unless gangrene develops in the colon, peritoneal irritation findings are not detected. Since non-perforated ischemic state does not deepen the clinical manifestation, it is difficult to differentiate simple volvulus from strangulated volvulus. However, irritation findings, fever and leukocytosis indicate gangrene. Defense appeared is a diagnostic finding when perforation and peritonitis occur. The present our case referred because of intermittent abdominal pain for 2 days. Abdominal pain gradually increased and defense was detected in the examination performed 6 hours after although no defense was detected in the initial physical examination.

Abdominal X-ray usually reveals dilated intestinal loops, air-fluid leveling which are nonspecific findings; diagnostic direct X-ray findings for volvulus include bill sign, reverse U shape (omega loop), large horseshoe [1,2]. Empty left iliac fossa in direct abdominal X-ray at standing position is accepted as a diagnostic finding [5]. An accurate diagnosis was established in 60 to 80% of the cases through direct abdominal X-ray; however diagnostic value of the X-rays is between 30% and 40% [5]. Whirlpool sign in CT provides accurate and reliable diagnosis of SV and this imaging method provides an accuracy of 100% in early stages of the disease [6]. The X-ray of our case revealed dilatation in intestinal loops, air-fluid leveling and reverse U finding were present. At that stage, intestinal obstruction was considered with findings of direct X-ray and abdominal CT evaluation was performed due to preliminary diagnosis of volvulus; evaluation results confirmed our diagnosis. Torsion of the sigmoid colon was clearly shown by dilated colon segments in CT.

Treatment of sigmoid volvulus is controversial for children. If clinical symptoms are stable and no sign for necrosis or intestinal perforation, non-operative induction, namely, barium enema or sigmoidoscopy should be performed [6,7]. However, performance of this maneuver was reported as difficult in the children [8]. Furthermore, recurrence was reported after endoscopic decompression in almost half of the cases [8]. Since the sigmoid volvulus is not distorted endoscopically or findings of ischemic intestine or peritonitis are indications for surgical operation; resection of the twisted segment and primary anastomosis or colostomy are performed surgically. Volvulus segment was detorsioned and dilate sigmoid segment resected through surgical procedure in our patient. Since there was not any finding for ischemia, prognosis of final treatment of sigmoid volvulus is promising on the condition of early diagnosis and immediate treatment [9].

In conclusion, SV is rarely caused of intestinal obstruction in children and adolescents. For this reason, pediatric surgeons should have a high degree of suspicion not to miss this diagnosis; any delay in treatment has a destructive effect on morbidity as well as morbidity. Early diagnosis and prompt treatment confer an excellent prognosis.

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Rapidly progressive tetraplegia and cognitive deterioration during rehabilitation: A case of neurodegenerative disease

Rehabilitasyon sırasında hızlı ilerleyen tetrapleji ve bilişsel bozulma: Bir nörodejeneratif hastalık olgusu

Sevgi İkbali Afşar [1], Oya Ümit Yemişçi [1]

[1] Department of Physical Medicine and Rehabilitation, Baskent University, Faculty of Medicine, Ankara, Turkey

ORCID ID of the authors
SİA: 0000-0002-4003-3646
OÜY: 0000-0002-0501-5127

Corresponding author / Sorumlu yazar:
Sevgi İkbali Afşar
Address / Adres: Fevzi Cakmak Cad. 5. Sokak No: 48, 06490, Ankara, Türkiye
e-Mail: ikbaliafsar@hotmail.com

Informed Consent: The authors stated that written informed consent was obtained from the patient's legal representative for this report.
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Abstract
Human prion diseases are fatal, progressive neurodegenerative disorders caused by neurolytic pathogen proteins, called prions. The most common human prion disease is sporadic Creutzfeldt-Jakob disease, with an approximate annual prevalence of 0.5-1 per million. The symptoms and signs include rapidly progressive dementia, ataxia, myoclonic seizures, akinetic mutism and other neurological and neurobehavioral disorders. The clinical spectrum of Creutzfeldt-Jakob disease is highly variable; therefore it can be difficult to diagnose premortem. This article describes a 78-year-old woman who initially presented with difficulty walking and balance disorder. As a result of the evaluation, the patient was transferred to rehabilitation clinic, with a diagnosis of cervical spinal stenosis. During hospitalization, she showed progressive decline in gait and balance and deteriorated rapidly. The patient was considered to be probable sporadic Creutzfeldt-Jakob disease after further investigations.
Keywords: Neurodegenerative disease, Creutzfeldt-Jakob disease, Rehabilitation

Öz
İnsan prion hastalıkları, prionlar olarak adlandırılan nörolitik patojen proteinlerin neden olduğu ilerleyici nörodejeneratif hastalıklardır. En yaygın insan prion hastalığı sporadik Creutzfeldt-Jakob hastalığı olup, yıllık prevalansı yaklaşık milyonda 0.5-1'dir. Semptomlar ve bulgular; hızla ilerleyen demans, ataksi, miyoklonik nöbetler, akinetik mutizm ve diğer nörolojik ve nörodavranışsal bozuklukları içerir. Creutzfeldt-Jakob hastalığının klinik spektrumu oldukça değişkendir, bu nedenle premortem teşhis etmek zor olabilir. Bu makalede, başlangıçta yürüme zorluğu ve denge bozukluğu ile başvuran 78 yaşında bir kadın hasta anlatılmaktadır. Yapılan değerlendirme sonucunda hasta servikal spinal stenoz tanısı ile rehabilitasyon kliniğine transfer edildi. Hastanede yatışı sırasında, yürüme ve dengesi progresif olarak kötüye giderek bozuldu. İleri tetkiklerden sonra hastanın olası sporadik Creutzfeldt-Jakob hastalığı olduğu düşünülmüştür.
Anahtar kelimeler: Nörodejeneratif hastalık, Creutzfeldt-Jakob hastalığı, Rehabilitasyon

Introduction

Sporadic Creutzfeldt-Jakob disease (sCJD) is a rare transmissible neurodegenerative disorder with an invariably fatal outcome [1]. The disorder starts in the middle to late ages and results in rapidly progressive dementia, myoclonus and psychiatric disorders [2]. The clinical presentation of sCJD can be highly variable and overlap with other central nervous system disorders. In this article, we present an individual with difficulty in walking and balance and whose complaints were progressively advancing during rehabilitation.

Case presentation

A 78-year-old female presented to our outpatient department with a 5-months history of obliviousness, bilateral lower limb weakness, progressive difficulty in walking, balance disorder, urinary incontinence and weakness of the hands. There was no family history of neurological illnesses and her previous medical history included mild hypertension and gastritis. She had already been evaluated by neurology and neurosurgery departments. Biochemical and hematological investigations, cerebrospinal fluid examination, brain magnetic resonance imaging (MRI) and diffusion-weighted imaging (DWI) were unremarkable. Electroneuromyographic evaluation revealed mild peripheral neuropathy. MRI of the whole spine revealed narrowing of disc space at multiple levels with spinal cord compression at cervical level. The patient was transferred to our rehabilitation clinic, with a diagnosis of cervical spinal stenosis.

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At first presentation; the patient was conscious, slightly disoriented and had difficulty in cooperating. Her mimics were apathetic and she had titubation-like oscillations of the head, she also complained of obliviousness. In motor examination, upper and lower extremity strength was 4/5 except for bilateral hip flexion which was 3/5. There was diffuse numbness on the legs. Both upper and lower extremity deep tendon reflexes were increased, Hoffman's sign was bilateral positive and Babinski reflexes were bilaterally negligent. Her cognitive functions regressed rapidly including obliviousness. Her speech became dysarthric and she developed limb rigidity, dementia signs, spontaneous myoclonus and aggressive personality changes two weeks after initial presentation. She could not be mobilized without the support of a person. She was enrolled in the rehabilitation program. During her hospital stay, she showed progressive decline in gait and balance. At this stage, diagnostic laboratory investigation was unremarkable, including full blood count, liver and renal functional tests, glucose profiles, serum electrolytes, thyroid function tests, vitamin B12 and folate concentrations, creatine kinase, paraneoplastic antibodies, heavy metals, and tumor markers. The electroencephalography (EEG) and brain DWI were re-evaluated. DWI demonstrated symmetrical diffusion limitation seen in bilateral caudate nuclei and the putamens (Figure 1) and EEG showed widespread marked slowing of cerebral bioelectrical activity. Cerebrospinal fluid analysis was positive for 14.3.3 protein. The patient became completely dependent despite rehabilitation and was transferred to the neurology clinic with a diagnosis of probable sCJD.

We obtained written informed consent from the patient's legal representative for this report.

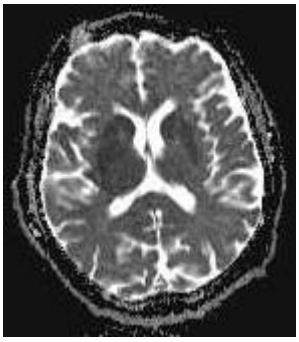

Figure 1: The brain diffusion-weighted images of the patient demonstrated symmetrical diffusion limitation in bilateral caudate nuclei and the putamens

Discussion

The most common human prion disease is sCJD, accounting for about 85% of all CJD, with an annual incidence of one person per million. The majority of the cases are sporadic while the remainder has a genetic component and early recognition is important in terms of genetic screening of the family. The median age of onset is 65 years, and the median duration of survival is four months [1]. It is due to the action of neurolytic pathogen proteins, called prions, which gradually damage central nervous system cells resulting in brain damage with distinct pathologic features [3]. The well-known clinical manifestations of sCJD are rapidly progressive dementia, myoclonus, and ataxia. At follow-up dementia with ataxia, personality changes and a variety of neurological and neuro-behavioral symptoms such as psychosis develop [4]. The diagnosis of sCJD is relatively straight forward when a patient with rapidly progressive dementia manifests myoclonus and periodic, synchronous, and generalized bi-/triphasic sharp-wave complexes on EEG [5]. Definitive diagnosis requires neuropathological examination; this is, however, no longer necessary because of the established WHO disease defining criteria [6] (Table 1) and a brain biopsy is discouraged unless required to exclude a treatable disease [1]. The most important reason for the initially misdiagnosis in our case was the lack of a clinically significant change in cognitive function at first presentation. In a case presented by Grant et al. [7], the 39-year-old patient was initially admitted with the diagnosis of spinal cord injury with weakness in the lower extremities and incontinence. Neuro-axis imaging studies failed to explain the symptoms and the patient's complaints were thought to have a large psychologic component. Cerebrospinal fluid analysis performed due to the development of neurological symptoms proximal to the presumed spinal cord injury level was suggestive of prion disease.

