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Assessment of risk factors affecting thrombosis in patients with essential thrombocytosis

Esansiyel trombositozlu hastalarda trombozu etkileyen risk faktörlerinin değerlendirilmesi

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Abstract

Aim: Arterial and venous thromboembolic complications are the leading cause of morbidity and mortality in Essential thrombocytosis (ET). The mechanism of thrombosis in ET is not fully explained. In present retrospective analysis, we aimed to investigate the association between thrombosis complication and age, gender, disease duration, laboratory findings, janus kinase 2 (JAK2) V617F mutation status in patients with ET.

Methods: Medical database of ET patients whom admitted to outpatient clinics of our institution, between April 2015 and April 2017, were retrospectively analyzed. Patients were divided into two groups, with and without arterial or venous thrombosis history. According to the thrombosis story, general characteristics, laboratory findings and JAK2 V617F mutation status of the groups were compared.

Results: 37 patients with thrombosis history and 15 patients without thrombosis history were detected. The number of leukocyte, platelet and lymphocyte in ET patients with thrombosis history was statistically significantly higher than without thrombosis history patients. JAK2 V617F mutation positivity was statistically significant in ET patients with thrombosis history.

Conclusion: This study confirmed the high leukocyte count, high platelet and lymphocyte count and JAK2 V617F mutation positivity as the thrombosis risk factor in patients with ET. In addition, the characteristics of the patients who applied to our clinic were compared with the literature and the differences were revealed.

Keywords: Thrombosis history, Essential thrombocytosis, Janus kinase 2 mutation, Leukocyte count, Platelet count

Öz

Amaç: Esansiyel trombositozda (ET) arteriyel ve venöz tromboembolik komplikasyonlar morbidite ve mortalitenin en önemli nedenlerdir. ET'de tromboz mekanizması tam olarak açıklanamamıştır. Mevcut retrospektif analizde, ET'li hastalarda tromboz komplikasyonu ile yaş, cinsiyet, hastalık süresi, laboratuvar bulguları, janus kinaz 2 (JAK2) V617F mutasyon durumu arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Nisan 2015 ile Nisan 2017 arasında kurumumuzun kliniğine başvuran ET hastalarının dosyaları retrospektif olarak analiz edildi. Hastalar arteriyel-venöz tromboz öyküsü olan ve olmayan olarak iki gruba ayrıldı. Tromboz öyküsüne göre, grupların genel özellikleri, laboratuvar bulguları ve JAK2 V617F mutasyon durumu karşılaştırıldı.

Bulgular: Tromboz öyküsü olan 37 hasta ve tromboz öyküsü olmayan 15 hasta tespit edildi. Tromboz öyküsü olan ET hastalarında lökosit, trombosit ve lenfosit sayısı tromboz öyküsü olmayan hastalardan istatistiksel olarak anlamlı yüksekti. Tromboz öyküsü olan ET hastalarında JAK2 V617F mutasyon pozitifliği istatistiksel olarak anlamlı idi.

Sonuç: Bu çalışma, ET'li hastalarda tromboz riski faktörü olarak yüksek lökosit sayısı, yüksek trombosit ve lenfosit sayısı ve JAK2 V617F mutasyon pozitifliğini doğrulamıştır. Ayrıca kliniğimize başvuran hastaların özellikleri literatürle karşılaştırıldı, benzerlikler ve farklılıklar karşılaştırıldı.

Anahtar kelimeler: Tromboz hikayesi, Esansiyel trombositoz, Janus kinaz 2 mutasyonu, Lökosit sayısı, Trombosit sayısı

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Introduction

Essential thrombocytosis (ET) is a myeloproliferative neoplasm characterized by clonal proliferation of megakaryocytic lineage in the bone marrow and peripheral thrombosis with high platelet count and an increased risk of thrombosis [1,2]. Gender, age (>60 years), janus kinase 2 (JAK2) V617F mutation, leukocytosis, thrombocytosis, thrombosis history, tobacco use, hypertension (HT) and diabetes mellitus (DM) are predictive factors for thrombosis risk in patients with ET. However, the criteria for risk classification and treatment initiation in ET are thrombosis history and greater than 60 years old [2].

Arterial and venous thromboembolic complications are the leading cause of morbidity and mortality in ET [2,3]. Neutrophil (neu) - white blood cell (WBC) - platelet activation, endothelial activation and inflammation have been suggested in the pathogenesis of thrombosis in ET [4-6]. However, the mechanism of thrombosis in ET is not fully explained.

In present retrospective analysis, we aimed to investigate the association between thrombosis complication and age, gender, disease duration, laboratory findings, JAK2V617F mutation status in patients with ET.

Materials and methods

After the approval of the authority of the institution, medical database of ET subjects who admitted to outpatient clinics of our institution between April 2015 and April in 2017 were retrospectively analyzed. Medical and laboratory data obtained from computerized database and patient file system and recorded. Patients were divided into two groups, with and without arterial or venous thrombosis history. Patients with coronary artery disease, HT, DM, hyperlipidemia, active infection and renal failure were not included in the study.

Statistical analysis

Data were analyzed by SPSS software (SPSS 15.0, IBM Inc., Chicago, IL, USA). Kolmogorov-Smirnov test conducted to observe distribution of variables in study groups. Homogenous variables were expressed as mean ± standard deviation and compared by independent samples t test, whereas, non-homogenous variables were expressed as median (minimum – maximum) and compared by Mann-Whitney U test. Comparison of categorical variables in study groups was conducted with Chi-square test. Correlation between parameters of the study was done with Pearson's correlation analyze test. A p value of <0.05 is considered as statistically significant.

Results

Study population was consisted of 52 subjects, 20 (39%) male and 32 (62%) female. In our study population, the mean age was 58.17±14 years, the mean platelet count was 539±240 K/uL, the mean WBC count was 9±3.5 K/uL, the mean hemoglobin (Hb) level was 13.4±1.6 g/dL, the mean neu count was 6.1±2.9 K/uL, and the mean lym count was 2±0.7 K/uL. JAK2 V617F mutation was positive in 36 patients (70%) and was negative in 16 patients (30%).

In our study, 37 patients with thrombosis and 15 patients without thrombosis were detected. 23 of 37 in with thrombosis history group and 9 of in without thrombosis history group were women. Gender was not statistically different between study groups (p=0.88). Mean age of the patient group with thrombosis history was 63 (21-86) years and mean age of the patient group without thrombosis history was 53 (40-82) years (p=0.75). Similarly, there was no statistically significant difference in disease duration between groups (p=0.63).

The mean WBC count (9.9±0.6 K/uL) in the group with thrombosis history was statistically higher than the mean WBC count (6.7±0.48 K/uL) in the group without thrombosis history (p=0.002). The mean Plt count (484 [297-1369] K/uL) of the group with thrombosis history was significantly higher than that of the group without thrombosis history (363 [170-782] K/uL)(p=0.006). The mean lym count of the patient group with thrombosis story was statistically higher than the group without thrombosis history (p=0.04). However, there was no significant difference between the groups in Hb, hematocrit (hct) and neu counts (p>0.05 for all). The characteristics of the study group and the laboratory data are given in table 1.

In 37 patients with thrombosis history, JAK2 V617F mutation was negative in 7 patients and positive in 30 patients. In 15 patients without thrombosis history, the JAK2 V617F mutation was negative in 9 patients and positive in 6 patients. In JAK2 V617F mutation-positive patients, the thrombotic event was statistically higher than JAK2 V617F mutation-negative patients (p=0.004).

A Pearson's correlation test was revealed that WBC was positively correlated with Plt (r=0.393, p=0.004).

Table 1: General characteristics and laboratory parameters according to the thrombosis history of the essential thrombocytosis patients

		Study Groups		
		With thrombosis history	Without thrombosis history	p
Age (year)		63 (21-86)	53 (40-82)	0.75
Gender	Female	23	9	0.88
	Male	14	6	
JAK2 V617F	Positive	30	6	0.004
mutation status	Negative	7	9	
Duration of disease (year)		4 (1-20)	4 (1-12)	0.63
White blood Cell (K/uL)		9.9±0.6	6.7±0.48	0.002
Platelet (K/uL)		484 (297-1369)	363 (170-782)	0.006
Lymphocyte (K/uL)		2.1 (0.85-5.4)	1.9 (0.89-2.46)	0.04
Neutrophil (K/uL)		5.39 (3.16-16.4)	4.8 (2.25-12.4)	0.06
Hemoglobin (g/dL)		13.7±0.29	12.8±0.28	0.1
Hematocrit (%)		39.6±1	37.7±0.7	0.28

Discussion

We showed in present retrospective study that the number of WBC, Plt and lym in ET patients with thrombosis history was statistically significantly higher than without thrombosis history patients. In this study, we also showed that JAK2 V617F mutation positivity was statistically significant in ET patients with thrombosis history.

ET patients are diagnosed at an average age of 55-60 years [7]. Age, especially over 60 years, is the criterion for both general survival risk factor and risk classification in patients with ET. Patients with ET over the age of 60 years are a criterion for starting medical treatment [8]. We found that the median age of our patient group was consistent with the literature. In our study, the mean age of the group with thrombosis history was higher than the group without thrombosis history. But there was no statistical difference. It is also reported that high age is a risk

factor for leukemic transformation [9]. In patients with ET, only male gender predicted venous thrombosis [8]. It has been reported that gender is not predictive of the risk of arterial thrombosis [8]. The number of female patients in our study was high. There was no difference in gender of the group with and without thrombosis history. Because of this, only male gender is a risk factor for the risk of thrombosis, so our study was considered to have a high number of female patients.

In ET, the effect of WBC on the risk of thrombosis has become increasingly prominent [10, 11]. However, the effect of WBC on the development of thrombosis remains uncertain. Previus studies have shown that activated leukocytes impair blood coagulation by releasing intragranule-associated proteases (i.e., elastase and cathepsin G), which are known to degrade numerous inhibitors of coagulation [12, 13]. In our study, WBC was statistically significantly higher in the group with thrombosis story. We confirmed the association of WBC count with thrombosis in our study. It has also been reported that WBC count >15 K / uL is a risk factor for leukemic transformation [9]. We can say that the risk of leukemic transformation is low because the mean WBC count is 9±3.5 K/uL in our study.

Thrombocytosis is the most prominent clinical feature of ET and persistently elevated thrombocyte activation is continuous [14-16], this suggests that there is a pathogenic relation between platelets and thrombotic complications. Despite uncertainties about the role of thrombocytosis on thrombosis, some evidence supports the contribution of activated platelets to the pathogenesis of thrombosis in ET [14, 17]. In one study, phosphatidylserine (PS) levels in platelets and lymphocytes were elevated significantly in ET patients [18] and this has been suggested to cause abnormal platelet and lym activation or apoptosis [14]. In another study, patients with ET had higher PS levels of platelets than controls, but no statistically significant difference [19]. In our study, platelet levels of the group with thrombosis history were significantly higher than the group without thrombosis history. The mean platelet level was below 1000 Ku/L in the group with thrombosis history. It has been reported that extreme thrombocytosis (> 1500 K/uL) increases the risk of bleeding [20]. In our study, we confirmed that the high platelet count increased the risk of thrombosis. Recent studies have shown that erythrocytes participate in thrombosis in ET [21, 22]. However, relatively little is known about the role of erythrocytes in thrombosis in patients with ET. In our study, Hb and Hct levels were high in the group with thrombosis history, but there was no statistical difference between groups. In our study, the absence of a relationship between thrombosis and the Hb level was thought to be due to the relatively low Hb levels of our patients.

JAK2-V617F mutation, observed in 50–60% of patients with ET, has been an independent risk factor for thrombosis [23] but little is known about the underlying mechanism of this relation [18]. JAK2 exon 12 mutations in ET are rare [24]. Patients with ET also have calreticulin (CALR) (15-24%) or myeloproliferative leukemia virus oncogene (MPL) mutations (4%) [25]. In one study, although the platelet count was lower, the absolute number of PS + platelets was reported to be dramatically higher in JAK2 than in the CALR mutation [18]. In our patient group, JAK2 V617F mutation rate was 69%. The relatively low number of patients suggests that JAK2 V617F caused mutation positivity to be high. In our study, JAK2 V617F positivity was statistically significant in the group with thrombosis history. This finding was consistent with the literature.

This study confirmed the high WBC count, high lym count and JAK2 V617F mutation positivity as the thrombosis risk factor in patients with ET. In addition, the characteristics of the patients who applied to our clinic were compared with the literature and the differences were revealed.