Table 1: World Health Organization clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease

Creutzfeldt-Jakob Disease
Progressive dementia
And at least two of the following four clinical features
Myoclonus
Visual or cerebellar disturbance
Pyramidal/extrapyramidal dysfunction
Akinetic mutism
And
A typical electroencephalogram during an illness of any duration and/or
A positive 14-3-3 CSF assay and a clinical duration to death <2 years
Routine investigations not suggestive of an alternative diagnosis

Brain DWI, assessment of 14-3-3 protein from cerebrospinal fluid and serial EEG recordings should be integrated into the diagnostic workup of sCJD [5]. In the literature, DWI is the most sensitive method in the diagnosis of sCJD. Its sensitivity is 96%, and the specificity is 93% [8]. The initially brain DWI was normal in our case which also played a role in the misdiagnosis. Shea et al. [9] described a 68-year-old male patient initially diagnosed with cervical myelopathy but who later developed rapidly progressive ataxia and was finally diagnosed with sCJD after extensive investigations. Similarly, initial DWI of the patient was unremarkable.

In our patient, the rapid and progressive course in walking difficulties, cognitive functions, progressive dementia, ataxia, myoclonus and personality changes suggested the possibility of the onset of sCJD. Laboratory findings for hypothyroidism, hypovitaminosis, tertiary syphilis and HIV infection were unremarkable. We did not consider dementia with Alzheimer's disease and Lewy bodies in differential diagnosis due to the rapid progression of dementia and cognitive functions. In addition, there was no remarkable history that suggested intoxication. Typical EEG, cerebrospinal fluid analysis and brain DWI findings in our patient suggested a probable sCJD. Biopsy/autopsy is required for a definite diagnosis.

In a sCJD case, reported by Gialanella et al. [3], the patient did not show any functional improvement despite rehabilitation. Similarly, functional improvement was not observed after rehabilitation in our case.

We conclude that in case of rapidly progressive dementia, ataxia and gait impairment, sCJD should always be considered even if unusual features are present and current diagnostic criteria are not completely fulfilled. sCJD is not a

treatable disease however diagnosis is important for palliative treatment of conditions such as pulses and myoclonus. Accurate diagnosis is also important to prevent the transmission of disease.

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Case report
Olgu sunumu

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Annular pancreas: A rare cause of duodenal obstruction

Anüler pankreas: Duodenal obstrüksiyonun nadir bir nedeni

Moussa Sylla [1], Pierlesky Elion Ossibi [1], Ismael Dandakoye Soumana [1], Somuah Tenkorang [2], Karim Ibn Majdoub [1], Imane Toughrai [1], Khalid Mazaz [1]

[1] Department of Visceral Surgery, Hassan II University Hospital, Fez. Morocco
[2] Department of Urology, Hassan II University Hospital, Fez, Morocco

ORCID ID of the authors
MS: 0000-0002-5739-7382
PEO: 0000-0003-2716-4518
IDS: 0000-0003-2451-4199
ST: 0000-0001-5657-7253
KIM: 0000-0002-0421-7296
IT: 0000-0003-0401-3012
KM: 0000-0001-7779-7802

Abstract

Annular pancreas is a rare congenital anomaly. It occurs in 1 in 20,000 of the population. Annular pancreas clinically manifests as digestive stenosis which may be complicated with peptic ulcer. Digestive derivation surgery remains the essential treatment for annular pancreas. We report the case of an 18-year-old female patient with duodenal stenosis caused by an annular pancreas.

Keywords: Annular pancreas, Duodenal obstruction, Congenital

Öz

Anüler pankreas nadir bir konjenital anomalidir. Nüfusun 20.000'inde 1'de görülür. Annüler pankreas klinik olarak peptik ülser ile komplike olabilen sindirim darlığı olarak kendini gösterir. Sindirim sistemi cerrahisi, anüler pankreas için temel tedavi olmayı sürdürmektedir. Bu yazıda, duodenal darlığı olan ve anüler pankreasın neden olduğu 18 yaşında bir kadın hasta sunuldu.

Anahtar kelimeler: Anüler pankreas, Duodenal tıkanıklık, Konjenital

Introduction

Annular pancreas occurs in 1 in 20 000 of the population. It develops during the fifth week of embryonic development when two lobes of a bilobed ventral pancreatic bud migrate in opposite directions around the duodenum [1]. The anatomy of annular pancreas was first described in 1818 by Tiedman but its name was first attributed in 1862 by Ecker [2]. About two-thirds of cases with annular pancreas remain asymptomatic for life, but several complications such as acute pancreatitis, duodenal stenosis, peptic ulceration, and chronic pancreatitis have been associated with this anomaly [3]. We report the case of an 18-year-old female patient with duodenal obstruction caused by an annular pancreas.

Case presentation

An 18 year old female patient was admitted for late postprandial vomiting associated with an altered level of consciousness. She had a history of being hospitalized a year ago for dehydration caused by chronic vomiting disorders in a context of apyrexia and general condition retention. Clinical examination found a confused (Glasgow score= 13), dehydrated, afebrile patient with stunted growth, tachycardia (110 beats per minute). Abdominal examination revealed a non-distended, supple and painless abdomen. There was no palpable mass. Laboratory investigation revealed the following: hyponatremia (Na=115 mEq/ l), hypokalemia (K=1.6 mEq / l) and renal insufficiency (Blood urea nitrogen=1.89 g / l and creatinine=36 mg / l). Upper gastrointestinal fibroscopy showed significant stasis with the presence of impassable post bulbar stenosis which was dilated with a balloon dilator revealing a normal duodenal mucosa. Abdominal computed tomography (CT) scan showed the head of the pancreas surrounding the pyloric region, D1 and part of D2 causing stenosis without suspected digestive thickening with a gastric distension (Figure 1).

The patient was consenting to her surgical management after being informed of her illness. The surgical procedure consisted of an omega loop gastric bypass (gastrojejunal anastomosis). The postoperative course was unremarkable.

Corresponding author / Sorumlu yazar:
Moussa Sylla
Address / Adres: Department of Visceral Surgery, Hassan II University Hospital, Fez. Morocco
e-Mail: syllams86@yahoo.fr

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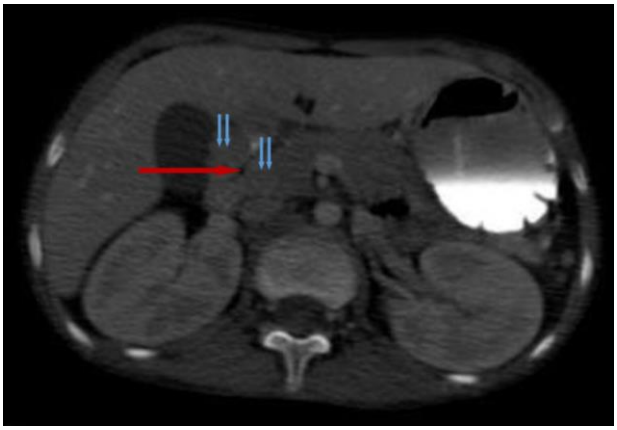

Figure 1: Blue arrow: CT image showing the head of the pancreas surrounding D2, Red arrow: CT image of the D2

Discussion

Annular pancreas is a rare congenital anomaly. It is second the most common congenital anomaly of the pancreatic ducts after pancreas divisum. Its prevalence varies between 5-15 / 100,000 adults on an autopsy series, 1 in 250 on a retrograde endoscopic cholangiopancreatography study (ERCP). The prevalence rate between infants and adults is approximately 0.008% vs. 0.005%, respectively [4].

Many theories have sought to explain its embryological basis; however, no consensus has yet been reached regarding the exact mechanism of aberration. More recently, molecular investigations have shed light on some of these theories, confirming the origination of annular tissue from the ventral pancreatic bud. These studies highlight the role of the hedgehog signaling pathway in the development of this anomaly. Overexpression of the ventral-specific gene transmembrane 4 superfamily member 3 (tm4sf3) has also been associated with annular formation [5].

The ring of normal pancreatic tissue produces symptoms when it obstructs the duodenum. It has been estimated that only about 33% of the cases are symptomatic. 50% of patients present in the pediatric age group, 86% of these present in the neonatal period. In adults, annular pancreas usually presents between age 20 and 50 and is most commonly associated with abdominal pain and gastric outlet obstruction, secondary to duodenal stenosis. Additional presentations including pancreatitis, peptic ulcer disease and obstructive jaundice have been reported. Annular pancreas associated with a pancreatic tumor has also been reported. The diagnosis is usually made with computed tomography scanning and confirmed with upper gastrointestinal contrast fluoroscopy [6]. The imaging finding of pancreatic tissue with posterolateral extension to the duodenum in a patient with suspected chronic pancreatitis or gastric outlet obstruction or the finding of a crocodile jaw appearance of the pancreatic head should raise concern about the presence of annular pancreas [7].

Gastric bypass surgery remains the treatment of choice for annular pancreas: the duodenal ring must not be cut because it contains a pancreatic duct which complicated into a pancreatic fistula when ruptured. Duodenojejunostomy is most effective in treating duodenal stenosis which is sometimes associated peptic ulcer. Gastroenterostomy is more rarely proposed cephalic duodenopancreatectomy remains exceptional for this disease [8].

Conclusion

Annular pancreas is a rare congenital malformation. Its diagnosis is difficult to establish but it must be considered in adults with duodenal obstruction even in ulcer cases that do not respond to medical treatment, especially when it recurs despite the endoscopic dilation. The treatment of choice is surgery for annular pancreas.

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Malignant retroperitoneal paraganglioma treated with radiotherapy: A case report

Radyoterapi ile tedavi edilen malign retroperitoneal paraganglioma: Olgu sunumu

Ghammad Sanae [1], Chebihi Hassani Ghita [1], Allouche Fadwa [1], Alami Zineb [1], Bouhafa Touria [1], Hassouni Khalid [1]

[1] **Department of Radiotherapy, Chu Hassan II Hospital, Fez, Morocco**

ORCID ID of the authors
GS: 0000-0002-7940-8396
CHG: 0000-0003-2714-1957
AF: 0000-0002-6793-4911
AZ: 0000-0003-3349-1793
BT: 0000-0002-9857-1594
HK: 0000-0002-1442-255X

Abstract

Paragangliomas are rare tumors arising from undifferentiated cells of the primitive neural crest. We report a case of a 33-year-old female patient who presented a large firm retroperitoneal tumor situated on the left flank above the left kidney. Levels of the serum epinephrine and norepinephrine were high. We performed a scanned biopsy; the histopathological examination and the immunohistochemical analyses concluded the diagnosis of a retroperitoneal paraganglioma. The tumor was judged secreting and inoperable; therefore it was decided to be treated with radiotherapy.

Keywords: Retroperitoneal paraganglioma, Radiotherapy, Secretory tumor, Pheochromocytoma

Öz

Paragangliomalar, ilkel nöral krest'in farklılaşmamış hücrelerinden kaynaklanan nadir tümörlerdir. Sol böbreğin sol böbrek üzerinde yer alan geniş retroperitonal tümör hastası olan 33 yaşında bir kadın hastayı sunduk. Serum epinefrin ve norepinefrin düzeyleri yüksek bulundu. Taranmış bir biyopsi yaptık; Histopatolojik inceleme ve immunohistokimyasal analizler retroperitoneal paraganglioma tanısını koydu. Tümör salgılanıp inoperabl olarak değerlendirildi; Bu nedenle radyoterapi ile tedavi edilmeye karar verildi.

Anahtar kelimeler: Retroperitoneal paraganglioma, Radyoterapi, Secretory tumor, Pheochromocytoma

Corresponding author / Sorumlu yazar:
Ghammad Sanae
Address / Adres: Department of Radiotherapy, Chu Hassan II Hospital, Fez, Morocco
e-Mail: sanoua1010@gmail.com

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Introduction

Retroperitoneal paragangliomas are uncommon neoplasms. They are usually non-functional tumors, as only a minority of cases secretes catecholamines [1]. It seems that 50% of these tumors are malignant, as metastases to distant organs may appear even years after the initial diagnosis [2,3]. Clinical presentation, diagnosis and treatment are similar to adrenal tumors. Patients should be closely monitored with serum and urine catecholamine determination. Traditionally the most common treatment has been surgical removal, but now there are repeated cases treated by radiotherapy [4]. We report in this article the case of a secretive retroperitoneal paraganglioma treated by radiotherapy with a favorable clinical response.

Case presentation

We describe an inoperable case of a large retroperitoneal paraganglioma diagnosed in a 33-year-old woman. The patient complained of an abdominal distention and a pain in the left lumbar inguinal and ombilic area with palpitation without other clinical signs. Blood tests, including liver and renal biochemistry were normal. On the physical exam, the patient is clinically stable with a mild arterial hypertension along with a firm and sensitive abdominal mass taking place in the lumbar fossa, the left flank and part of the umbilical region measuring approximately 15 cm in longest diameter. A computed tomography of the abdomen revealed a large retroperitoneal and abdominal mass (17x11cm in diameter) with mixed component fleshy and liquid, covering the aorta and the left renal pedicle with an unknown starting point (renal, adrenal gland, pancreas) and without distant metastases in the cerebral, thoracic and pelvic stages (Figure 1 and 2).

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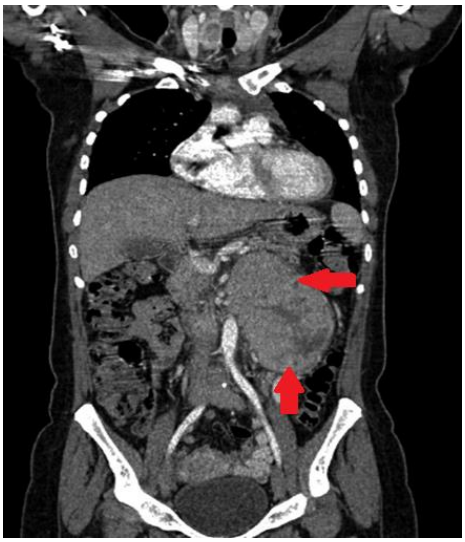

Figure 1: The coronal cuts of the computed tomography of the abdomen

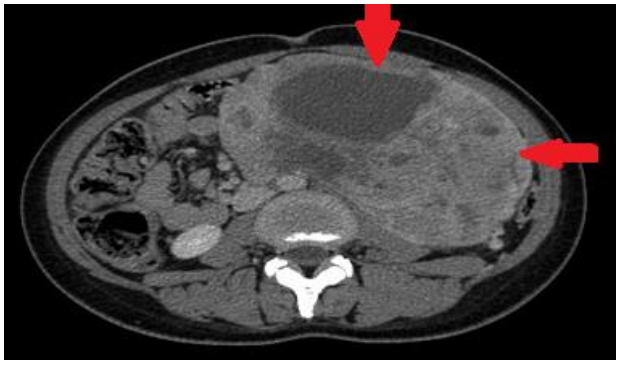

Figure 2: Axial contrast enhanced computed tomography of abdomen at portal time shows a hypervascular retroperitoneal mass with enlarged surrounding vessels

In the magnetic resonance imaging (MRI) the mass of the left flank measures 17 x 13 x 12 cm and it sits in front and below of the left kidney which is pushed up. Inside it exceeds the median line and pushes the small intestines to the right. The left colon is laminated to the left. The lesion remains relatively good limited with lobulated contours, with a vascular structure of a 13 mm axis at the level of the lower part, compatible with a dilation of the left ovarian vein

We performed a biopsy guided with scan and the histological examination revealed a tumor with an organoid 'zellballen' pattern of cellular growth (Figure 3). Immuno-histochemical examination for neuron-specific enolase and vimentin were also positive (Figure 4), whereas epithelial and endothelial markers S-100, actin, myosin and CD117 (c-kit) were negative. The tumor was characterized as a 'retroperitoneal paraganglioma'.

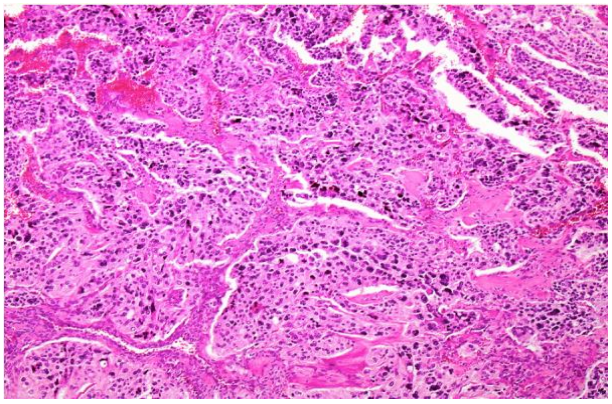

Figure 3: Hematoxylin and eosin stain, paraganglioma

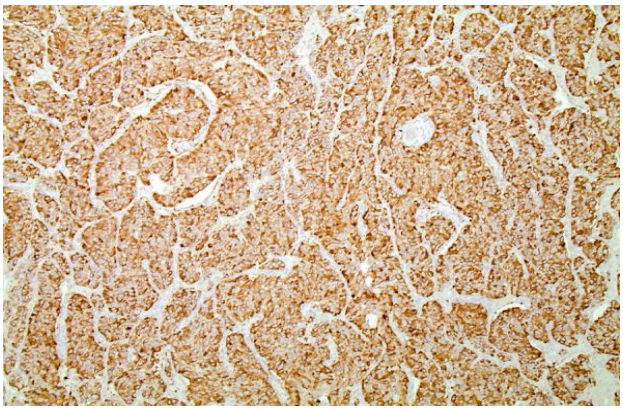

Figure 4: Immunohistochemistry, cells expressing chromogranin

Dosage of catecholamine is higher than normal

* Normetanephrine (catabolite of norepinephrine): 23444.1 µg / 24h (normal value is 0,04µg /L)

* Metanephrine (catabolite of adrenaline): 7812.8 µg / 24h (normal value is 0,02 µg / L)

* 3-Methoxytyramine (catabolite of dopamine): 95845.5 µg / 24h (normal value is 0,02 µg / L)

The tumor is judged secreting and inoperable. The patient was referred to the Radiotherapy-Oncology Department. After conformal radiotherapy planning (Figure 5 and 6), the patient started a course of fractionated radiotherapy using 2 Gy daily fractions to a total dose of 50 Gy (in 5 weeks) with a good tolerance to radiotherapy.

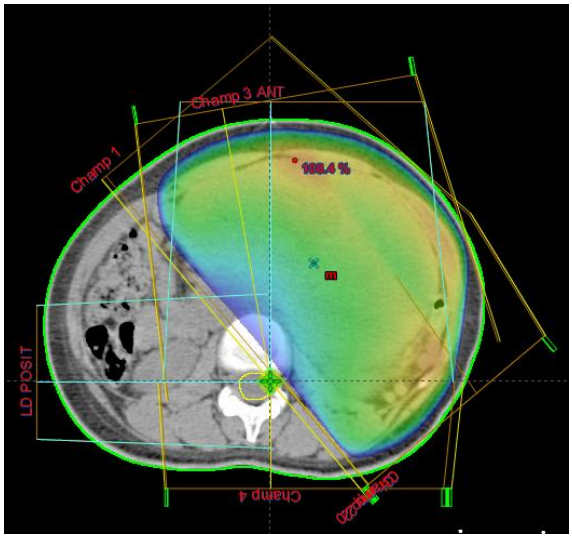

Figure 5: Radiotherapy planning of retroperitoneal paraganglioma using 4 treatment fields

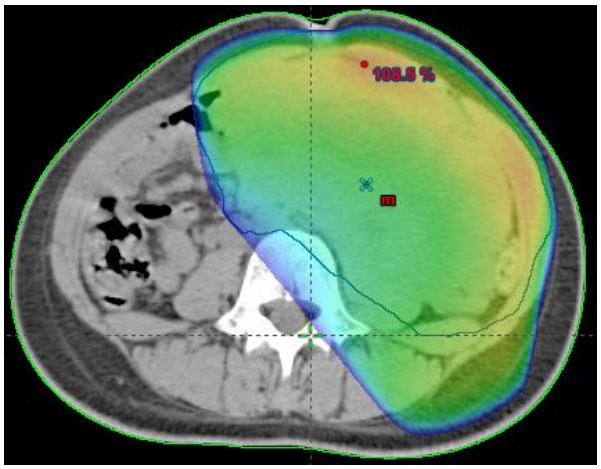

Figure 6: Dose distribution on retroperitoneal paraganglioma (blue structure is PTV)

Full symptomatic relief was rapidly achieved. The tumor was slowly regressing (computed tomography scans carried out every three months) and a 30% regression of dimensions with extensive central necrosis of the tumor heterogeneously enhanced after injection of contrast product was documented 8 months after ending treatment, clinically disappearing from the abdominal mass 12 months later.