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Comparison of proximal femoral nail and dynamic hip screw for treating intertrochanteric fractures

İntertrokanterik femur kırıklı olgularda proksimal femur çivisi ile dinamik kalça vidasının karşılaştırılması

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Abstract

Aim: In this study, the use of proximal femoral nail and dynamic hip screw for treatment of intertrochanteric hip fractures were compared in terms of mortality and morbidity.

Methods: 131 patients who had an operation due to intertrochanteric hip fractures were evaluated demographic characteristics and surgical data (72 female, 59 male, mean age 77.85, range 65-98 years). 98 patients (74.8%) PFN method, 33 patients (25.2%) DHS method was applied. The age and gender of patients, etiology, type of anesthesia, preoperative waiting period, preoperative ASA (American Society Anesthesiologists) score calculated by anesthesia physicians, Singh index, track time, the type of fracture, complication rate, the degree of reduction, tip-apex distance, shortening the existence and mortality were investigated. The Harris Hip Score was used for functional assessment.

Results: The average post-operative follow-up period was 25.23 (1-66) months. The group that were applied DHS were found significantly different for reduction success ($p<0.05$). Harris Hip Scoring of patients in the DHS group were found significantly better ($p<0.05$). The success of the reduction in the DHS group was significantly related with the Harris HipScore ($p<0.05$).

Conclusion: We have concluded that the preoperative waiting time has no impact on mortality, increasing age increases the systemic disease, therefore increases ASA score. So that increasing ASA score increases the mortality. Unstable intertrochanteric fractures of the femur PFNA, due to the higher success rate of reduction should be preferred. But between two methods there were no significant differences about healing time and mortality. In conclusion, surgical techniques to be used should be selected according to the fracture type and age of the patient.

Keywords: Femur fracture, Osteosynthesis, Mortality

Öz

Amaç: Bu çalışmada Intertrokanterik kalça kırığı tedavisinde kullanılan Proksimal femur çivisi ve dinamik kalça vidası cerrahi yöntemleri mortalite ve morbidite açısından karşılaştırıldı.

Yöntemler: Intertrokanterik kırık nedeniyle opere olan 131 hastanın (72 kadın, 59 erkek, ort yaş 77.85; dağılım 65-98 yıl) demografik özellikleri ve ameliyat verileri değerlendirildi. Doksan sekiz hastaya (%74,8) PFNA, otuz üç hastaya ise (%25,2) DHS uygulanmıştır. Hastaların yaş, cinsiyet, kırık olan kalça tarafı, kırık etyolojisi, anestezi tipi, preoperatif bekleme süresi, anestezi hekimince hesaplanan preop ASA (American Society Anesthesiologists) skoru, Singh indeksi, takip süresi, kırık tipi, komplikasyon oranı, redüksiyon derecesi, tip-apeks mesafesi, kısalık varlığı ve kaynama düzeyi ve mortalite incelendi. Fonksiyonel değerlendirmede Harris Kalça Skoru kullanıldı.

Bulgular: Ameliyat sonrası ortalama takip süresi 25.23 (1-66) ay idi. Redüksiyon başarısı açısından DHS grubu lehine anlamlı fark saptanmıştır ($p<0.05$). DHS grubundaki hastaların Harris Kalça Skorları istatistiksel olarak daha iyi bulundu ($p<0.05$). Redüksiyon başarısı açısından DHS grubu lehine anlamlı ilişki saptandı ($p<0.05$). DHS grubunda redüksiyon başarısı ile Harris Kalça Skoru doğru orantılı olacak şekilde anlamlı bulundu ($p<0.05$).

Sonuç: Preoperatif bekleme süresinin mortalite üzerine bir etkisinin olmadığına, yaş arttıkça sistemik hastalıkların, dolayısıyla da ASA skorlarının arttığına ve ASA skorunun artmasının da mortaliteyi arttırdığı sonucuna varıldı. İnstabil intertrokanterik femur kırıklarında PFNA, redüksiyon başarısı oranlarının daha yüksek olması sebebiyle tercih edilmelidir. Ancak kaynama zamanı ve mortalite açısından belirgin bir fark saptanmadı. Hangi cerrahi yöntemin kullanılacağına hastanın yaşına ve kırık tipine göre kararlaştırılmasının daha uygun olacağına kanaat getirildi.

Anahtar kelimeler: Femur kırığı, Osteosentez, Mortalite

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Introduction

Intertrochanteric femur fractures are frequent and common fractures in the elderly population. It has been reported that 90% of hip fractures are older than 65 years [1]. In the same population, when compared to other fractures, it is the first in terms of death, disability and medical costs [1,2].

Nowadays, the scientific development of living conditions in parallel with a good situation has a significant increase in the average life span. People in the advanced age group can develop osteoporosis in proportion to inactivity and inadequate nutrition. As a result, simple traumas and intertrochanteric fractures occur.

Although intertrochanteric femur fractures are associated with low energy in elderly patients, high-energy trauma in younger patients may lead to similar forms of fracture [2].

The treatment plan of patients with intertrochanteric femur fractures is made by evaluating the pre-fracture functional adequacy, life expectancy, mental status and social life in which they are present. Currently, Proximal Femur Nails (PFN) and Dynamic Hip Screws (DHS) are used for osteosynthesis for intertrochanteric fracture treatment. In this study, we retrospectively investigated the relationship between DHS and PFN surgical methods used in intertrochanteric fracture treatment, mortality and morbidity.

Materials and methods

A total of 131 patients over 65 years of age who underwent surgery with intertrochanteric femoral fracture between March 2009 and December 2013 were evaluated retrospectively in Ege University Medical Faculty Hospital Orthopedics and Traumatology Department.

Of these 131 patients, 98 (74.8%) were treated with PFN and 33 (25.2%) with DHS.

Patients with stable or instable intertrochanteric fractures over 65 years of age were included. Patients younger than 65 years, pathologic fractures and subtrochanteric fracture patients were excluded from the study. Between the two groups; age, sex, fracture etiology, type of anesthesia, preoperative waiting period, preoperative ASA score, Singh index, follow-up period, fracture type, complication developed, shortness and union rate were investigated. Results were evaluated as excellent, good, moderate and poor according to the scoring obtained by applying the Harris Hip Score to assess hip function (Table 1).

In the preoperative radiological evaluation of patients, fractures were classified using AO classification, fracture displacement before surgery and Singh index were evaluated (Table 2).

Postoperative radiological evaluation; postoperative reduction rate, varus-valgus and anteversion-retroversion angle were determined. The measured collodiafizer angle was compared to the nontrumatic opposite hip. Angles below 5° as anatomic reduction, angles between 5° and 10° were considered as acceptable reductions, and angulations above 10° were accepted as poor reductions [3]. The tip-apex distances were assessed by anterior-posterior and lateral radiographs as described by Baumgartner [4]. In his work, Baumgartner evaluated the position of the lag screw within the femur head and improved the TAD (Tip-Apex Distance) concept. TAD distance is calculated in millimeters. In the post-operative radiographs, the side that is treated was compared with the other side and the amount of shortness was calculated in cm. Patients were evaluated radiologically in terms of duration of union, complication, revision and mortality.

Surgery was performed in the supine position and on the radiolucent traction table. Anesthesia was left to the choice of the anesthetist. The lateral incision was made through the large trochanteric tip that the surgeon detected with the index finger. Fixation was applied after reduction. PFNA or DHS was used for fixation. Patients receiving PFNA were mobilized with load of 20% of body weight for 15 days, 50% of body weight after 15 days and full load after 45 days. Patients with DHS were mobilized with no load for 15 days, 20% of body weight after 15 days, and full load after 45 days.

Patients were called to the clinic for remove the stitches at week 2. One-and-a-half months, 3 months, 6 months and 12 months after routine examination made with X-ray graphs.

Statistical analysis

Statistical analysis were performed using the IBM SPSS Statistics 21.0 program (IBM SPSS Statistics for Windows, version 21.0, Armonk, NY: IBM Corp.) and the SAS 9.3 program. Values of $p<0.05$ were considered significant. The mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used for descriptive statistics. The Mann-Whitney-U test was used for quantitative variables. Correlations between categorical variables were examined by the Pearson Chi-square test and Fisher's exact probability test. Union was estimated by multiple logistic regression.

Results

Of these 131 patients, 98 (74.8%) were treated with PFN and 33 (25.2%) with DHS. Patients undergoing PFN were referred to as group 1, and patients with DHS as group 2. The mean age of the patients in group 1 was 78.51 (65-98) while the mean age of the patients in group 2 was 78.91 (65-91).

Of the general population, 72 (55%) were female and 59 (45%) were male. There were 58 (59.2%) female and 40 (40.8%) male patients in the group 1 and 14 (42.4%) female and 19 (57.6%) male patients in group 2. The mean follow-up time was 23.86 (1-66) months in group 1 and 29.30 (1-64) months in group 2. In the general population, 121 (92.4%) patients had simple fall, 10 (7,6%) had car accidents. Of the 98 patients in the group 1; 93 (94.9%) were simple falls, 5 (5.1%) were traffic accident and in group 2; 28 (84.8%) were simple falls, 5 (15.2%) were traffic accident. Patient's time to surgery were 5.83 (1-22) days in the general population, 5 (1-19) days in group 1 and 5 (1-22) days in group 2. In general, the distribution of fractures was 68 (51.9%) right and 63 (48.1%) left. In group 1, 56 (57.1%) right and 42 (42.9%) left side treated. In group 2, this distribution was left in 12 (36.4%) and right in 21 (63.6%). 121 patients (92.4%) were treated with spinal anesthesia, 8 (6.1%) with epidural and spinal anesthesia and 2 (1.5%) with general anesthesia. In Group 1, 91 (92.9%) were treated with spinal anesthesia, 5 (5.1%) were spinal-epidural anesthesia and 2 (2%) were general anesthesia. In Group 2, 30 patients (90.9%) were

treated with spinal anesthesia and 3 patients (9.1%) were spinal-epidural anesthesia, but no general anesthesia was applied. In group 1, 8 died in the first month (8.2%), whereas in group 2, this number was 3 (9.1%). The number of patients who died within the first 3 months was 11 (11.2%) in group 1 and 4 (12.1%) in group 2. The number of patients who died within the first 12 months was 18 (18.4%) in group 1 and 6 (18.2%) in group 2 (Table 3) (p>0.05).

Table 1: Comparison of hip scores between groups

Harris Score	Grup 1 (64)	Grup 2 (25)	Total (89)
Excellent	-	3 (%12)	3 (%3.4)
Good	18 (%28.1)	10 (%40)	28 (%31.5)
Moderate	29 (%45.3)	7 (%28)	36 (%40.4)
Poor	17 (%26.6)	5 (%20)	22 (%24.7)
Average	70.50 (14-87)	77.32 (14-91)	72.42 (14-91)

Table 2: Singh index comparison between groups

Parameter Singh index	PFN (98)	DHS (33)	Total (131)
1	-	-	
2	8 (8.2%)	-	8 (6.1%)
3	14 (14.3%)	7 (21.2%)	21 (16%)
4	32 (32.7%)	8 (24.2%)	40 (30.5%)
5	39 (39.8%)	12 (36.4%)	51 (38.9%)
6	5 (5.1%)	6 (18.2%)	11 (8.4%)

PFN: Proximal Femoral Nail, DHS: Dynamic Hip Screw.

Patient's preoperative ASA scores were determined by looking at the anesthesia cards found in their files. The relationship between ASA scores and death was statistically significant (p=0.028). A statistically significant difference was identified between the ages and the ASA scores of the population (p<0.05). Age increased in direct proportion with the ASA Scores (Table 4).

Table 3: Mortality and death time relationship between groups

Parameter	PFN (98)	DHS (33)	Total (131)	p
Mortality	34 (34,7%)	8 (24,7%)	42 (32,1%)	0.266
Death time (months)	13.71 (1-45)	13 (1-44)	13.57 (1-45)	0.539

PFN: Proximal Femoral Nail, DHS: Dynamic Hip Screw.