Discussion

Paraganglioma is a rare tumor commonly seen in the 3rd to 4th decade, with no sex predilection. 40% of paragangliomas produce high catecholamine levels, which result in symptoms such as headache, palpitations, excessive sweating, and elevated urinary metanephrine or vanillylmandelic acid levels. In the retroperitoneum the most common site for a paraganglioma is the organs of Zuckerkandl, which are located anterior to the aorta at the origin of the inferior mesenteric artery. [5]

Primary retroperitoneal neoplasms are rare benign and malignant mesenchymal tumors that arise in the retroperitoneum, outside of the major organs [6]. Paragangliomas are extra-adrenal pheochromocytomas that arise from chromaffin cells in the sympathetic (localized in retroperitoneum and thorax) or parasympathetic (next to aortic arch, neck, and skull base) neural paraganglioma [7]. They account for 10% of adult pheochromocytomas. About 70% of sympathetic paragangliomas are intraabdominal, usually found in the perinephric and paraaortic spaces. The remaining 30% are located in the chest. Malignant retroperitoneal paragangliomas range from 30% to 50% [8]. Paragangliomas metastasize approximately in 20% to 42% of the cases. Dissemination can be hematogenous or through the lymphatic system, with the most common site of metastasis being the regional lymph nodes, bone, lung, and liver. Because benign and malignant paragangliomas have the same histological appearance, the best predictor for outcome is metastasis or recurrence [7].

The diagnosis is usually established with high urine catecholamine metabolites, VMA, and metanephrine levels [9].

Thirty percent of the patients presented with these diseases in a hereditary context. The biological diagnosis relies on the identification of excessive secretion of the metanephrines which are more sensitive and specific than those of catecholamines. The published recommendations give the opportunity to choose between the metanephrines in serum or urines. The concentrations of the free plasmatic metanephrines reflect the ongoing production of the tumor. They are little sensitive to the renal failure. [10].

If a secretory tumor is diagnosed, the patients undergo paroxysmal episodic hypertension, as well as the typical triad of symptoms associated with pheochromocytomas: palpitations, headache, and profuse sweating. The nonsecretory type most commonly presents an abdominal pain or mass; a large proportion of these tumors are incidentally discovered in normotensive patients during imaging evaluation for other reasons [10].

Once the diagnosis of chromaffin tumor is established, the next step is to determine the extension of the disease. The imaging modality of choice for primary tumor evaluation and staging is a CT scan of the thorax, abdomen, and pelvis. If no lesion is detected, further imaging of the organ of Zuckerkandl and the bladder is performed. CT imaging demonstrates 93–100% sensitivity for localizing adrenal tumors, and 90% for extra-adrenal tumors [11]. In the CT scan the paraganglioma is usually seen as a large well-defined lobular tumor with areas of hemorrhage and necrosis. Punctate calcification is seen in 15% of cases, and a fluid-fluid level can be seen that is due to hemorrhage. Because of the hypervascular nature of paraganglioma, intense contrast enhancement is seen.

MRI is more sensitive than CT in detecting extra-adrenal tumors. At MR imaging, signal voids can be seen with T1-weighted spin-echo sequences. Variable signal intensity is seen on T2- weighted images. Although paraganglioma may be “bright”, the tumor is usually complex and heterogeneous (because of hemorrhage) and almost never demonstrates “lightbulb” high signal intensity with current imaging techniques [5]

Scintigraphy with 123-I labeled MIBG offers superior specificity than CT and MR imaging [12].

The possibility for malignant transformation of paragangliomas makes surgical excision the treatment of choice. Radiation therapy has been advocated for patients who cannot undergo surgery or for unresectable tumors [8]. Aggressive surgery is mandatory to obtain disease free survival. Therapy with radionucleotides may be used for tumors exhibiting uptake on diagnostic scan [11]. Octreotide can be used for treatment of inoperable paragangliomas [13]. Tumor recurrences can also be successfully excised surgically with low morbidity [14].

Traditionally, the main treatment for paragangliomas has been surgical removal but repeated cases were treated by radiation therapy alone for local control of these tumors [15,16]. The authors recommended doses in the 4000 to 4500 cGyrange delivered over 4-5 weeks. Essentially, chemotherapy has no defined role for their treatment, but only used for metastatic stage [16]. Metastatic lesions have a poor prognosis, with a 5-year survival rate of 36% according to one study [17].

Conclusion

Paragangliomas of the retroperitoneum are a rare group of tumors with malignant potential that cause considerable difficulty both in diagnosis and treatment [18]. The management of paragangliomas is controversial. Observation, surgery, EBRT and SRS may, alone or in combination, be appropriate depending on the size and the extent of the tumor, previous treatment, patient age, general health, and neurologic condition. Few data exists regarding long-term tumor control and late effects after EBRT or SRS, But most of these studies affirm that external-beam RT and SRS are safe and effective for large and/or symptomatic paragangliomas [19].

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Rectus sheath hematoma after abdominal trauma with snowball: A case report

Kartopu ile karın travması sonrası rektus kılıf hematomu: Olgu sunumu

Yasemin Kayadibi [1], Deniz Esin Tekcan Şanlı [2], Emel Ure Esmerer [3], Suna Ors [1]

[1] Van Training and Research Hospital, Department of Radiology, Edremit, Van, Turkey
[2] Kahramanmaraş Necip Fazıl State Hospital, Department of Radiology, Dulkadiroğlu, Kahramanmaraş, Turkey
[3] Cerrahpasa Medical Faculty, Department of Radiology, Kocamustafapasa, İstanbul, Turkey

ORCID ID of the authors
YK: 0000-0003-1590-5382
DETŞ: 0000-0002-6545-5757
EUE: 0000-0002-8273-976X
SO: 0000-0001-5027-186X

Corresponding author / Sorumlu yazar:
Yasemin Kayadibi
Address / Adres: Van Eğitim ve Araştırma Hastanesi, Radyoloji Anabilim Dalı, Edremit, Van, Türkiye
e-Mail: ysmnkayadibi@gmail.com

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Abstract
The rectus sheath hematoma (RSH) is the most common benign disease of the rectus abdominis muscle (RAM), but is one of the rare causes of acute abdominal pain. Mostly it is misdiagnosed with other causes of acute abdomen. A 65-year-old man admitted to our emergency service with complaints of localized abdominal pain and swelling after snowball playing and he had no anticoagulant drug history. He was diagnosed as RSH by computed tomography (CT) imaging. In elderly patient population, the clinician should be awake about RSH if the patient presented with local abdominal pain and infra abdominal mass. Early diagnosis by CT imaging is very important for exact diagnosis for prevention from unnecessary surgical procedures.
Keywords: Computer tomography, Rectus sheath hematoma, Snowball

Öz
Rektus kılıfı hematomu (RKH) rektus abdominis kasının (RAK) en sık benign hastalığı olmakla birlikte akut karın ağrısının nadir bir nedenidir. Genellikle diğer akut batın patolojileri ile karışır. Antikoagülan ilaç öyküsü olmayan 65 yaşında erkek hasta kartopu oynadıktan sonra batında şişlik ve karın ağrısı şikayeti ile hastanemizin acil servisine başvurdu. Bilgisayarlı tomografi (BT) görüntülemesi ile RKH tanısı konuldu. Lokal karın ağrısı ve infra abdominal kitle ile başvuran yaşlı hastalarda klinisyen RKH açısından dikkatli olmalıdır. Gereksiz cerrahi tedaviden kaçınmak için BT inceleme ile erken teşhis önemlidir.
Anahtar kelimeler: Bilgisayarlı tomografi, Rektus kılıfı hematomu, Kartopu

Introduction

The rectus sheath hematoma (RSH) is the most common benign disease of the rectus abdominis muscle (RAM). Hematoma may occur either by bleeding into the sheath secondary to inferior or superior epigastric artery injury or by primary RAM rupture [1,2]. RSH is usually seen in older women, but younger case reports have also been reported [3]. The most common predisposing factor is the usage of anticoagulant drugs in these elderly patients with cardiac comorbidities. Local trauma, hypertension, atherosclerosis, chronic cough, epigastric vessel injury during trocar insertion are other reported etiologies [4]. Herein we report a very interesting case of RSH caused by throwing a snowball which has not been reported yet.

Case presentation

A 65-year-old man referred to our clinic with complaints of left-paramedian sided swelling and pain. In his history, it was learned that the one day before, when he was playing snowball a sudden pain and following swollen in his abdominal wall was occurred. The patient had no known chronic disease and there was no such thing as anticoagulant use or bleeding diathesis. On physical examination, there was a swelling in the left mid-lower quadrant of his abdomen. The laboratory findings were within normal limits. Abdominal computed tomography (CT) scans showed relatively hyperdense hematoma in his left rectus sheath which was extending to transverse and oblique abdominal muscles. In addition, extravasation of contrast material posteriorly in the left rectus sheath was also noted after contrast injection (Figure 1-3). The patient was diagnosed with type 2 RSH and followed conservatively. In his daily following sonographic imagines the decrease in hematoma size was revealed.

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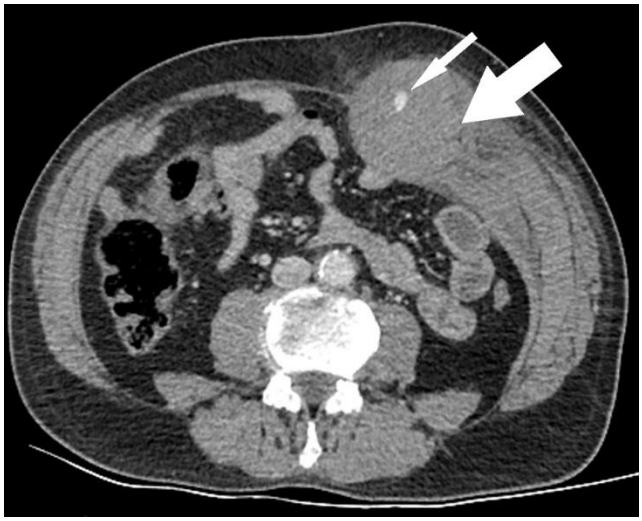

Figure 1: Axial contrast-enhanced abdominopelvic CT shows relatively hyper dens left sided RSH that extending to transverse and oblique abdominal muscles and facias (thick arrow). Note the contrast extravasation (thin arrow)

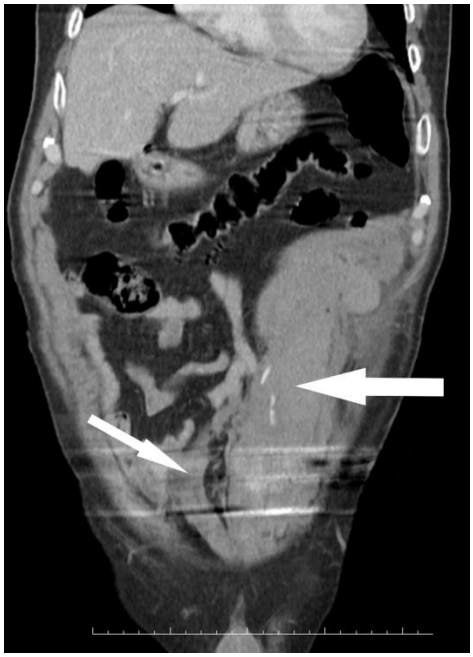

Figure 2: Coronal CT image shows left-sided infra-arcuate line located RSH and contrast extravasation (thick arrow). Right rectus abdominis is in normal size (thin arrow)

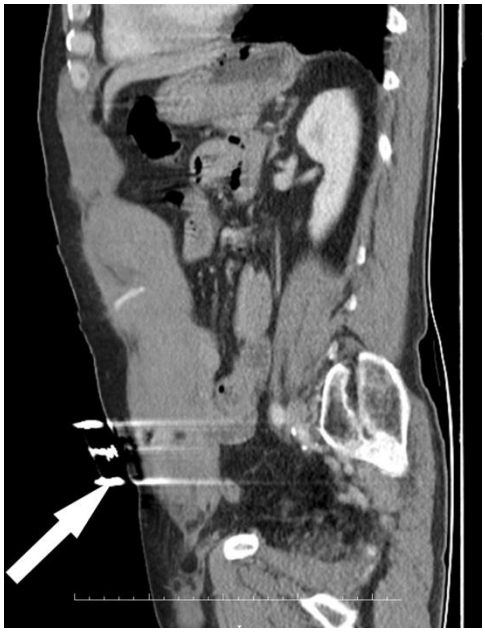

Figure 3: Sagittal CT image shows the extension of RSM to the level below the umbilicus (arrow).

Discussion

RSH usually presents with acute local abdominal pain and swelling. If the measures of the hematoma are above 5 cm, the pain affects general abdomen, thus RSH could be misdiagnosed as other acute abdominal clinics [4]. Except for abdominal pain, abdominal wall swelling, ecchymosis, fever, nausea, vomiting, distension, and cramps could be other presenting symptoms. Abdominal wall swelling is the most important finding in clinical examination. Fothergill and Carnet sign may be helpful in understanding whether the stiffness is caused fromby the abdominal wall or from the intraabdominal pathologies. If the swelling doesn't change with RAM's flexion and doesn't extend to cross, this is probably a positive finding for RSH (Fothergill sign). Another clinical finding is the increase of abdominal pain and sensitivity with RAM contraction (Carnet sign). Additionally, there would be no general condition disorder in patients with RSH unlike other acute abdominal pathologies [5]. RAM is divided into two main parts by arcuate line. Above the arcuate line, rectus sheath is supported by aponeurosis of oblique and transversal abdominal muscles. Below the arcuate line, this aponeurosis continues with the anterior part of the sheath but the posterior part of the sheet supported only by the layer from the transverse abdominal muscle. For this reason, the sheath is relatively weak in the posterior part below the arcuate line. Inferior and superior epigastric arteries provide an intensive vascular network by anastomosing at the umbilicus level. The hematoma usually occurs in the lower and posterior part of the sheath. In addition, strong muscle contractions are more susceptible to damage arterial structures because of their better adhesion to the muscle at this level [2].

Three types of RSH are described according to CT findings. Type 1: intramuscular and unilateral, type 2: bilateral intramuscular with extension to transverse fascia, type 3: intra- or extra-muscular, with perivesicular or intraperitoneal extension [6].

Hemoglobin value and patients clinic usually stay stable in type 1 RSH while in type 2 hematoma minor changes seen in hemoglobin value. Hematologic instability usually develops in Type 3 hematomas [6]. If the patient is stable, type 1 and 2 rectus sheath hematomas can be followed by supportive treatment such as resting, analgesia, anticoagulation, and transfusion. If the patient is unstable, surgical operation and ligation of the arterial supply should be considered. Percutaneous arterial embolization may be performed if hemorrhage is recurring. Removal of the hematoma is not always necessary as it may deactivate the tamponade effect and cause uncontrolled hemorrhage [2].

USG is the first choice imaging method in the patient presenting with abdominal pain; because it is easy, inexpensive and x-ray- free. However, USG is insufficient in an intraabdominal or exraabdominal distinction of the mass [5]. Due to the higher sensitivity and specificity, CT scan is the gold standard in the diagnosis of RSM. It has relatively hyperdense mass appearance relative to the muscle leading to expansion. Active bleeding can be seen with contrast injection. The detection of fluid densities in the abdomen is suspicious for intraperitoneal rupture. Follow-up ultrasound can also be used for patients requiring long-term follow-up [3]. Hypovolemic shock, infection, abdominal compartment syndrome,

myonecrosis, acute renal failure, small bowel infarction, and death have been reported complications of RSH [2].

The prevalence of RSH which was rarely seen in the past is rapidly increasing, due to the increased usage of anticoagulants in the elderly population. For the clinician to be awake for the patients who are suffering from swelling and pain on the abdominal wall and choose CT scan first is very important for exact diagnosis.

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Spontaneous rupture of the ureter: A rare case

Spontan üreter rüptürü: Nadir bir olgu

Cihan Bedel [1], Sefa Türkoğlu [2]

[1] University of Health Sciences, Antalya Training and Research Hospital, Department of Emergency Medicine, Antalya, Turkey
[2] Denizli State Hospital, Department of Radiology, Denizli, Turkey

ORCID ID of the authors
CB: 0000-0002-3823-2929
ST: 0000-0002-9623-0083

Abstract
Spontaneous rupture of the ureter is a rare condition defined as non-traumatic urinary leakage from the ureter. It is generally associated with calculous diseases. It can be present with acute abdomen and may be misdiagnosed as other surgical conditions. Ureteral rupture can lead to numerous complications, including abscess formation, urinomas and urosepsis. We have presented a rare case of spontaneous rupture of the ureter and have observed the diagnosis and treatment methods in the light of the available literature.
Keywords: Spontaneous rupture, Ureteral rupture, Ureter

Öz
Spontan üreter rüptürü, üreterin travmatik olmayan idrar kaçağı olarak tanımlanan nadir bir durumdur. Genellikle böbrek taşı türünden hastalıklarda görülür. Akut karın ile ortaya çıkabilir ve diğer cerrahi hastalıklar olarak yanlış tanı alabilir. Üreter rüptürü apse formasyonu, ürinom ve ürosepsis gibi çeşitli komplikasyonlara yol açabilir. Biz burada nadir olarak görülen spontan üreter rüptürü olgusunu tanı ve tedavi yöntemleriyle mevcut literatür eşliğinde sunduk.
Anahtar kelimeler: Spontan rüptür, Üreter rüptürü, Üreter

Introduction

Spontaneous rupture of the ureter, which is defined as nontraumatic urinary leakage from the ureter, is a rare urological disorder and only a small number of cases have been reported in the literature [1]. It occurs due to trauma, ureteral obstruction by a calculus, stricture, tumor, retroperitoneal fibrosis and posterior urethral valves [2]. Peritoneal irritation by urine may lead to symptoms of acute abdomen, sometimes except any urinary symptoms or urinalysis abnormalities. It is often misdiagnosed as appendicitis or diverticulitis due to its presentation [3]. We have presented a rare case of spontaneous rupture of the ureter and have observed the diagnosis and treatment methods in the light of the available literature.

Case presentation

A 32-year-old male presented to the emergency department (ED) with acute abdominal pain accompanied by nausea and vomiting for the past six hours. The patient's past medical history was unremarkable. He was well nourished and in a good general condition. Upon admission, his body temperature was 37.2°C, heart rate was 120 beats/min, respiratory rate was 18 breaths/ min and blood pressure was 100/60 mmHg. Physical examination revealed only diffuse tenderness in the right lower quadrant radiating to the right flank. His bowel sounds were normal.

Corresponding author / Sorumlu yazar:
Cihan Bedel
Address / Adres: Sağlık Bilimleri Üniversitesi, Antalya Eğitim Ve Araştırma Hastanesi, Kazım Karabekir Caddesi, Posta kodu: 07100, Muratpaşa, Antalya, Türkiye
e-Mail: cihanbedel@hotmail.com

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Laboratory evaluation revealed normal creatinine and blood urea nitrogen levels. Other biochemical results, including complete blood count, hepatic function tests and C-reactive protein level, were also within normal ranges. Urine analysis showed microscopic hematuria. Plain abdominal radiography was unremarkable, while abdominal ultrasonography (USG) showed mild right hydronephrosis and there was a fluid collection at the right perirenal and pelvic spaces. Despite of intravenous proton pump inhibitor, analgesic, antiemetic and intravenous normal saline of 1000 mL, his pain did not decrease. He continued vomiting and abdominal computed tomography (CT) scan was performed for differential diagnosis. Contrast-enhanced CT showed mild right hydronephrosis with a marked fluid collection at the right perirenal and pararenal spaces. There was contrast medium leakage around the right ureteropelvic junction, causing an absence of enhancement of the right ureter (Figure 1-2). A tiny calculus was also noted at the right ureterovesical junction.