Table 4: Comparison of AO classification and ASA score among groups

Parameter	PFN (98)	DHS (33)	Total (131)	p
AO classification				0.012
31A1	19 (19.4%)	14 (42.4%)	33 (25.2%)	
31A2	52 (53.1%)	9 (27.3%)	61 (46.6%)	
31A3	27 (27.6%)	10 (30.3%)	37 (28.2%)	
ASA score				0.820
ASA 1	4 (4.1%)	5 (15.2%)	9 (6.9%)	
ASA 2	56 (57.1%)	13 (39.4%)	69 (52.7%)	
ASA 3	26 (26.5%)	12 (36.4%)	38 (29%)	
ASA 4	12 (12.2%)	3 (9.1%)	15 (11.5%)	

PFN: Proximal Femoral Nail, DHS: Dynamic Hip Screw, ASA: American Society Anesthesiologists

Tip-apex distance measurement was also performed on the anterior and posterior radiographs of the patients postoperatively. The mean TAD distance was measured as 29.01 (20-45) mm in group 1 and 27.61 (18-40) mm in group 2 as described by Baumgartner (p=0.183). Eight patients (6.1%) of the general population had cutout on x-rays taken during follow-up. Seven (7.1%) of them were in group 1 while the other one (3%) was in group 2 (p=0.679).

Reduction success was compared between groups. Of the 98 patients in Group 1, 27 (27.6%) had anatomic reduction, while 63 (64.3%) had acceptable reduction and 8 (8.2%) had poor reduction. In Group 2, 18 (54.5%) of 33 patients had anatomic reduction, while 14 (42.4%) had acceptable reduction and 1 (3%) had a poor reduction. There was a significant correlation between groups in terms of reduction success in favor of group 2 (p=0.017).

Discussion

In recent years, the average life span of the endeavor has been growing and the population of elderly people is increasing [5]. In our country, the incidence of intertrochanteric femur fracture increases with the increase of the elderly population. Literature is examined and it is observed that the female-male ratio of the intertrochanteric femur fractures is in different levels and the female dominance is preserved [6,7]. The number of women in our study was more in line with the literature. Reduced physical capacities of advanced age groups, accompanying systemic illnesses, loss of vision and hearing, protection from environmental impairments resulting from weakening of reflexes increase the risk of suffering simple trauma. Intertrochanteric fracture patients are often elderly people and almost all have additional systemic diseases. These patients should be mobilized early in order to be formed from a population of older age group. In order to avoid complications that increase mortality and morbidity such as deep vein thrombosis, pulmonary embolism, uremia, urinary tract infections, pressure ulcers, will cause by immobilization, the pre-fracture functional level should be acquired immediately [8,9]. For this reason, surgery should be the first choice in treatment; conservative treatment should be considered in terms of existing systemic diseases, instable and surgical interventions that increase the mortality and morbidity of the patient [6]. In our work; 9 (6.9%) were ASA1, 69 (52.7%) were ASA2, 38 (29%) were ASA3 and 15 (11.5%) were ASA4. Haentjens et al. [10] 80% of the study cases, Akçalı et al. [11] in 78% of cases, Kesemenli et al. [12] had systemic disease at 100%. As can be seen, patients have a high incidence of systemic disease at significant age with advanced age, which poses a risk for operation. Surgical treatment of intertrochanteric fractures should be done as soon as possible. According to Kenzora et al. [13], the annual mortality rate is significantly higher in the first 24 hours of surgery. They advocated detailed medical evaluation of the patient in the first 12-24 hours postoperatively, post-traumatization and the patient should be operated after optimal surgical conditions are achieved. Zuckerman et al. [14] found that in one series of 367 cases, the one-year mortality of patients who were treated after the second day of trauma was doubled. Moran et al. [15] examined the mortality rates of 2148 hip fracture patients who underwent surgery. In the first 30 days, the death rate was 9%, while the death rate in 90 days was 19% and the mortality rate in 1 year was 30%. The early (first 24 hours) or late (1-4 days or 4 days) surgical treatment did not change the mortality rate within the first 30 days. The first 24 hours or 1 to 4 days of surgical treatment did not change the 90-day and 1-year mortality rates. However, 90 days and 1 year mortality rates are increased in surgical treatment after 4 days [15]. In our study, preoperative waiting period was 5 days (1-22 days). There were 77 (58.8%) patients who had surgery after 4 days and their first, third, and 12th months did not show a significant increase in mortality rates. There were 6 patients who underwent surgery in the first 24 hours and one of them died after 15 months.

In the elderly, it should be discussed which implant is more suitable for the treatment of intertrochanteric femur fractures [16]. The success of treatment depends on the reduction and stability of the fracture rather than the selected fixation method [17]. In our study, the reduction success and the shortening of the union time were also observed. Although 45 patients with anatomical reduction had no shortness, it was seen that the cases with acceptable and weak reduction had shortness.

Harris hip scores were evaluated and it was observed that DHS-treated patients had better results than PFNA-treated patients independently of reduction. This can be explained by the surgeon doing his own randomization, that is, the more stable fractures and the younger patients preferred DHS. In addition, when applying PFNA, the screw leading to the head can be explained by the height of the nail in the medulla and the fact that the screw surgeon who is in charge is completely under control when applying DHS while connected to the shape.

Infection occurred in only 1 patient (0.8%) and this patient was re-operated to remove the implant (DHS). Antibiotic spacer application was performed after serial debridement. Orhun et al. [18] reported an infection rate of 1.9%. In Haentjens [10], the rate of infection was 2% in cases of osteosynthesis. Similar applications are attracting attention in the literature. In studies conducted, Burnett [19] reported a reduction of 4.7% infection by 0.7% with prophylaxis.

In the study performed by YZ Xu et al. on pertrochanteric patients with 51 PFNA and 55 DHS; It has been reported that the incision is shorter in PFNA, the blood loss is less, the duration of operation is less than DHS, the complication is less in patients with PFNA, and the length of mobilization is shorter in patients with PFNA given full load according to DHS [20] . A multicenter meta-analysis of Henry Wynn Jones et al. compared intramedullary nailing and sliding screw plate system in a total of 3202 patients with stable and unstable proximal femur fractures. This wide series meta-analysis showed that the fixation loss and re-operation rate of all types of fractures were greater than the intramedullary nailing than sliding plate system and that intramedullary nailing did not have any superiority to the sliding screw plate system in stabilized and unstable trochanteric fractures and intramedullary nail may be superior to sliding screw plate system in transverse and reversed oblique fractures [21]. Klinger et al. compared PFN and DHS on a total of 173 unstable intertrochanteric femur fracture patients. 122 patients underwent PFN and 51 patients underwent DHS. The functional outcomes of the patients were assessed according to the Merle D'Aubigne score, unlike our study. There was no significant difference in functional outcomes of DHS and PFN patients. The duration of PFN surgery and hospital stay were shorter than DHS. Patients with PFN were reported to mobilize at full load in a shorter time period and revision requirement in PFN was reported as 17.2% and DHS was 21.6%. In conclusion, they have shown that PFN is superior to DHS, especially in unstable fractures [22]. Pajarinen and colleagues [23] in 2005 evaluated PFN and DHS in terms of restoration of postoperative gait ability on 108 patients with pertrochanteric fractures and found that patients with PFN had a shorter restoration of postoperative walking ability than patients with DHS. They attributed this condition to a better restoration of the hip anatomy of the PFN by DHS. After intertrochanteric fractures, avascular necrosis of the femur head is a very rare complication and the pathophysiology is still unknown. Baixauli et al. [24] detected avascular necrosis as 0.55% in their case series. Our 131 cases did not have femur head avascular necrosis in our series. Wilson et al. [25] reported venous thrombosis in 13 cases (1.3%) in 1015 cases series. Laohapoonrungsee et al. [26] did not have deep vein thrombosis in their cases. For every patient with intertrochanteric femur fracture, if there is no contraindication besides extremity exercises, low molecular weight heparin is started preoperatively and postoperatively, and we give treatment for 1 month. We did not have pulmonary embolism or deep vein thrombosis in all patients. Foulongne et al. [27] compared two groups which intramedullary nails and dynamic hip-screw methods in a case-control study of 30 patients. Intramedullary nailing was found to be superior in terms of operation time, duration of hospital stay, functional outcome, and bone healing. In our study, functional hip scores were higher when dynamic hip screws were applied. In a prospective randomized study by Guo et al. [28] 90 patients with intertrochanteric femur fracture treated with proximal compression plate or proximal femoral nail were compared in terms of operative time, intraoperative and peroperative blood loss, duration of hospital stay, postoperative complication rates and functional outcomes at the end of follow-up. No statistically significant difference was found for the comparison criteria between these two implants. In a study conducted by Chua et al, 63 (25 PFNA, 38 DHS) patients with intertrochanteric femur fractures greater than 60 years who had dynamic hip screws or proximal femoral nails were evaluated. Patients were compared for functional recovery. Two patients who treated with PFNA underwent cutout due to poor reduction, and 1 patient had avascular necrosis after cutout. The authors found that PFNA was superior in terms of the functional status of the patient and return to pre-fracture mobilization as opposed to our study [29]. Varela-Egocheaga and colleagues conducted a prospective, randomized study of 80 patients with stable intertrochanteric femur fractures aged over 60 years old who were treated with a proximal compression plate or proximal femoral nail. There was no statistically significant difference between the two implant types in terms of hospitalization time, perioperative blood loss, functional results after 1 year follow-up, neck-shaft angle, fracture collapse and mortality [30]. Shen and colleagues have evaluated 5 randomized control trials involving patients with pertrochanteric femur fractures treated with dynamic hip screws or proximal femoral nails in a meta-analysis study. Authors who determined that PFNA resulted in less blood loss and fewer complications did not find a significant difference in terms of mortality and duration of operation similarly in our study [31]. In a meta-analysis study of 1344 patients with 17 prospective studies, Yuan X et al reported that PFNA significantly reduced fixation loss, did not impair fracture union duration, and had significant height in Harris hip score. Postoperative 1 year mortality, femur head avascular necrosis, and femur fracture during operation did not show any significant difference [32]. In our study, reduction success and Harris hip scores were found to be better in cases with DHS.

In conclusion, patients should be examined in terms of systemic diseases in the preoperative period and necessary

internal consultations should be done to ensure that they enter the operation in the most suitable health conditions. It was found that cutout formation was also effective in osteoporosis as well as TAD distance. Bone trabeculae were more prominent, and in cases not described as osteoporotic, reduction success was achieved and consequently bone union success was higher, and functional outcomes were also better in these patients. We concluded that there was no effect on the mortality of the preoperative waiting period, as the age increased, the systemic diseases, thus increasing the ASA scores and increasing the ASA score, also increased the mortality. Harris hip scores increased with the increase in reduction success.

Fracture type, age, fracture type and osteoporosis grade were effective on Harris Hip Score. Reduction success also affected the shortening of the union time and the absence of shortness. In the DHS group, Harris hip scores were higher because reduction success was better.

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Examination of the relationships between different birthweights and various gestational parameters

Farklı doğum kiloları ile bazı gebelik parametreleri arasındaki ilişkinin değerlendirilmesi

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Abstract

Aim: The aim of the study is to assess the relationship between different birth weights and some pregnancy parameters. If there is a relationship, which is the relationship between birth parameters and birth weight. What are the importance levels of these relationships?

Methods: The significant levels of the relationships for these data were statistically examined. 18-39 years old, total 276 patients were investigated, the birth weights were grouped into 7 groups were included. Multiple comparison tests were performed between the groups by weight levels for the examined parameters, and different groups were determined by testing significance levels at 95% confidence interval using Multivariate Analysis of Variance (MANOVA). For the 7 different weight groups formed, correlation analysis was performed in order to determine the correlation coefficients among the gestational parameters, i.e., age range, gravida, mode of delivery, gestational age, zinc range and live/stillbirth status and the correlation levels among these parameters were determined

Results: Birth weights decreased with increasing maternal age and gravida during pregnancy. Significant correlations were found between birth weight and examined birth parameters.

Conclusion: Based on the results of this study, it is suggested that birth weight of the patient should be taken into account and the risky birth weight patient group should be followed according to gravida, zinc range, gestational age and live/stillbirth status.

Keywords: Pregnancy, Birth weight, Age, Zinc, Gravida

Öz

Amaç: Farklı doğum ağırlıkları ile bazı gebelik parametreleri arasındaki ilişkiyi değerlendirmek ve eğer bir ilişki varsa bunun önem düzeyinin ne olduğunu belirtmek amaçlanmıştır.

Yöntemler: Bu veriler için ilişkilerin anlamlılık düzeyleri istatistiksel olarak incelendi. 18-39 yaş aralığında toplam 276 hasta araştırılmış, doğum ağırlıkları 7 gruba ayrılmıştır. Gruplar arasında incelenen parametreler için ağırlık düzeylerine göre çoklu karşılaştırma testleri yapılmış ve farklı gruplar çok değişkenli Varyans Analizi (MANOVA) kullanılarak anlamlılık düzeylerini% 95 güven aralıklarında test ederek belirlenmiştir. Oluşan 7 farklı ağırlık grubu için, gebelik parametreleri, yaş aralıkları, gravida, doğum şekli, gestasyonel yaş, çinko aralığı ve canlı / ölü doğum durumu arasındaki korelasyon katsayılarını ve korelasyon katsayılarını belirlemek için korelasyon analizi yapılıp bu parametreler belirlenmiştir.

Bulgular: Doğum ağırlığının maternal yaşla ve gravida ile doğru orantılı olarak azaldığı görülmüştür. Doğum ağırlıkları ile incelenen doğum parametreleri arasında anlamlı korelasyonlar bulunmuştur.

Sonuç: Hastanın doğum ağırlığının dikkate alınması ve riskli doğum ağırlıklı hasta grubunun gravida, çinko aralığı, gebelik haftası ve canlı / ölü doğum durumuna göre izlenmesi önerilmektedir.

Anahtar kelimeler: Gebelik, Doğum Kilosu, Yaş, Çinko, Gravida

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Introduction

With the rapid pace of development of the society and economy, macrosomia, defined as the birth weight of ≥4000 g, has become more common in affluent societies [1]. The mechanisms underlying this relationship have not been clearly identified yet. It is important to understand which maternal characteristics are causally related to birth weight because understanding these relationships will facilitate targeted development of interventions to be tested in randomized controlled trials, leading to clear and evidence-based recommendations in pregnancy [2]. Previous studies have demonstrated a relationship between fetal macrosomia and cesarean section [3]. Birth weight less than 2500 g was defined by the World Health Organization (WHO) as low birth weight (LBW) [4]. The United Nations International Children's Emergency Fund (UNICEF) and WHO reported that more than 20 million infants (15.5% of all births) were born LBW worldwide in 2000 [5]. In the studies conducted, it was reported that an association was present between maternal age and LBW. Reduced LBW rate was observed in cases with a maternal age of more than 20 [6]. A study on 1041 pregnant women demonstrated that the incidence of macrosomia was associated with the weight gain compared to the related gestational week, maternal age; the incidence of macrosomia was higher in male infants. However, it was not associated with parity and pre-pregnancy BMI (body mass index) .The rate of LBW increased in cases with low maternal age, female gender, low gestational age, and primipara [7]. In a study on 450 cases consisting of 15 newborns from each of 30 villages, young maternal age, grand multiparity, maternal anemia and the presence of a short interval between pregnancies were found to be associated with LBW [8]. In 2016, 123 normal weight and 123 LBW newborns were evaluated, and LBW incidence was found to be high in cases who had 1-3 visits during pregnancy, with young maternal age, with intervals between pregnancies shorter than two years and multi-gravidity. In those who were encountering their second or third pregnancies, the rate of delivery of infants with birth weights of less than 2500 grams was 46.42%; this difference was considered statistically significant [9]. In a study that retrospectively examined 237 pregnant women with a maternal age of ≥35 in Turkey, it was reported that, in advanced age group, the rates of preeclampsia, gestational diabetes, low Apgar score and intrauterine fetal death were higher, whereas the rate of prematurity, LBW and fetal anomalies were similar, compared to the young maternal age group [10]. It was stated that zinc levels were found to be low in preterm infants and zinc supplementation was required during the first trimester [11]. It was reported that zinc deficiency might cause inflammation in the placenta, leading to SGA and LBW [12]. However, in a study that investigated whether deficiencies of vitamin A and zinc during antenatal second and third trimesters were associated with LBW by measuring the weights of 575 infants during the first 72 hours after delivery, the rate of LBW was 16.5%; however, no association with zinc and vitamin A could be demonstrated [13].

In the present study that investigated the relationships between different birth weights and various gestational parameters, the newborns were divided into 7 groups, based on their weights. It was demonstrated in detail whether significant changes in the gestational parameters were present or not, and if present, in which gestational parameters.

Materials and methods

The present study included 326 patients who were at the 12th week of pregnancy or earlier. In order to reduce the factors that may influence the study results, patients with the systemic disease or multiple gestations were excluded from the study. From the subjects who agreed to participate in the study by reading and signing the informed consent form, 3 cc blood samples were collected in biochemistry tubes and centrifuged within 30 minutes at 3000 rpm for 15 minutes. The blood samples were stored at –80°C until the analysis. During the gestational follow-up until the delivery, the data of 276 patients were accessed. Zinc levels were determined using the "Thermo-atomic absorption spectrophotometry" method, which was in the range of 49 to129 µg/dl. Serums were diluted to 1/5 and worked. The normal range of zinc was 70-115 µg/dl. The test range was 15-250 µg/dl. The lower limit of detectable zinc level was 10 µg/dl. Among the parameters examined, zinc levels were evaluated in 8 groups as 49-59, 60-69 and so on, with increments of 10 units until reaching 120-129 µg/dl. Mode of delivery was defined as abortion, normal delivery, cesarean section, and presence of history of cesarean section, ectopic and voluntary abortion. Gestational age was defined as abortion, 24-37 weeks, 37-41 weeks, more than 41 weeks and ectopic pregnancy. Birth weight was defined in 7 groups as abortion, less than 1500 g, 1500-2000 g, and with increments of 500 g until reaching more than 4000 g. Birth status was defined as live birth, stillbirth, and no birth. Gravida was defined in 3 groups as 1, 2-3 and ≥ 4. The no birth group involved those with abortion, voluntary abortion and ectopic pregnancy.

The data from the patients examined within the scope of the study were assessed based on the weight levels in 7 groups. For this purpose, the data obtained from the patients were tabulated by weight levels. The data obtained were analyzed using the SPSS 16 package; their descriptive statistics were determined, multiple comparison tests were performed between the groups by weight levels for the examined parameters, and different groups were determined by testing significance levels at 95% confidence interval using Multivariate Analysis of Variance (MANOVA). For the 7 different weight groups formed, correlation analysis was performed in order to determine the correlation coefficients among the gestational parameters, i.e., age range, gravida, mode of delivery, gestational age, zinc range and live/stillbirth status and the correlation levels among these parameters were determined. It was determined whether these correlations were positive or negative, which parameters were important in the groups formed according to weights, and whether these parameters significantly changed according to the groups.

Analyses were performed to find whether the patients examined in 7 groups constituted according to birth weight were different in terms of age range, gravida, mode of delivery, gestational age, zinc range and live/stillbirth status. Multiple comparison tests were performed to test whether there were significant differences between birth weights and examined

parameters, and different groups were determined by testing significance levels at 95% confidence interval using Multivariate Analysis of Variance (MANOVA). P value <0.05 was counted as statistically significant.

Results

The parameters that were different according to birth weight were shown in Table 1. The table shows that there were differences between the groups formed according to birth weight in terms of gravida, zinc range, gestational age and live/stillbirth status with significance levels of 0.016, 0.05, 0.003 and <0.001, respectively. During the data analysis, the birth weights were analyzed in 7 groups formed as abortion, less than 1500 g, 1500-2000 g, and with increments of 500 g, until reaching more than 4000 g. The descriptive statistics of the data were shown in Table 2.

Table 1: Multiple comparisons for the gestational parameters examined according to birth weight

Gestational parameters	Birth weight p
Age range	0.451
Gravid	0.016
Zinc range	0.050
Birth week	0.003
Birth types	0.676
A live birth - Still born	<0.001

Correlation analysis was performed to describe the relationships between the birth weights and the gestational parameters by their significance levels. The relationships between the birth weights and the gestational parameters were determined and presented as tables. The correlation coefficients found in the analysis were interpreted as described below. According to this, the correlation coefficients were classified as follows:

0.00-0.25 “Correlation is very poor”
0.26-0.49 “Correlation is poor”
0.50-0.69 “Correlation is moderate”
0.70-0.89 “Correlation is high”
0.90-1.00 “Correlation is very high”

The birth weights were defined as 7 groups, and the correlations of the examined parameters with birth weights were analyzed in detail for each birth weight group. The results were shown in Table 3.

Table 3: Correlation coefficients between birth weights and the pregnancy parameters

Pregnancy parameters	Birth weight (gr) <1500	1500-2000	2000-2500	2500-3000	3000-3500	3500-4000	>4000
Age	-0.096	-0.380	-0.265	-0.428	-0.383	-0.019	-0.479
Gravida	0.548	0.099	-0.879	-0.105	-0.178	0.161	-0.049
Zink level	0.059	-0.039	-0.067	-0.005	0.071	0.130	-0.038
Birth week	-0.728	-0.498	-0.724	0.113	0.041	0.368	0.710

Table 2: Descriptive statistics of pregnancy parameters analyzed according to birth weights

Analyzed pregnancy parameters		Birth weight (gr) <1500	1500-2000	2000-2500	2500-3000	3000-3500	3500-4000	>4000	Birth no	Total
Age range	18≥x	0	0	1	2	0	0	0	2	5
	19≥x>24	0	0	1	9	19	4	2	9	44
	24≥x>29	1	2	4	20	26	13	7	12	85
	29≥x>34	2	2	5	18	36	18	7	18	106
	34≥x>39	0	0	0	5	11	7	4	7	34
	39≤x	0	0	0	0	0	0	1	1	2
Total		3	4	11	54	92	42	21	49	276
Gravida	1	0	1	6	19	35	10	7	10	88
	2 or 3	2	3	4	31	55	28	11	29	163
	4 or more	1	0	1	4	2	4	3	10	25
Total		3	4	11	54	92	42	21	49	276
Birth way	Abortion	0	0	0	0	1	0	0	34	35
	Normal delivery	3	3	8	36	48	20	12	0	130
	Cesarean section	0	1	3	8	19	10	6	0	47
	Previous C/S	0	0	0	10	24	12	3	0	49
	Ectopic	0	0	0	0	0	0	0	3	3
	Terminated	0	0	0	0	0	0	0	12	12
Total		3	4	11	54	92	42	21	49	276
Birth week	Abortion	2	0	0	0	1	0	0	34	37
	24-37	1	2	7	16	27	6	0	0	59
	37-41	0	2	4	27	56	28	11	0	128
	>41	0	0	0	11	8	8	10	0	37
	Ectopic	0	0	0	0	0	0	0	3	3
	Terminated	0	0	0	0	0	0	0	12	12
Total		3	4	11	54	92	42	21	49	276
Zinc range	49≤x<59	0	0	2	1	3	0	1	6	13
	59≤x<69	0	0	2	7	10	5	2	6	32
	69≤x<79	1	1	2	7	18	5	5	12	51
	79≤x<89	0	3	1	13	21	8	7	10	63
	89≤x<99	0	0	1	15	15	9	3	10	53
	99≤x<109	1	0	1	8	13	13	2	4	42
	109≤x<119	1	0	2	3	8	2	0	1	17
	119≤x<129	0	0	0	0	4	0	0	0	4
	129≤x	0	0	0	0	0	0	1	0	1
Total		3	4	11	54	92	42	21	49	276
Live-Dead birth	Live birth	2	2	7	50	90	42	21	2	216
	Dead birth	1	2	4	4	1	0	0	0	12
	Birth no	0	0	0	0	1	0	0	47	48
Total		3	4	11	54	92	42	21	49	276

Discussion

The retrospective study of maternal age in Turkey is 237 patients ≥35; preeclampsia, gestational diabetes, low Apgar scores and intrauterine fetal mortality rates were higher in older age group; Prematurity, the proportion of low birth weight infants and fetal anomalies are reported to be similar to the young maternal age group [11].

In our study, it was understood that there was a negative relationship between the age of the pregnant women and all the birth weight groups, and that as the age of the pregnant women increased, the whole birth weights decreased. However, this decrease was found to be at the highest level of 4000 gr with birth weight of -0.48, and at birth weight of -0.38 with 1500-2000 gr weight (Table 3).

The incidence of macrosomia is associated with weight gain and maternal age at the gestational week, with a higher incidence in male infants; However, 1041 pregnancies that were not associated with parity and pre-pregnancy BMI (body / mass index) were shown in the study conducted in 2015 [14]. However, the occurrence of LBW was highly possible in those with low maternal BMI (body mass index), inadequate food intake, a history of low birth weight or preterm delivery [15].