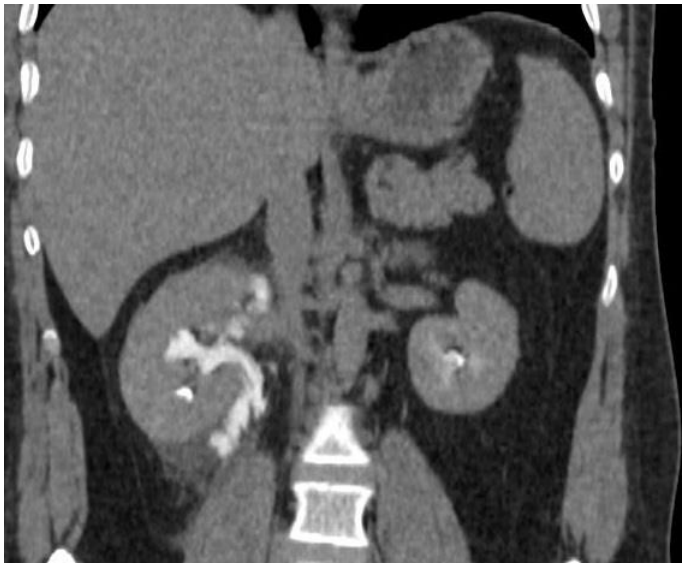

Figure 1: Coronal view of the abdominal CT shows contrast extravasation from the right upper ureter

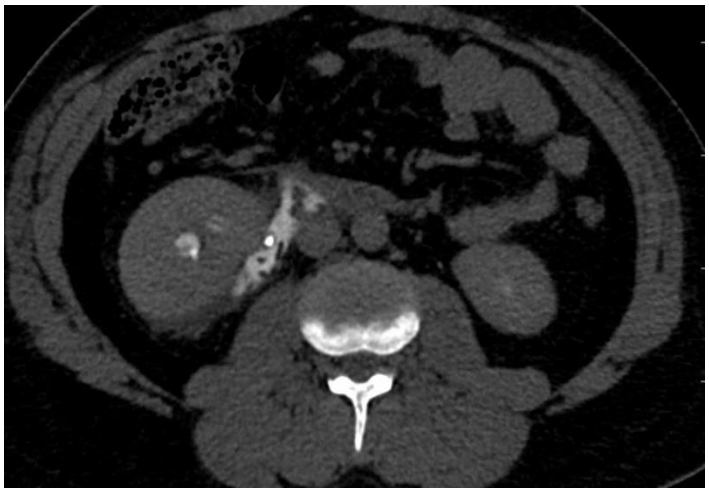

Figure 2: Axial CT image shows leakage of radiocontrast media at the level of the upper ureter

The patient was initially managed by an endourological procedure and a double-J catheter was inserted. His Foley catheter was removed the next day and he was discharged with no complications. Two months later, his catheter was removed, without any complication. His ruptured ureter healed completely.

Discussion

Spontaneous rupture of the ureter is a rare disease. It is usually caused by ureteral stones. There is no reasonable explanation in the literature yet; only two theoretical mechanisms have been proposed. First, impaction of stones may cause erosion of the ureteral wall, which is directly causes ureteral rupture. Second, a downward-moving calculus may lead to ureteral rupture at the distal ureteral obstruction, with elevation of the intraureteric pressure [4,5]. In addition, malignancy, retroperitoneal fibrosis, bladder outlet obstruction, connective tissue disease such as Klinefelter syndrome were also reported. In some cases, the cause is unknown [6-9]. In our patient, similar to the literature rupture occurred due to the ureteral calculi.

Patients with spontaneous rupture of the ureter may present to the hospital with very different clinical findings. Patients usually have symptoms such as sudden onset abdominal pain and flank pain associated with nausea and vomiting. In some cases, diagnosis may be difficult due to nonspecific symptoms. The differential diagnosis includes urinary lithiasis, appendicitis, cholecystitis, diverticulitis and other possible causes of abdominal pain [10]. In our case, the patient presented to ED with similar complaints.

Previously, intravenous pyelogram was the gold standard for the diagnosis of ureteral rupture. However, advances in technology, USG and CT scan have gained popularity. USG can easily accessible and time saving in the ED. In cases of ureteral rupture, USG can detect fluid collection and hydronephrosis and exclude other abdominal pathologies. CT is also an excellent tool in evaluating urological disease. It also helps in the diagnosis of diseases other than urogenital problems , including vascular disease including abdominal aortic or iliac artery aneurysm and gastrointestinal diseases such as acute appendicitis, diverticulitis or cholecystitis [11,12]. We prefer USG and abdominal CT scan in assessing patients with suspicious ureteral rupture in ED, rather than intravenous pyelogram.

Due to the rarity of spontaneous ureteral rupture, there is no standardized management for this situation. Complications such as urinoma, perinephric or retroperitoneal abscess formation, and urosepsis require prompt evaluation and intervention [8,13]. Akpinar et al [8], were reported spontaneous healing of the rupture was documented in 7 days or less by CT scan after conservative medical management. If conservative management fails, endourological intervention may be necessary.

In a conclusion, spontaneous rupture of the ureter is a rare entity that can be present with acute abdomen and may be misdiagnosed as other surgical conditions. Patient's symptoms, physical examination and urinalysis are unreliable. Thus, a high level of alertness is important. Further examination including ultrasonography or abdominal CT should be considered for suspected cases. In patients with acute abdominal or flank pain, physicians should properly evaluate this diagnosis, imaging and treatment should be done quickly.

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Small bowel obstruction secondary to an adhesion between ovary and small intestine loops: Case report

Ovaryan ve ince bağırsak iltihabı arasındaki yapışmaya bağlı ince bağırsak tıkanıklığı: Olgu sunumu

Houssam Belghali [1], Younes Hamdouni [1], Karim Ibn Majdoub Hassani [1], Imane Toughrai [1], Khalid Mazaz [1]

[1] Visceral Surgery Service, Hassan II University Hospital, Faculty of Medicine and Pharmacy of Fez, Sidi Mohammed Ben Abdallah University, Fez, Morocco

ORCID ID of the authors
HB: 0000-0002-6734-2094
YH: 0000-0002-8037-8542
KIMH: 0000-0002-0421-7296
IT: 0000-0003-0401-3012
KM: 0000-0001-7779-7802

Corresponding author / Sorumlu yazar:
Houssam Belghali
Address / Adres: Visceral Surgery Service, Hassan II University Hospital, Faculty of Medicine and Pharmacy of Fez, Sidi Mohammed Ben Abdallah University, Fez, Morocco
e-Mail: hbelghali10@gmail.com

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Abstract

Adhesion-related small bowel obstruction is a common pathology in visceral surgery. Postoperative adhesion is the most common etiology of acute intestinal occlusion. We report the case of an intestinal occlusion caused by an adhesion between the ovary and the small bowel loops. In order to share the epidemiological, clinical, prognostic and therapeutic aspects of this affection, and also the unusual localization of the adhesion, this is described in our case report. Computed tomography has improved the diagnosis of adhesive small bowel obstruction and its findings in bowel ischemia are helpful to guide the therapeutic attitude. The treatment was surgical and the postoperative course was simple.

Keywords: Obstruction, Small bowel, Adhesion

Öz

Adezyon ile ilişkili ince bağırsak tıkanıklığı, visseral cerrahide bir komatolojik patolojidir. Postoperatif yapışıklıklar, akut bağırsak tıkanıklığının en sık etyolojisidir. Bu durumu Epidemiyolojik, klinik, prognostik ve terapötik yönlerini paylaşmak için, ovaryan ve ince bağırsak ilmekleri arasındaki bir yapışma sonucu oluşan bir bağırsak tıkanıklığı olgusunu ve aynı zamanda, adezyonun alışılmadık lokalizasyonunu da olması sebebiye bildiririz. Bilgisayarlı tomografi yapıştırıcı ince bağırsak tıkanıklığı teşhisinde faydalıdır, ve bağırsak iskemisindeki bulguları, terapötik tutumu yönlendirmek için yararlıdır. Tedavisi cerrahi olup, hastanın postoperatif dönemi problemsiz idi.

Anahtar kelimeler: Obstrüksiyon, İnce bağırsak, Adezyon

Introduction

Adhesive occlusion has been reported as a common cause of hospitalization in gastrointestinal surgery [1]. It is the first etiology of acute intestinal obstruction, either by strangulation or compression or both. They can occur at any time during the life of operated patients. However spontaneous adhesions with no history of abdominal surgery are rare, but possible. It is a diagnostic and therapeutic emergency, the severity of occlusion is an important factor that affect the management of adhesive small bowel obstruction and which must be estimated to choose the appropriate treatment, which can be surgical or conservative. In patients without signs of severity, medical treatment finds its justification. However, it carries a risk of intestinal necrosis, requiring resection associated with a significant increase in mortality and morbidity.

Case presentation

A 32-year-old women, who had underwent a caesarean section 15 months ago, reoperated 2 weeks later for an undocumented gynecological problem. She was admitted to our hospital for with a three-day history of abdominal pain, retention of gas and stool and bilious vomiting. On physical examination, she was conscious, hemodynamically and respiratory stable, with a heart rate of 105 beats/min, and afebrile. Physical examination also revealed the presence of a pfannenstiel and midline abdominal scars, and a mild abdominal distension associated with tympany. The rest of the somatic examination did not reveal any pathological findings.

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A plain abdominal X-ray film showed dilatation of small bowel loops and the presence of multiple air-fluid levels (figure 1). The abdominal CT-scan demonstrated dilated loops of small bowel 3 cm proximal to the point of obstruction, an image of swirling strands of soft tissue and fat attenuation in the right inguinal region realizing the whirl sign and a double bird's beak sign due to the mesenterico-axial volvulus (figure 2).

Surgical exploration revealed the presence of a small bowel volvulus secondary to an adhesion band between the ovary and the small intestine responsible if an intestinal distension located 1.3 m upstream of the ileocecal valve, without visible necrosis. A lysis of the adhesion was performed, with a small bowel reduction and retrograde evacuation of the proximal segment (figure 3). The postoperative period was uneventful; the patient was discharged on postoperative day four.

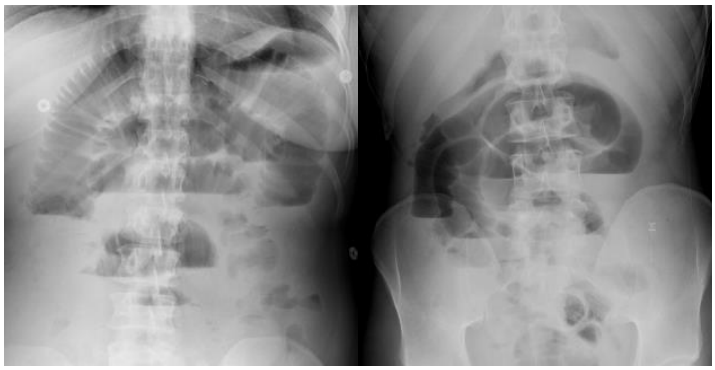

Figure 1: A plain abdominal X-ray film showed dilatation of small bowel loops and the presence of multiple air-fluid levels.

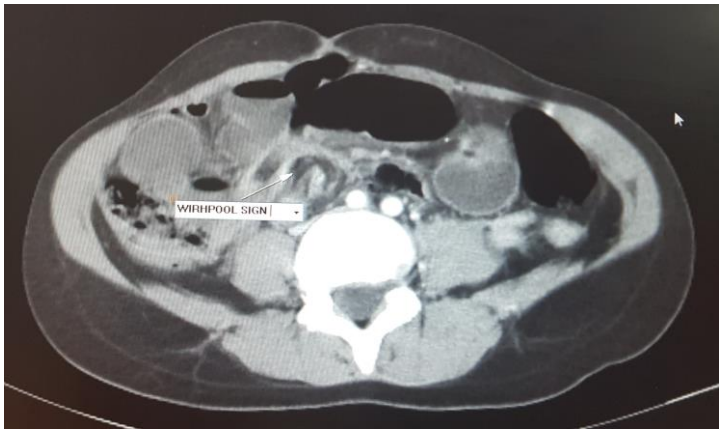

Figure 2: The whirl sign and a double bird's beak sign due to the mesenterico-axial volvulus.