When we analyzed our data, it was observed that the gravida had a negative correlation between birth weight and birth weight. However, the increase in gravida was highly correlated with the level of -0.88 in the birth group weighing 2000-2500 gr. In this weight group it was understood that birth weight had a significant decrease in birth weight as the gravidity increased (table 3). It has been reported that zinc deficiency may cause SGA and LBW as a cause of inflammation in the placenta [16]. It was seen that there was a weak but positive relationship between the zinc level and the birth weight in the group between 3000-4000 gr. It was found that when the zinc level was increased for this group, the weights were increased if the weights were lower but the others were weaker for the negative ones (table 3).

In a study on 450 cases consisting of 15 newborns from each of 30 villages, young maternal age, grand multiparity, maternal anemia and the presence of a short interval between pregnancies were found to be associated with LBW [17].

When the data were analyzed, it was found that there was a negative correlation between the birth week and birth weight of less than 2500 gr, and the birth weight decreased as birth week increased. It was understood that the relationship between birth week and birth weight was between -0.72 and -0.72 between the group with 2000-2500 gr, which had a high level of relationship with the negative, especially in this group, as the birth week increased, the birth weight decreased with -0.72 relation level. On the other hand, in the groups with more than 2500 gr birth weight, there was a positive correlation between the birth week and the birth weight and it was determined that the birth weight increased as the birth week increased. As the week of birth increased, weight gain was found to be 0.37 for a group with a birth weight of 3500-4000 g and a relationship with a higher level was found at a level of 0.71 for groups over 4000 g. As the birth week increased, the birth weight increased by 0.71 (Table 3).

With the birth weight, "birth type" and "live-still birth, no birth" cases were also analyzed. According to this; there was a negative relationship between birth weight and birth patterns. There was a weak correlation between birth weight and abortion with -0.17, a weak correlation with -0.14 in the first cesarean group, a weak correlation with -0.22 in the pre-cesarean group whereas a negative correlation between birth weight and normal birth was -0.56 with moderate negative an increase in birth weight was found to reduce normal birth. Relationship levels between birth weight and live-stillbirth were examined and it was understood that there was a positive correlation between birth weight and live birth with 0.45 and that live birth increased as birth weight increased. There was a moderate negative correlation between birth weight and stillbirth (-0.57), indicating that the birth weight decreased as the birth weight increased (table 3).

In conclusion, the relationship between birth weights and obstetric outcomes were different statistical results when we analyzed the data by dividing the birth weight by eight groups. It was concluded that new studies were needed by increasing the number of patients.

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Evaluation of Lichtenstein and posterior wall darn techniques in inguinal hernia surgery: A prospective cohort study

İnguinal herni ameliyatlarinda Lichtenstein ve ağ örme tekniklerinin değerlendirilmesi: Prospektif kohort çalışma

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Abstract

Aim: Inguinal hernia repair is the most common surgical operation in the world. Although the inguinal hernia is as frequent as 75% of all hernias and 3.8% of the whole population, the best form of repair has not yet become clear. The purpose of the hernia repair is simple, easy to apply, safe operation which requires minimal dissection and sufficient exploration, early patient care, reduction of operation cost, loss of labor force, hospital stay and return to work, and minimizing recurrences. Our aim in this study is to compare Lichtenstein tension free technique and posterior wall darn repair (Moloney) techniques.

Methods: This study was designed as a prospective study and was performed in patients who underwent surgery for inguinal hernia in the General Surgery Clinic of Istanbul Training and Research Hospital. A total of 100 patients were divided into two groups (50 posterior wall darn repair, 50 Lichtenstein repair). All patients were hospitalized and their time to return to work was recorded. Patients were called to the controls and checked for recurrence. Criteria such as postoperative patient comfort, complications, active life start time and recurrence were evaluated. The groups were compared statistically.

Results: In our study, there was no significant difference between the two groups in terms of return to work, mobilization and recurrence ($p>0.05$). Lichtenstein technique was applied statistically in terms of hospitalization time, complication and duration of operation compared to the other groups ($p<0.05$).

Conclusion: We favor Lichtenstein technique in the treatment of inguinal hernia because of the short duration of operation, short hospitalization time and low complication rate compared with posterior wall darn technique, with similar recurrence rates in both groups.

Keywords: Inguinal hernia, Lichtenstein repair, Posterior wall darn repair

Öz

Amaç: İnguinal herni onarımı dünyada en yaygın yapılan genel cerrahi ameliyatıdır. İnguinal herniler, tüm herniler arasında %75 ve tüm toplumun %3,8'inde görülebilecek kadar sık olmasına karşın, en iyi onarım şekli henüz açıklık kazanmamıştır. Herni onarımında amaç basit, kolay uygulanabilir, minimal diseksiyon gerektiren ve yeterli eksplorasyon sağlayan güvenli bir teknikle erken dönemde hasta konforunu gözetmek, ameliyat masrafını, işgücü kaybını, hastanede kalış süresini ve işe dönüş süresini azaltmak ve nüksleri en aza indirmektir. Bu çalışmayı yapmaktaki amacımız; Lichtenstein tension free tekniği ile ağ örme onarımı (Moloney) tekniklerini karşılaştırmaktır.

Yöntemler: Bu çalışma prospektif bir araştırma olarak tasarlanıp İstanbul Eğitim ve Araştırma Hastanesi Genel Cerrahi Kliniğinde inguinal herni nedeniyle ameliyat edilen hastalarda yapıldı. Toplam 100 hasta iki gruba ayrıldı (50 ağ örme, 50 Lichtenstein). Tüm hastaların hastanede yatış süreleri, işe dönme süreleri kaydedildi. Hastalar kontrollere çağrılıp nüks açısından kontrol edildiler. Postoperatif hasta konforu, komplikasyonlar, aktif yaşantıya başlama süreleri ve nüks gibi kriterler değerlendirildi. Gruplar istatistiksel olarak kıyaslandı.

Bulgular: Çalışmamızda her iki grup arasında işe dönüş süreleri, mobilizasyon, nüks, açısından anlamlı bir fark saptanmadı ($p>0,05$). Lichtenstein tekniği uygulananlarda hastanede yatış süresi, komplikasyon, ameliyat süresi açısından diğer grubu göre istatistiksel olarak anlamlı bulundu ($p<0,05$).

Sonuç: Her iki grupta benzer nüks oranlarına sahip olmakla birlikte Lichtenstein tekniğinin, ağ örme tekniğine nazaran, ameliyat süresinin kısalığı, hastanede yatış süresinin kısalığı, düşük komplikasyon oranı nedeniyle inguinal herni tedavisinde Lichtenstein tekniğinin uygulanması taraftarıyız.

Anahtar kelimeler: İnguinal herni, Lichtenstein onarım, Ağ örme onarım

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Introduction

Despite the use of personal additions by many technical surgeons in the inguinal hernia repair, there are still different methods to reduce high recurrence rates and to increase patient quality of life. Among the many hernia repair techniques, although it is connected to the surgeon, there is no big difference and it is observed that surgeons play their personal habits and education in the technical selection. Although the inguinal hernias are frequently seen in the society, the best hernia repair technique has still not been gained clearly [1].

Inguinal hernias are seen in approximately 3-8% of the population [1]. It was the most common cause of intestinal obstruction before low awareness of patients about severity of condition and high recurrence of repair techniques [2]. In males, 75-85% of the hernias are observed. Inguinal hernias constitute 80-83% of all hernias (50% indirect inguinal, 25% direct inguinal, 5% femoral). In both sexes, the most frequently observed inguinal hernia is indirect hernia. Femoral hernia is commonly seen in women [1,2]. The importance of the posterior wall of the inguinal canal was noticed in the etiology and repair of inguinal hernia. In the formation of hernias, transverse muscle was determined to play an important role in the transverse fascia. The aim of the repair is to re-fix the fascia in such a way that it does not cause transverse tension [2,3].

Patients often apply swelling (coughing, straining and sneezing) and pain complaints in the groin area. Hernia is usually determined by patients and can push the swelling back with their hands. Sometimes the swelling caused by the hernia cannot be pushed into the abdomen. Inguinal hernias can be congenital or acquired. Congenital ones have a potential hernia sac. This pouch is part of the abdominal membrane that is laying the entire abdomen inside. The relaxation that occurs in this row is manifested as a hernia after years or after birth. Among the acquired causes of inguinal hernia, we can count any incidents that increase intra-abdominal pressure, undergone surgeries, obesity, tumors, fluid collection in the abdomen, heavy lifting, and prostate diseases. Inguinal hernias are seen more frequently in males. In men, we can show that testicles are out of the abdomen, unlike the ovaries in women, and that the path followed at any time is caused by weakening and causing it to happen. Same principles may be applied to other hernia, e.g., internal hernia [4,5].

The only treatment of inguinal hernias is surgery. The herniated tissue is supported by repairing various methods. The common pubic bond between the public is not a treatment method. On the contrary, this bond weakens the inguinal canal with pressure. Surgical methods can be performed under local or general anesthesia, and the laparoscopic method is done only under general anesthesia. Inguinal hernias are diseases that must be treated surgically. Classical surgical procedures, if performed under local anesthesia, the patient can be discharged that night. After laparoscopic surgery, the patient also returns to work early as he feels little pain because of the small part of the incision. There are no big differences between the two methods. There is a possibility of recurrence of the disease after inguinal hernia surgeries. This is usually due to the ability of the surgeon, such as the accuracy of the method applied to the patient [5,6].

Common recurrence problem and testicular complications in conventional anterior hernia repairs have led surgeons to find different methods. The methods, such as Bassini, Shouldice, Halsted, McVay, have left their place in the methods of using prosthetic Mesh, such as "free Tension" Lichtenstein, Nyhus, Plug mesh and laparoscopic hernia repair. Initially, the mesh was used for incisional hernia repairs. But over time, it has been used frequently in inguinal hernias. Today, more than 80% of hernia surgeries performed in the United States are repaired with mesh [3,5,6].

In this study, we aimed to compare the mesh (Lichtenstein) technique and posterior wall darn (Moloney) technique for the repair of inguinal hernia.

Materials and methods

A prospective cohort study is designed. The sample size has been identified as 96 to show 50% difference with 10% α-error in confidence interval of 95% to present 20,000 patients. Four patients are added to reduce the margin of error, and a total of 100 patients were scheduled for the study. One-hundred consecutive inguinal hernia patients who underwent surgery at the Istanbul Education and Research Hospital, general surgery clinic were selected, and recorded a prospective database. Recurrent inguinal hernias were excluded from the study. Two groups were created for comparison from the patients in the study. Fifty patients in the first group underwent posterior wall darn repair (PWD). In second group, remaining 50 patients underwent hernia repair with Lichtenstein Tension Free (LTF) technique. Polypropylene patch used for LTF technique. No: 1 Propilen suture was used in hernia operations with PWD technique. Postoperative follow-up dates of the patients were day 1, 7 and 30. All patients were called every 6 months, and those who didn't come were followed by telephone.

Recorded parameters of the patients were surgery times, anesthesia types, early mobilization times, hospital stay periods, turn-around times, postoperative early complications and recurrence.

Statistical analysis

Statistics were performed with Statistics Package for Social Sciences (IBM SPSS statistics version 23, IBM Corporation, USA). Normally distributed descriptive continuous variables which were expressed as mean±standard deviation (SD), median, frequencies and ranges. T-test was used for comparison of descriptive variables with normal distribution and Mann-Whitney U without normal distribution. The Chi-square test was used to assess an association between qualitative variables. Differences were considered statistically significant if the p value was equal to or less than 0.05.

Results

All patients involved in the study were 30 women and 70 were men. Mean age was 54 (22-78) years. 68 patients had right inguinal hernia (female: 20, male: 48), 30 left inguinal hernia (female: 10, male: 20), 2 bilateral inguinal hernia (female: 0, male: 2). Right inguinal hernia was found significantly higher in males compared to females ($p<0.05$). Direct inguinal hernia (female: 20 in total 100 patients) 14 males: 6), 74 of indirect inguinal hernia (female: 12 males: 62), 6 patients were diagnosed

with direct + indirect inguinal hernia (female: 4, Male: 2). Indirect inguinal hernia was found higher in males ($p<0.05$) (Table 1).

Table 1: Characteristics of groups

Operation	n	Gender	
		Male	Female
LTF	50	30	20
PWD	50	40	10
Total	100	70	30

LTF: Lichtenstein tension free, PWD: posterior wall darn

An additional disease history (direct inguinal hernia: 10, indirect inguinal hernia: 4) was detected in 14 of 100 patients. Five of the patients had chronic obstructive pulmonary disease, three hypertension, two diabetes mellitus and four goiters. All comorbid patients were under medical treatment. As a result of the statistical evaluation, there was no significant difference between the types of hernia in terms of additional disease history ($p>0.05$). Twenty of the patients who operated with LTF technique (n=50) were female. Ten of the patients who operated with the PWD technique (n=50) were female.

The patients who repaired LTF were 44 indirect inguinal hernia, 12 direct inguinal hernia, and six were direct + indirect inguinal hernia. The average operating time in the LTF group was 25 minutes and 35 minutes in the PWD group. The statistical evaluation concluded that operation time of LTF method was significantly less than PWD ($p<0.05$).

Patients used in LTF technique could be mobilized in 2 hours after surgery, while the PWD has an average of 4. Statistically, there was no significant difference in the mobilization of both groups ($p>0.05$).

Average duration of hospitalization was 1 day in LTF and 2.5 days in PWD group. Both groups were compared in terms of average hospitalization; the hospitalization time was significantly shorter in LTF technique. The time for return to work in LTF technique was calculated as 14 days, and 12 days in PWD. There was no significant difference between the two groups in the statistical evaluation ($p>0.05$).

Table 2: Evaluation of complications between groups

Groups	n	Complications	p
LTF	50	4 (1 hematoma, 2 infection, 1 seroma)	0.002
PWD	50	10 (3 hematoma, 2 infection, 4 seroma, 1 paresthesia)	
Total	100	14	

LTF: Lichtenstein tension free, PWD: posterior wall darn

The PWD and LTF groups were compared to the number of complications after the surgery. The postoperative complications of LTF technique was found to be less than PWD group ($p<0.05$) (Table 2). One recurrence was observed in the LTF technique and two recurrences in the PWD technique. There was no significant difference in comparison of recurrence of both groups ($p>0.05$) (Table 3).

Table 3: Evaluation of recurrence between groups

Groups	n	Recurrence	p
LTF	50	1	0.980
PWD	50	2	
Total	100	3	

LTF: Lichtenstein tension free, PWD: posterior wall darn

Discussion

Although inguinal hernia is one of the most common surgeries in general surgery and many repair methods have been identified, efforts to search for new methods have not yet come to an end. The underlying factor in this quest is the desire to reduce the recurrence rate. In addition, in recent years, the challenges of applied technique, complication rate, length of stay in hospital and return to normal activity, and cost-effectiveness are also questioned. In such studies, it has been suggested that tension-free hernia repair with a synthetic patch is a superior alternative to open and laparoscopic techniques [7, 8].

Tension in the suture line occurs in conventional hernia repair techniques. The suture line tension can be reduced with the relaxation incision, but it cannot be eliminated. The primary etiologic factor of Herniorapy's failure is to bring the non-conflicting tissues against each other by stretching them. This is also contrary to the basic surgical principles. Sutures are caused by tearing or necrosis of nasally edged fascial repairs. Graft repair does not cause suture line tension, it permits repair of hernia without altering normal anatomy, and it reduces recurrence rate. Also technique is simple, fast, less painful and effective. Since it does not create tension, bilateral hernia repair is possible [9].

The success of the inguinal hernia operation of the transcendental love is assessed by the recurrence rate. In a study conducted by Kark et al. [10]; 1098 hernia repair was performed with LTF technique, and a recurrence of 0.1% was detected. Bellona et al. [11] performed 119 LFT repair technique and found a recurrence of 0.8%. Mc Gillicuddy [12] performed 717 hernia repair operation with LTF and Shouldice technique in 672 patients. In comparison of these techniques, 0.2% recurrence in LTF technique and 1% in Shouldice technique was detected. Soybir et al. [13] applied 116 tension-free hernia repair technique and no recurrence was detected. In a study conducted by Amid et al. [14] reported 4000 groin hernia, patients were followed for an average of 5 years, with a recurrence rate of 0.1%. In our study groups, one recurrence was observed in the LTF technique and two recurrences in the PWD technique. No statistically significant difference was found in the recurrence comparison between the techniques.

Lichtenstein used a mesh to reconstruct the inguinal floor and to eliminate tension in the suture line in "tension-free" hernia repair. Even general surgeons who did not specialize in the repair of inguinal hernias reported less than 1% recurrence rates when using Lichtenstein repair. In 1984, at the Lichtenstein Hernia Center, the technique was applied, which means that the inguinal floor was fully reinforced with a wide mesh. Her conclusion was not found in the results reported in 1989. However, a few recurrences were reported later. This technique has been widely accepted worldwide in the repair of primary and recurrent hernias [15,16]. In a 26304 case series published by Nielsen et al. [17] in 2001, use of Lichtenstein's mesh repair was reported to be 33% in 1998 and 62% in 2000.

In 1996 Voyles et al. [18] investigated the return time of cases operated for inguinal hernia in a 4688 case-based multi-center study. The cases were examined in three groups. In the first group, cases with anatomical repair (Bassini, Shouldice, net knit, etc.), in the second group with mesh repair (Lichtenstein, mesh plug etc.) and in the third group with laparoscopic inguinal hernia repair were investigated. The time to return to work was as follows: 1st group 27.3 days, 2nd group 16.4 days and 3rd

group 15.6 days. In our study, the return time of patients to work was found to be 14 days in patients who underwent non-mesh repair and 12 days in patients who underwent mesh repair. However, as a result of statistical evaluation, no significant difference was found between the two groups.

Eryılmaz et al. [19] found chronic pain in the study of 5.3% after hernia repair, 6% after polypropylene mesh repair and 4% after Bassini repair with posterior wall darn method. In a study conducted by Koukourou et al. [20]; a total of 100 patients, 54 patients underwent mesh suture repairs, remaining underwent non-mesh repair, no significant difference was found between postoperative pain scores and analgesic requirements, early and late complications and return to normal activity, and recurrence rate was reported to be 4% in both groups.

Posterior wall darn technique provides support for the weak areas of the inguinal canal. Over time, the weaves are filled with fibrous tissue and become a natural graft. With the passage of time, the back wall of the inguinal canal becomes more solid. The material used maintains its strength for a long time. Because it is resistant to infection and elasticity it prevents recurrence. This technique is a good surgical technique that can always be applied safely in inguinal hernia repair. Because the inguinal region anatomy, repair can be made without tension. Therefore there is no tension and tear in the tissues with this technique. In the post-operative period, the patients feel less pain and live comfortably. Today's economic evaluations are taken into account in the success of surgery. It is considered that the method applied to the active work life of the patient is successful if it takes place in the short postoperative period [21,22]. In our study, pain and tension in the groin during the postoperative period, difficulty in walking were not observed in both groups. We refer to this as non-steroidal anti-inflammatory treatment after surgery. These results are easy to apply in both techniques and are an indication that the method improves the postoperative comfort of the patient and is less expensive than laparoscopic methods. One of the important advantages of both techniques is that it can be applied to bilateral inguinal hernias. Simultaneous surgery of the bilateral hernia creates less psychological stress for the patient; the patient is less likely to work for less and is cheaper. Bilateral inguinal hernias are suggested because of the absence of tension on the tissues and the lower recurrence rate [21,22]. In our study, no problems were encountered in postoperative follow-up of the patients.

Many centers in the world are applying LTF repair with local anesthesia. The results are quite pleasant. With this method, patients can be discharged to their homes the same day. In our study, a total of 93 patients underwent local anesthesia and seven patients under general anesthesia. Patients who did not have any problems in the postoperative follow-ups of these patients and who were operated with LTF technique were found to have an average of 2.5 days on the postoperative day, and 2.5 times on the PWD technique. They were discharged to their homes in a day. In addition, LTF technique was applied in a shorter period and statistically significant [23,24].

Some limitations are available in our study. Studied number of patients to evaluate the recurrence rate of such common diseases may be accounted as main limitation. We found aforementioned parameters different between LTF and PWD. Our study design was a non-randomized one; this will lessen the strength of our study. New prospective randomized controlled studies are needed to reveal this issue more promptly.

In conclusion, many surgeries around the world have done research on what they do; The LTF technique is a simple, reliable and effective method for hernia treatment. This technique is advantageous when compared with other conventional methods, with postoperative comfort, early return to normal daily activity, low recurrence, low cost, early return to work, low complication rate. It is also an important advantage that it can be applied with local anesthesia. In this way, patients can be discharged to their homes on the day of operation. LTF is also an important advantage for hernia repair because it is a safe method that can be used safely in recurrent hernias. We have found that our study is close to almost the same advantages except recurrent hernias. As a result of this study; although we have similar advantages in both groups, we favor the application of LTF technique in inguinal hernia primarily because of the short operation time, short hospitalization time, and low complication rate compared to the PWD technique.

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The co-evaluation of endosalpingeal karyorrhexis and salpingitis after the erythropoietin effect on fallopian ischemia reperfusion injury

Endosalpingeal karyorrhexis ve salpingitis 'nin eritropoietin etkisinin ardından ortak değerlendirilmesi

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Abstract

Aim: This study co-evaluated the 2 quoted histologic variables after the cytokine erythropoietin (Epo) administration. The calculation was based on the results of 2 preliminary studies, each one evaluating a respective histologic variable of endosalpingeal karyorrhexis (EK) or salpingitis (S) in an induced ischemia reperfusion (IR) animal experiment.

Methods: The 2 main experimental endpoints at which the EK and S scores were evaluated, were the reperfusion 60th min (for A & C groups) and the reperfusion 120th min (for B & D groups). Specially, the groups A and B were processed without drugs, whereas the groups C and D after Epo administration.

Results: The first preliminary study showed that Epo hardly non-significantly increased the EK scores by the grade "without lesions" 0.0181818 [-0.0679319 - +0.1042955] (p-value=0.6715). The other preliminary study found that Epo did not influence the S scores (p-value=1.0000). Both studies were co-estimated since they belong to the same experimental setting. This study co-evaluated the combined diagnostic values of both variables together.

Conclusions: Epo again hardly non significantly increased both scores for these histologic parameters at the grade of "without lesions" 0.0090909 [-0.0339659 - +0.0521478] (p-value=0.6715) since they were co-evaluated together.

Keywords: Ischemia, Erythropoietin, Endosalpingeal karyorrhexis, Salpingitis, Reperfusion

Öz

Amaç: Bu çalışma sitokin eritropoietin (EPO) uygulamasından sonra 2 atfedilen histolojik değişkenleri ortaklaşa değerlendirdi. Hesaplama, her biri endosalpingeal karyorrhexis (EK) veya salpingitis (S) bir indüklenen iskemi reperfüzyonu (IR) hayvan denemesi içinde ilgili histolojik değişken değerlendiren 2 ön çalışmanın sonuçlarını temel aldı.

Yöntemler: EK ve S puanlarının değerlendirilmesi gereken 2 ana deneysel uç noktası reperfüzyon 60 dk (A & C grupları için) ve reperfüzyon 120 dk (B & D grupları için) idi. Özel olarak, A ve B grupları ilaç olmadan işlendi, oysa C ve D EPO uygulamasından sonra işlendi.

Bulgular: İlk ön çalışmada EPO çok önemli ölçüde anlamlı "lezyonlar olmadan" 0,0181818 [-0,0679319-+ 0,1042955] (p-değer = 0,6715) notu tarafından ek puanları artış gösterdi. Diğer ön çalışmada EPO, S puanlarını etkilemez bulundu (p-değer = 1,0000). Her iki çalışmada aynı deneysel ayarlara sahip olduğundan birlikte tahmin edilmiştir. Bu çalışma her iki değişkenin kombine tanı değerlerini birlikte değerlendirir.

Sonuç: EPO yine de çok önemli ölçüde bu histolojik parametreler için "lezyonlar olmadan" 0,0090909 [-0,0339659-+ 0,0521478] (p-değer = 0,6715) sınıfında birlikte değerlendirildiğinde her iki skoru artmıştır.

Anahtar kelimeler: İskemi, Eritropoietin, Endosalpingeal karyorrhexis, Salpenjit, Reperfüzyon

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Introduction

Erythropoietin (Epo) was investigated whether having antioxidant capacities. 2 histologic variables in a fallopian ischemia reperfusion (FIR) experiment were tested for this purpose. The one variable was that of endosalpingeal karyorrhexis (EK) which was recessed by "without lesions" 0.0181818+0.04393556 (p-value=0.6715) [1]. The other variable was that of salpingitis (S) but did not influence the S scores (p-value=1.0000) [2]. Although Epo is met in over 29,975 published biomedical studies, only a 3.52% of them negotiate its antioxidant capacities. The present experimental work tried to co-evaluate these EK and S variables together and to compare its outcome with each one separately, from the same rat induced FIR protocol.