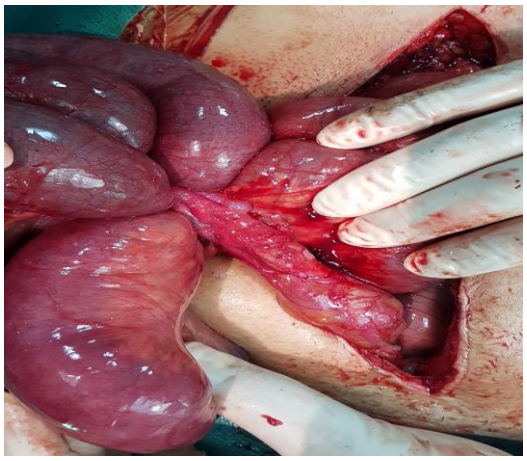

Figure 3: Flange between ovary and small intestine loops.

Discussion

Adhesive occlusion is a common cause of hospitalization in surgery. It occurs mainly in young patients with a history of abdominal surgery, the age of our patient was 32 years, which is consistent with others series, like the series of Mr. Maliki Alaoui [2] where the mean age was 41.9 years, Miller 46 years [3], Diakité 39.7 years [4] and Harouna [5] 32 years. However Catel [6] and Hiki [7] found an elderly population (61 and 59.6 years respectively). This can be explained by the young age of the Moroccan population. Adhesive occlusion affects mainly male with a sex ratio of 1.6. This has also been observed in other African studies [1-8]. On the other hand, there was a women predilection in Western series [3-4]. Numerous studies have shown that lower abdominal surgery is certainly associated with more adhesive occlusion [9-10], which is consistent with our case. In the literature we found that for Yazidi and Shapiro, colorectal surgery seems to be the most exposed to adhesions [11], for Shih and Irabor Do. [12] gyneco-obstetric surgery is a significant cause of small bowel occlusion [13], according to A. Audebert near one out of 20 readmissions related to adhesions after gynecological laparotomy is due to a small bowel obstruction. An analysis of hospitalizations for intestinal obstruction non related to a tumoral process showed that in 50.4% of cases, occlusion was due to a prior gynecological intervention, most commonly an abdominal hysterectomy [14,15].

The time between index intervention and the first episode of small bowel obstruction varies widely from 8 days to 60 years [11]. In our case; occlusion was late, occurring 1 year and 6 months after the surgery. The clinical manifestations that were observed in our case are: abdominal pain, vomiting, and inability to pass gas abd stool, which is consistent with the results of Harouna's series [5]. The delay between the first symptoms and the consultation is an important factor that influences considerably the severity of the disorders, and the prognosis of the patients. The longer the delay, the more vitality of the intestine is at stake. In our case, the patient consulted within 72 hours. A complete physical examination should be performed to detect signs of severity [16]. The plain abdominal X-ray allows a first diagnostic and etiological assessment of the occlusive syndrome, its specificity and sensitivity remain low [10]. The abdominal CT scan confirm the diagnosis of small bowel obstruction with a sensitivity of 94 to 100% and a specificity of 90 to 95%. It not only makes the positive and accurate etiological diagnosis (sensitivity of 73 to 95%), but also identifies time-sensitive complications including ischemia and perforation, and thus determines a treatment strategy [6,17]. In addition, a laboratory tests are often used to evaluate the hydroelectrolytic disorders and to carry out a preoperative assessment. Therapeutically, there is no consensus about the choice between surgical treatment at the outset and conservative treatment, which finds full justification in patients without signs of clinical and biological severity. However, this treatment may miss a necrosis that would then require resection [11]. The duration of the conservative treatment can range from a few hours to 14 days [16].

In our case, we opted for a surgical treatment at the outset because of signs of ischemia (tachycardia, fever, and

leukocyte at 17000), with the CT scan showing mesenteric-axial volvulus. We performed a midline laparotomy straddling the umbilicus. Laparoscopic treatment of adhesive occlusions is an alternative to laparotomy in selected patients. Its best indication might be single adhesive band. This alternative to laparotomy could reduce the formation of adhesions [18, 19], and reduce the number of next occlusive episodes. The rate of conversion to laparotomy varies from 8 to 46% [19], it would be necessary for many reasons including: the non-visualization of the localization of the occlusion, an intestinal injury caused by the manipulation of dilated loops, the necessity to proceed to resection or a difficult dissection due to a multi-adherential abdomen. In addition, laparoscopy provides a certain number of advantages by reducing the operative time, the time of intestinal transit recovery, the postoperative stay and postoperative complications according to Ghariani [19]. In our case, we performed a laparotomy. The surgical technique consists first of all in an evacuation as complete as possible of the upstream bowel; it is only feasible in laparotomy. Evacuation allows: to ensure the decompression of the intestine to reduce the distension in order to prevent ischemia, to explore in a reliable manner the entire abdominal cavity. However, there is no evidence that it facilitates the transit recovery [20]. The section of a single adhesion band is usually performed without major difficulty. This can be difficult when the adhesion is very short, with much dilated upstream loops hindering the exposure of the initial lesion, or when the adhesion band is located in a difficult access area. In case of multiple adhesions, adhesiolysis can be difficult with a major risk of inadvertent bowel injury, so wisdom incites to treat only the obvious cause by performing partial adhesiolysis [20]. Once the obstacle is removed, it is important to assess the vitality of the intestinal loops, and in case of doubt, resection is required. Indeed, the risk is to leave in place a poorly vascularized intestinal segment that can be complicated in short-term by perforation and postoperative peritonitis or in long-term by ischemic stenosis. The resection of a small bowel loop has no special technical feature, but it is necessary to ensure the construction of a well-vascularized anastomosis. The duration of postoperative hospital stay depends on the therapeutic modality and the occurrence of complications; longer in patients who have undergone resection, than in those with viable bowel, or when opted for a conservative treatment before switching to surgery.

Conclusion

Continuous progress in the management of adhesive occlusions has been achieved as a result of a more careful clinical approach, nowadays it cannot be said that CT and laparoscopy has true impact on the prognosis of adhesive occlusion. It is certainly towards prevention strategies, thanks to panoply of better codified gestures and improved anti-adhesion devices that the surgeon must turn to reduce the frequency of a surgical complication that is often frustrating because of its relative unpredictability.

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Case report
Olgu sunumu

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Sarcomatoid carcinoma of the urinary bladder: A case report and short review of the literature

Mesanenin sarkomatoid karsinomu: Olgu sunumu ve literatürün kısa gözden geçirilmesi

Engin Kölükçü [1], Şahin Kılıç [2], Nihat Uluocak [3], Doğan Atılgan [3], Faik Alev Deresoy [4]

[1] Tokat State Hospital, Department of Urology, Tokat, Turkey
[2] Fethiye State Hospital, Department of Urology, Fethiye, Mugla, Turkey
[3] Gaziosmanpasa University, Faculty of Medicine, Department of Urology, Tokat, Turkey
[4] Gaziosmanpasa University, Faculty of Medicine, Department Of Pathology, Tokat, Turkey

ORCID ID of the authors
EK: 0000-0003-3387-4428
ŞK: 0000-0003-2458-1893
NU: 0000-0001-8315-466X
DA: 0000-0001-8584-2124
FAD: 0000-0002-2243-9394

Abstract

Although the most common malignant formations in the bladder are urothelial carcinomas, there are also tumors with different differentiation degrees like sarcomatoid carcinoma of the urinary bladder. It is a rare and highly aggressive type of tumor and consists of malignant epithelial and sarcomatous components. The literature about the subject is extremely limited, and there is no consensus on treatment protocols. This case report aims to present a case of 71-year-old man who presented with macroscopic hematuria and diagnosed with sarcomatoid carcinoma of the urinary bladder.
Keywords: Sarcomatoid, Carcinoma, Bladder

Öz

Mesanede en sık izlenen malign oluşumlar ürotelyal karsinomlar olmakla birlikte sarkomatoid karsinom gibi farklı diferansiyasyon gösteren tümörler de bulunmaktadır. Bu nadir izlenen tümoral yapılar malign epitelyal ve sarkomatöz komponentler içeren oldukça agresif davranışlı oluşumlardır. Bu konu ile ilgili literatür bilgileri son derece sınırlı olup tedavi protokolleri hakkında fikir birliğine varılan bir rejim mevcut değildir. Bu olgu sunumunda makroskopik hematüri ile başvuran ve mesanenin sarkomatoid karsinomu tanısı alan 71 yaşındaki erkek hastanın literatür bilgileri eşliğinde tartışılması amaçlanmıştır.
Anahtar kelimeler: Sarkomatoid, Karsinom, Mesane

Introduction

Bladder cancer is a significant health problem with increasing incidence in parallel with the growing prevalence of tobacco smoking worldwide. It is the ninth most common cancer in the world and ranks second among all types of cancer in the urinary tract. Besides, clinical studies showed that more than 100,000 patients were diagnosed with a muscle-invasive or advanced disease each year around the globe [1,2]. The majority of bladder tumors (95-98%) consist of transitional cell (urothelial) cancers [2]. There are also some rare malignant tumors such as hemangiopericytoma, leiomyosarcoma, liposarcoma, rhabdomyosarcoma, small cell bladder cancer, angiosarcoma, chondrosarcoma, malignant fibrosis histiocytoma, malignant peripheral nerve sheath tumor, sarcoma, and primitive neuroectodermal tumor in the bladder [3].

Sarcomatoid carcinoma of the urinary bladder accounts for approximately 0.3% of all bladder tumors [4]. It is defined by the World Health Organization as a biphasic tumor consisting of malignant epithelial and mesenchymal components [5]. More than 70% of the diagnosed patients are advanced-stage, and the most common presenting complaint is hematuria. Compared with conventional urothelial carcinomas in the bladder, it appears as a cancer with rather a poor prognosis showing more invasive and aggressive behavior [6].

A literature search showed that there are a very limited number of publications on sarcomatoid cancer of the bladder, as opposed to the common malignant formations of the bladder. Herein, we aimed to present a case with bladder cancer whose pathological results indicated sarcomatoid carcinoma.