Materials and methods

Animal management

The Vet No 3693/12-November-2010 & 14/10-January-2012 licenses, the auspices company, the experimental location and the Pathology Department are mentioned in preliminary references 1, 2. The human animal care of female Wistar Albino rats, the one week pre-experimental ad libitum diet, the intra-experimental anesthesiologic techniques, the acidometry, the electrocardiogram and the oxygen supply and post-experimental euthanasia are also described in preliminary references. Rats were 16 – 18 weeks old. They were randomly assigned to four (4) groups consisted in N=10. The common stage of 45 min ischemia was preceded in all 4 groups. Afterwards, 60 min reperfusion was followed in group A; 120 min in group B; immediate Epo intravenous (IV) administration and 60 min reperfusion in group C; and immediate Epo IV administration 120 min in group D. The dose height was assessed at pre-experimental phase as 10 mg/Kg body mass.

Ischemia was induced by laparotomic clamping the inferior aorta upper the renal arteries level with forceps for 45 min. The forceps removal was restoring the inferior aorta blood patency and reperfusion. Epo was administered at the time of reperfusion; through an inferior vena cava catheter. The EK and S scores were determined at 60th min of reperfusion (for A and C groups) and at 120th min of reperfusion (for B and D groups). The pathologic score grading was maintained the same as in preliminary studies: (0-0.499) grade without lesions, (0.5-1.499) grade mild lesions, (1.5-2.499) grade moderate lesions and (2.5-3) grade serious lesions damage. Relation was rised between animals' mass with neither EK scores (p-value=0.7202) nor with S ones (p-values=1.0000).

Table 1: Endosalpingeal karyorrhexis (EK), salpingitis (S) and their mean and SD scores

	Mean EK score ±SD	Mean S score ±SD	Mean EK&S score ±SD
Group A	without lesions 0±0.00	without lesions 0±0.00	without lesions 0±0.00
Group B	without lesions 0±0.00	without lesions 0±0.00	without lesions 0±0.00
Group C	without lesions 0.2±0.421637	without lesions 0±0.00	without lesions 0.1±0.2108185
Group D	without lesions 0±0.00	without lesions 0±0.00	without lesions 0±0.00

The ischemia-reperfusion injury model

Placebo groups

The 20 placebo rats were the same for preliminaries and this study.

Group A

60 min reperfusion concerned 10 placebo rats of combined EK and S (EK&S) score as the mean of EK score and S one (Table 1).

Group B

120 min reperfusion concerned 10 placebo rats of combined EK&S (cEE&S) score as the mean of EK and S one (Table 1).

Epo group

The 20 Epo rats were the same for preliminaries and this study.

Group C

60 min reperfusion concerned 10 Epo rats of cEK&S score as the mean of EK score and S one (Table 1).

Group D

120 min reperfusion concerned 10 Epo rats of cEK&S score as the mean of EK score and S one (Table 1).

Statistical analysis

Successive comparisons among the 4 cEK&S groups were performed applying Wilcoxon signed-rank test (Table 2). Then, the generalized linear models (glm) were applied with dependant variable the cEK&S scores. Epo administration or no, the reperfusion time and their interaction were used as independent variables.

Table 2: The values difference for groups (DG) after Wilcoxon signed-rank test for mean EK&S scores

DG	Difference	p-value
A-B	0	1.0000
A-C	-0.1	0.1573
A-D	0	1.0000
B-C	-0.1	0.1573
B-D	0	1.0000
C-D	0.1	0.1573

Results

Epo administration hardly non-significantly increased the cEK&S scores by without alterations 0.05 [-0.02084505 - 0.12084505] (p=0.1558) by both Wilcoxon signed-rank test and glm methods respectively. Reperfusion time did not influence the cEK&S scores by "without alterations" 0.00 [-0.07084505 - 0.07084505] (p=0.1558) by similar methodology. Finally, Epo administration and reperfusion time together also hardly non significantly increased the cEK&S scores by "without alterations" 0.0090909 [-0.0339659 - 0.0521478] (p-valus=0.6715) (table 3). A concise form of the above findings is depicted at table 4.

Table 3: The alteration influence of Epo in connection with reperfusion time

Alteration	95% c. in.	Reperfusion time	wilkoxon	glm p
without alterations 0.1	-0.0508105 0.2508105	1h	0.1573	
without alterations 0.1	-0.0400615 0.2400615	1h		0.1510
without alterations 0.05	-0.0196642 0.1196642	1.5h		0.1544
without alterations 0.05	-0.0220259 0.1220259	1.5h	0.1573	
without alterations 0.00	0.00 - 0.00	2h	1.0000	
without alterations 0.1	-0.0400615 0.2400615	2h		0.1510
without alterations -0.05	-0.1196642 0.0196642	reperfusion		0.1544
without alterations 0.05	-0.0220259 0.1220259	reperfusion	0.1573	
without alterations 0.0090909	-0.0339659 0.0521478	interaction		0.6715

Table 4: Concise form of the table 3

Increase	95% c. in.	Reperfusion time	p-value
without alterations 0.1	-0.045436 0.245436	1h	0.1541
without alterations 0.05	-0.02084505 0.12084505	1.5h	0.1558
without alterations 0.05	-0.02003075 0.12003075	2h	0.5755
without alterations 0.00	-0.07084505 0.07084505	reperfusion	0.1558
without alterations 0.0090909	-0.0339659 0.0521478	interaction	0.6715

Discussion

Adamyan LV et al [3] considered the principal advantage of fibrin glue anastomoses than microsurgical anastomoses to reduce surgical trauma to oviduct stumps and absence of tissue ischemia. These features promote reparative regeneration and decrease adhesion formation, resulting in complete recanalization of fallopian tubes. Castadot RG [4] protected against salpingitis, other pelvic infections and against tubal pregnancies after combined oral contraceptives administration. Estrogens are clearly responsible for some of the complications, apparently due to a weakening of the fibrinolytic systems, but progestagens or estrogen-progestagen combinations are also implicated. Guennoun A et al [5] reported the case of a pregnant presenting with acute lateropelvic pain. Normal adnexal torsion is rare during pregnancy. Çılgın H et al [6] indicated that plasma heat shock protein 70 level could be used as a serum marker in the early detection of adnexal torsion since its significant increase in the study group was 1.50-fold and 1.47-fold respectively (P = 0.001) than that in the laparotomy and control groups, following 12 h of adnexal torsion. Ayachi A et al [7] reported two cases of adnexal torsion during the second trimester of pregnancy; presenting with appendix syndrome the one and acute left iliac fossa pain the other. Early treatment could avoid irreversible damages due to ischemia which could be fertility-threatening. Laparotomy revealed the torsion of a hydatid of Morgagni whose necrotic appearance due to twisting required hydatid ablation. Sukkong K et al [8] evaluated clinical risk factors predictive of torsion with gangrenous adnexa estimated at ~ 46.2%. Adnexal torsion results in ischemia of structures distal to twisted pedicle and acute onset of pain is responsible for about 3% of all gynecologic emergencies especially in young nulliparous women. Lee MH et al [9] reviewed all computed tomography signs of adnexal torsion with the exception of deviation of the uterus to the twisted side. However, for a twisted vascular pedicle, there was moderate agreement in patients with a mass and no agreement for patients without a mass. Damasceno RW et al [10] concluded a decrease in elastic fibers with ultrastructural abnormalities and an overexpression of elastin-degrading enzymes as the consequence of local ischemia, inflammation, and/or chronic mechanical stress. Aging with progressive loss of tone and laxity may affect the adnexal tissues, resulting in different clinical symptoms and signs. Spinelli C et al [11] described the conservative treatment for adnexal torsion, consisting of detorsion, as the best surgical approach to guarantee the future reproductive capacity of patients. Tunç SY et al [12] observed degeneration of epithelium, loss of cilia, dilation of blood vessels, and hemorrhages in sections of the ischemic group in the fallopian tube structure following ovarian torsion. The studied fallopian section revealed a significant decrease in density of desmin in the torsion group. Moreover, strong positive cytoplasmic CD68 expression was observed in the torsion group. Türk E et al [13] found that adnexal torsion and detorsion significantly increased the tissue level of malondialdehyde, superoxide dismutase and reduced glutathione, whereas hypothermia inhibited their production as well the histopathological changes in rats. Calis P et al [14] found only the loss of cohesion to be significantly different by 1.28-fold than control sides (p=0.017) in terms of the means of total tissue damage. Significantly lower PCNA counts were revealed in the 16-hour torsion group only in a rat model with adnexal torsion. PCNA confirms the viability of the counted follicles and appears to be a more precise approach necessary for demonstrating the functional status than net mean primordial+primary follicle count which were comparable in twisted and control sides. Navve D et al [15] associated the lateral whirlpool sign with enlarged masses the mean volume of which among cases was significantly greater by 2.81-fold than those with the medial whirlpool sign (P = 0.035). Sánez HA et al [16] described that adnexal torsion over its pedicle produces lymphatic and venous stasis, later it develops into ischemia and necrosis, when is not treated. Hirth D et al [17] identified cell necrosis by high mobility group box 1 protein and apoptosis by Caspase 3a staining of tissue samples taken at 3 endpoints postburn. Furthermore, endothelial cell necrosis was deeper than interstitial cell necrosis at 1 hour ($p < 0.001$). Endothelial cell necrosis at 1 hour divided the zone of injury progression (Jackson's zone of stasis) into an upper subzone with necrotic endothelial cells and initially viable adnexal and interstitial cells at 1 hour that progressed to necrosis by 24 hours and a lower zone with initially viable endothelial cells at 1 hour but necrosis and apoptosis of all cell types by 24 hours in a validated porcine model of vertical burn injury progression. Ozler A et al [18] found the mean number of preantral and small antral follicles lower and only AMH levels significantly decreased following the 3-hour IR ($P < 0.05$) in detorsion group than those of the sham group ($P < 0.01$). After torsion, anti-Müllerian hormone (AMH), estradiol, and inhibin B levels were decreased significantly than preoperative and postoperative periods (P = 0.032).

Table 5: The Epo influence (±SD) on the levels of 35 seric variables of complete blood count and blood chemistry tests versus reperfusion (rep) time [19]

35 Variables	1h rep	p-value	1.5h rep	p-value	2h rep	p-value	interaction of Epo and rep	p-value
Mean	+3.39%±12.15%	0.5636	+4.44%±14.50%	0.3711	+5.49%±18.55%	0.3496	+2.83%±7.13%	0.4045

A numeric evaluation of the Epo efficacies was provided by a meta-analysis of 35 seric variables of complete blood count and blood chemistry tests versus reperfusion time coming from the same experimental setting (table 5) [19].

Conclusion

Epo hardly non significantly increased the cEK&S scores by "without alterations" (p-values=0.6715) creating a suspicion for beneficial usage in situations such as tubal pregnancies, fertility, elastic and desmin ultrastructure, aging, tone, laxity and cohesion, regeneration of epithelium, conservation of cilia, blood vessel diameter regulation and lymphatic and venous stasis, cytoplasmic CD68, antioxidant markers, PCNA counts, mobility group box 1 protein, caspase 3a staining, anti-Müllerian hormone, estradiol and inhibin B presence or absence, ischemia, cell necrosis and apoptosis.

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The influence of anemia on maternal and neonatal outcomes in adolescent pregnant

Adölesan gebelerde aneminin maternal ve fetal sonuçlar üzerine etkisi

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Abstract

Aim: The aim of this study was to investigate the influence of anemia on maternal and neonatal outcomes in adolescent pregnant.

Methods: The files of 1407 adolescent women who gave birth in our hospital, from January 2010 to June 2015 were retrospectively investigated. Demographic characteristics, hemoglobin concentrations before birth, obstetric and neonatal outcomes were evaluated.

Results: The mean age of the study group was 17.95±1.09 years. Anemia frequency was found as 36%. Anemia was significantly higher with the lack of health insurance. Similarly, anemia in those who had an educational level of elementary school or lower was significantly higher than for high school graduates. Pregnant adolescents who had irregular antepartum care during pregnancy also had a 1.62 times higher anemia risk. A significant correlation was found between anemia and postpartum complications; postpartum transfusion (OR: 9.09) and hemorrhage (OR: 4.76). No statistically significant impact of anemia was found on type of delivery, preterm birth, preeclampsia or gestational diabetes ($p>0.05$). Neonatal Intensive Care Unit admission was significantly higher for the infants of anemic patients (OR: 2.68). No statistically significant impact of anemia was found on birth weight, gestational age, small for gestational age or Apgar scores of the infants ($p>0.05$).