Corresponding author / Sorumlu yazar:
Engin Kölükçü
Address / Adres: Tokat Devlet Hastanesi, Üroloji Bölümü, Tokat, Türkiye
e-Mail: drenginkolukcu@gmail.com

Informed Consent: The author stated that the written consent was obtained from the patient presented in the study.
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Case presentation

A 71-year-old male patient presented with a 1-year history of occasional macroscopic hematuria. A detailed history revealed that he had been smoking three packs a day for 40 years. Besides, he had undergone transurethral resection due to a bladder tumor at another hospital about ten years ago and yet he did not attend follow-ups. The operative and pathological details were not available. He had no other history of surgery or a systemic disease. On physical examination, the only pathological finding was suprapubic sensitivity. His laboratory test results were as follows: creatinine 1.31 mg/dl; urea 47.45 mg /dl; hemoglobin 7.11 g/dl.

The patient was hospitalized and three units of blood transfused. Computed tomography revealed a heterogeneously enhancing mass which boundaries cannot be selected clearly and reaching the widest 160mm x102 mm dimensions and covering the bladder lumen almost completely. It was considered as bladder tumor and tumor-associated hematoma. The perivesical fat tissue was normal. Imaging procedure showed no additional major pathological finding (Figure 1).

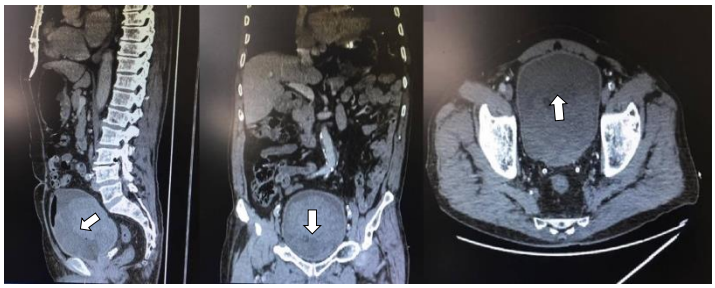

Figure 1: Computed tomography scan showing heterogeneously enhancing bladder mass with hematoma (white arrows)

Bladder irrigation was performed through catheterization and endourological examination was carried out under general anesthesia. Pre-cystoscopy bimanual palpation was unremarkable. Cystoscopy revealed hematoma filling the bladder lumen almost completely, and a broad-based solid tumor with necrotic material on the surface occupying the trigon and right wall of the bladder. Transurethral resection was performed. Surgical pathology report revealed that sarcomatoid carcinoma was present, and the muscularis propria was positive for tumor. Then the patient underwent radical cystectomy and ileal loop diversion. The microscopic evaluation of tissue samples demonstrated that the tumor was composed of epithelioid cells with irregular vesicular nuclei and pale cytoplasm with indistinct borders. Some cells showed spindle morphology with bipolar nuclei and formed bundles with storiform-like growth pattern. The tumor infiltrated both the detrusor muscle and perivesical fat tissue (Figure 2). Immunohistochemical analysis revealed bladder mucosa to be the primary site of origin (Figure 3).

The patient was followed up in the intensive care unit due to respiratory disorder postoperatively and died of respiratory failure on postoperative day three.

Our study was conducted in accordance with the Helsinki Declaration Principles, and was performed after patient's approval with informed consent.

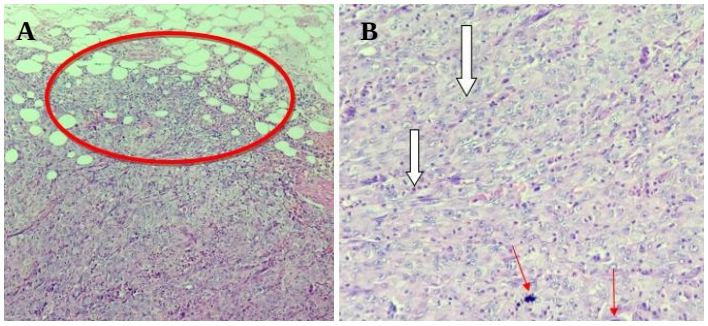

Figure 2: Histopathological examination of the bladder mass, A: Tumoral invasion through muscularis propria to the perivesical fat tissue (red ellipse) (x10), B: Semi epitheloid-spindle cells arranged in trabeculae and bundles (white arrows), frequent mitoses and highly variable nuclear atypia (red arrows) (x20)

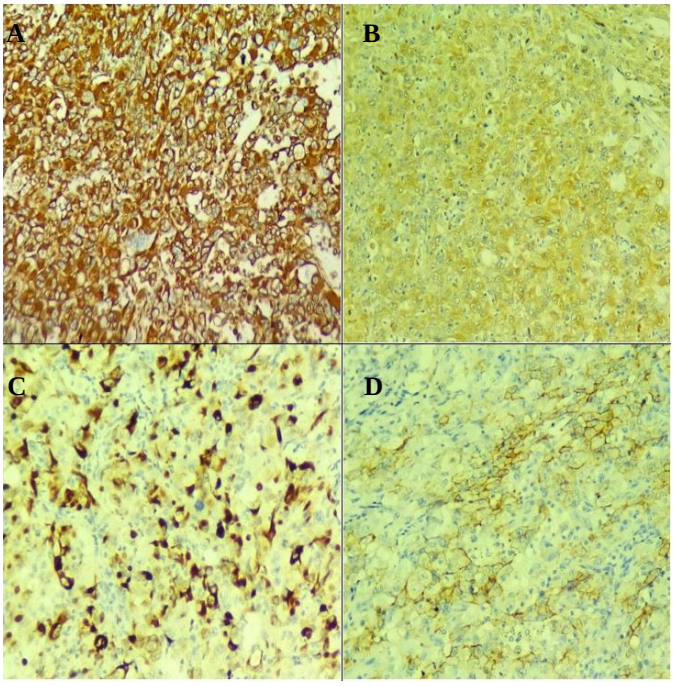

Figure 3: Immunohistochemical analyses of the bladder mass: Vimentin (A), Fascin (B), CK7 (C) and EMA (D) expressions in tumor cells

Discussion

Sarcomatoid carcinoma can be seen in many different parts of the body such as the genital system, thymus, skin, breast, spleen, pancreas, peritoneum and upper and lower respiratory system. However, the most common organ involved is the uterus in postmenopausal women, and the bladder in men [4,7]. The location of sarcomatoid cancers is also important in the clinical course of the tumor. Those seen in the upper respiratory tract or gastrointestinal system have a rather better prognosis. However, the tumors diagnosed in the urogenital system, such as the bladder, show a highly aggressive course [4]. Sarcomatoid cancers are seen most commonly in individuals over 60 years of age and less frequently in women than men. In previous publications, sarcomatoid cancers of the bladder have been described using a variety of terminologies such as carcinosarcoma, metaplastic cancers, Müllerian tumors, spindle cell cancer, heterologous differentiated tumors or malignant mixed mesodermal tumors [4,8].

Symptomatology in sarcomatoid cancers of the bladder is very similar to the transitional cell tumors frequently observed in the bladder. As the macroscopic hematuria is the main complaint, the recurrent urinary tract infections, suprapubic pain, and dysuria are the other signs and symptoms [3,9]. Similarly, the main symptom was macroscopic hematuria in our case. There

are many factors strongly associated with sarcomatoid cancer of the bladder such as smoking, radiation exposure, cyclophosphamide use, and recurrent cystitis [6,10]. The patient discussed in this report had a history of heavy smoking. Previous studies showed that tumor diameters were highly variable. The most common site of tumor cells is in the bladder base, and most of them are exophytic, ulcerated, invasive in-nature with bleeding and necrotic areas [4,11]. Pathological evaluation revealed that the tumor consists of transitional epithelial cells as well as sarcomatoid components. The sarcomatoid component comprises a mixture of a spindle or round pleomorphic cells resembling those seen in leiomyosarcoma, chondrosarcoma or other sarcomatoid neoplasms. The carcinomatous component may show a papillary or non-papillary configuration with features of adenocarcinoma, squamous cell carcinoma or small cell carcinoma; or may be present only as carcinoma in situ. The tumor may contain myxoid or sclerosing areas, as well as necrosis [12].

Perret et al. [13] analyzed 47 patients with sarcomatoid cancers of the bladder and concluded that 83% of them had muscularis propria involvement. Erdemir et al. [4] evaluated 159 patients who underwent radical cystectomy in their department and found that only 0.031% of them had sarcomatoid cancer. They also reported that all patients diagnosed with sarcomatoid cancer were in stage 2 and above. In a similar study, Beltran et al. [10] found that all patients evaluated in their clinical analysis were in advanced stages. Similarly, the case in our study was in the advanced stage.

There are several treatments for sarcomatoid cancers of the bladder. These are transurethral tumor resection, partial cystectomy, radical cystectomy, and radiotherapy and/or chemotherapy protocols applied with these treatment modalities. However, all these treatment options have highly limited efficacy [4,14]. The survival time is quite short, below 24 months after surgery [4]. A retrospective study involving 221 cases with sarcomatoid cancers of the bladder reported that the 5-year cancer-specific survival rate after radical cystectomy was 20.3%. In the same study 1, 5 and 10 year survival rates were reported to be 53.9%, 28.4% and 25.8%, respectively [15]. In another study evaluating patients with the diagnosis of sarcomatoid cancers of the bladder, Wright et al. [6] performed transurethral resection in 119 patients and cystectomy in 79 patients, and a total of 34 patients received postoperative radiotherapy. The researchers reported the mean survival time was 14 months. In our study, the patient died of postoperative respiratory failure. Therefore, we do not have disease-related survival data.

Transurethral resection is a very critical procedure for diagnostic and therapeutic purposes in patients with an image suggesting a mass within the bladder lumen. With this endourological intervention applied in almost all urology clinics, the type and extent of the cancer cells and the prognosis are determined, and treatment of the disease is planned. The patient in our report had presented with macroscopic hematuria. The first invasive procedure he underwent was cystourethroscopy followed by transurethral resection. There is no standardized approach to the treatment of sarcomatoid cancers of the bladder. However, many urology units carry out radical cystectomy and then chemotherapy or radiotherapy [14]. In our case, radical cystectomy was decided following the tissue diagnosis. No additional steps for treatment could be taken after radical cystectomy since the patient died before being discharged.

In conclusion, we think that clinicians should consider rare biphasic tumors such as sarcomatoid carcinomas of the bladder in patients presenting with hematuria in the differential diagnosis and a multidisciplinary treatment approach should be adopted.

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