Conclusion: Due to its high frequency and adverse maternal and fetal outcomes anemia should be carefully considered during pregnancy in adolescent girls.

Keywords: Adolescent, Pregnancy, Anemia, Outcome, Postpartum

Öz

Amaç: Bu çalışmanın amacı adölesan gebelerde aneminin obstetrik ve neonatal sonuçlar üzerindeki etkisinin incelenmesidir.

Yöntemler: Ocak 2010-Haziran 2015 tarihleri arasında hastanemizde doğum yapan 1407 adölesan gebenin dosyaları retrospektif olarak incelendi. Gebelerin demografik özellikleri, doğum öncesi hemoglobin konsantrasyonları, obstetrik ve neonatal sonuçları değerlendirildi.

Bulgular: Çalışma grubunun yaş ortalaması 17,95±1,09 yıl idi. Anemi sıklığı% 36 olarak saptandı. Sağlık güvencesi olmayan hastalarda anemi sıklığı anlamlı derecede yüksekti. Benzer şekilde, eğitim düzeyi ilkokul ya da daha düşük olanlarda, lise mezunlarına oranla anemi daha sık bulundu. Düzensiz antepartum bakım alan adölesan gebelerde, anemi riski 1,62 kat daha yüksekti. Anemi ve postpartum komplikasyonlar arasında anlamlı bir korelasyon saptandı; postpartum kan transfüzyonu (OR: 9,09) ve kanama (OR: 4,76). Aneminin doğum şekli, preterm doğum, preeklampsi veya gestasyonel diyabet üzerine istatistiksel olarak anlamlı etkisi bulunmadı ($p>0.05$). Anemik gebe bebeklerinin daha yüksek düzeyde Yenidoğan Yoğun Bakım Ünitesi ihtiyacı olduğu saptandı (OR: 2,68). Aneminin doğum ağırlığı, gestasyonel yaş, gebelik haftasına göre düşük doğum ağırlığı ve Apgar skorları üzerine istatistiksel olarak anlamlı bir etkisi bulunmadı ($p>0,05$).

Sonuç: Adölesan gebelerdeki yüksek anemi sıklığı ve maternal ve fetal sonuçlar üzerindeki olumsuz etkileri göz önünde bulundurulmalı ve özellikle bu yaş grubu gebelerde anemi göz ardı edilmemelidir.

Anahtar kelimeler: İskemi, Eritropoietin, Endosalpingeal karyorrhexis, Salpenjit, Reperfüzyon

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Introduction

Anemia during pregnancy which is the most common nutritional disorder in pregnancy across the world is defined as a condition where hemoglobin (Hb) level in the blood is less than 11 g/d [1,2]. According to World Health Organization, prevalence of anemia in pregnant women in Turkey is 40% which should be considered as a serious public health problem. Although it is common at all stages of the life cycle, it is most frequently seen in young children and pregnant women [1]. Moreover, teenage mothers are considered as another risky group for anemia because of the increased iron needs and malnutrition as well as early marriage and pregnancy [3]. Adolescents constitute about one fifth of the world population (17.5%) and in the developing countries this group comprises an even higher proportion (23%) of the population [4]. Nearly16 million adolescent girls between 15-19 ages give birth each year, accounting 11% of all births worldwide including the majority of it in developing countries [3]. In our country, adolescent age group constitutes 17.2% of the population and the proportion of those who gave birth in the 15-19 age group is 16.2% [5]. Pregnancy in very young women is generally considered to be a very high risk event which can cause several medical problems. Anemia, which is also one of these medical problems, is strongly associated with teenage pregnancy [6]. Although adolescent pregnancies have often been reported to be associated with adverse pregnancy outcomes such as preterm birth, low birth weight, small for gestational age infant and higher rates of neonatal and post-neonatal mortality, the impact of anemia on adverse pregnancy outcomes in adolescent pregnant is controversial. Some studies found significant associations whereas others didn't between the low Hb concentration and adverse obstetric and neonatal outcomes [7-12]. Thus the current study aims to investigate the influence of anemia on maternal and neonatal outcomes in Turkish adolescent pregnant.

Materials and methods

This retrospective observational study was done by investigating the files of 1407 adolescent women who gave birth in a major maternity hospital of Ankara-capital of Turkey- in a semi-urban region with partly low or middle socioeconomic level from January 2010 to June 2015. Adolescence was defined as per the WHO definition, 'young individuals between the ages of 10 and 19 years' [13]. All pregnant women aged ≤19 who delivered in our hospital during the study period were included in the study. Maternal age was defined as age in completed years at delivery and was calculated from the date of birth recorded from an official document during admission to the hospital. The demographic characteristics, hemoglobin concentrations before birth (in the last trimester or just before birth), obstetric complications, gestational age at birth, birth weights, apgar scores of the infants and neonatal intensive care unit (NICU) admission of the newborns were evaluated. The presence of anemia was defined as a hemoglobin concentration lower than 11.0 g/L according to World Health Organisation's definition [14]. The study group were divided into two groups according to the precense of anemia; anemic group (Hb<11gr/L; n=507) and non-anemic group (Hb≥11 gr/L; n=900) and maternal and neonatal outcomes of the groups were compared. The study was approved by Ethics Committee.

Maternal and neonatal outcomes

The maternal outcomes were type of delivery (normal vaginal/cesarean), preterm birth (less than 37 completed weeks of gestation), preeclampsia (occurrence of new-onset hypertension- a systolic blood pressure ≥ 140 mm Hg, a diastolic BP ≥ 90 mm Hg or both, at least two occasions 4 hours apart- plus new-onset proteinuria-≥ 0.3 g/24 h -measured after the 20th week of pregnancy [15]), gestational diabetes (any degree of glucose intolerance with the onset or first recognition during pregnancy), postpartum transfusion and postpartum hemorrhage (a blood loss of 500 ml or more within 24 hours after birth).

Neonatal outcomes were low birth weight (less than 2500 g at birth which was measured within the 24 hours after birth using digital infant scales in our hospital), gestational age at birth (full weeks were calculated to describe the gestational age), small for gestational age infant (weight less than the tenth percentile for gestational age), APGAR score (5 minute<7) and NICU admission (before discharge from the hospital for any reason).

Statistical Analysis

Statistical analyses were performed using SPSS software (Statistical Package for the Social Sciences, version 20.0; SPSS Inc., Chicago, IL, USA). The suitability of the measurements to normal distribution were determined by "Kolmogorov-Smirnov Test" according to the sample size (n>30). As the data were not appropriate for normal distribution non-parametric tests were used. Mann-Whitney U test was used in the comparison of two independent groups as a non-parametric test. Categorical variables were analysed with "Chi-Square Test" statistics. Logistic regression models were also used to determine the impact of the factors on anemia. Statistical significance was considered at a two-tailed value of $p<0.05$.

Results

The mean age of the study group was 17.95±1.09 years (range, 14-19 years). 80.6% (n=1134) of the patients were educated at elementary school or lower and 19.4% (n=273) were high school graduates. Only 10.2% were employed (n=144). 85.3% (n=1205) had civil marriages and 88.2% (n=1245) had health insurance. 65.9% (n=926) of the patients had regular antepartum control (≥4 times) during their pregnancy. 7% (n=99) had antepartum control three times, 5.8% (n=82) two times, and 3.6% (n=50) one time, whereas 17.7% (n=249) had never been followed-up during pregnancy. 0.4% of the patients had multiple pregnancy (n=5) and 0.4% had stillbirths (n=6).

Anemia frequency was found as 36% (n=507). In the anemic group, 58.2% (n=295) had mild (10.0≤Hb≤10.9), 40.6% (n=206) had moderate (7.0≤Hb≤9.9) and 1.2% (n=6) had severe (Hb<7.0) anemia.

The socio-demographic and clinical characteristics of the anemic and non-anemic groups are shown in Table 1. Among all the socio-demographic factors and infant characteristics, educational level, civil marriage, health insurance and regular antepartum control were found to be significantly different between the groups. Other socio-demographic factors were not statistically significant (Table 1). Low educational status and

lack of civil marriage, health insurance and regular antepartum control were found to be higher in the anemic group (p=0.000; p=0.006;p=0.000;p=0.000).

Anemia was significantly higher with the lack of civil marriage (OR:1.52) and with the lack of health insurance (OR:1.87). Similarly, anemia in those who had an educational level of elementary school or lower was significantly higher (OR:3.44) than for high school graduates. Pregnant adolescents who had irregular antepartum control during pregnancy also had a 1.62 times higher anemia risk (95% CI=1.29-2.03) (Table 2).

Table 1: Socio-demographic and clinical characteristics among anemic and non-anemic adolescent pregnant women

Characteristic	Presence of Anemia Anemic (Hb<11)	Non-Anemic (Hb≥11)	p value
Age (Median)	18	18	Z=-0.254
[Min-Max]	[14-19]	[14-19]	p=0.799
Gestational Age (Median)	39	39	Z=-1.058
[Min-Max]	[25-42]	[23-42]	p=0.290
Birth Weight (Median)	3130	3100	Z=-1.415
[Min-Max]	[840-4390]	[510-4330]	p=0.157
Hemoglobin Levels (Median)	10.1	12.1	Z=-31.318
[Min-Max]	[6.5-10.9]	[11.0-15.3]	p=0.000
Educational Level			
Elementary school/lower (%)	462 (%91.1)	672 (%74.7)	χ^2=56.170
High School (%)	45 (%8.9)	228 (%25.3)	p=0.000
Employment Status			
Employed (%)	49 (%9.7)	95 (%10.6)	χ^2=0.280
Unemployed (%)	458 (%90.3)	805 (%89.4)	p=0.597
Civil Marriage			
Yes (%)	417 (%82.2)	788 (%87.6)	χ^2=7.429
No (%)	90 (%17.8)	112 (%12.4)	p=0.006
Health Insurance			
Yes (%)	427 (%84.2)	818 (%90.9)	χ^2=14.153
No (%)	80 (%15.8)	82 (%9.1)	p=0.000
Regular Antepartum Control			
(≥4 times) Yes (%)	298 (%58.8)	628 (%69.8)	χ^2=17.443
No (%)	209 (%41.2)	272 (%30.2)	p=0.000
Iron Supplementation During Pregnancy			
Yes (%)	230 (%45.4)	442 (%49.1)	χ^2=1.824
No (%)	277 (%54.6)	458 (%50.9)	p=0.177
Fertility Treatment			
Yes (%)	15 (%3.0)	45 (%5.0)	χ^2=3.310
No (%)	492(%97.0)	855 (%95.0)	p=0.069
Smoking			
Yes (%)	83 (%16.4)	138 (%15.3)	χ^2=0.264
No (%)	424 (%83.6)	762 (%84.7)	p=0.608
Mode of Delivery			
Vaginal (%)	316 (%62.3)	601 (%66.8)	χ2=2.830
Cesarean (%)	191 (%37.7)	299 (%33.2)	p=0.093
Gender of the Infant			
Girl (%)	430 (%47.8)	257 (%50.7)	χ^2=1.101
Boy (%)	470 (%52.2)	250 (%49.3)	p=0.294

Table 2: Socio-demographic and clinical variables in association with anemia in adolescent pregnant women

Variable	OR (95% CI)	p
Civil Marriage		
Yes	Reference	
No	1.52 (1.12-2.05)	0.007
Educational Level		
Elementary school or lower	Reference	
High School	0.29 (0.20-0.40)	0.000
Employment Status		
Employed	Reference	
Unemployed	1.10 (0.77-1.59)	0.597
Health Insurance		
Yes	Reference	
No	1.87 (1.34-2.60)	0.000
Regular Antepartum Control		
Yes	Reference	
No	1.62 (1.29-2.03)	0.000
Iron Supplementation During Pregnancy	Reference	
Yes	1.16 (0.93-1.44)	0.177
No		
Smoking		
Yes	Reference	
No	0.93 (0.69-1.25)	0.608
Fertility Treatment		
Yes	Reference	
No	1.73 (0.95-3.13)	0.072

Results of logistic regression analysis are given in Table 3. We found that anemia increased the risk of postpartum transfusion (OR: 9.09) and postpartum hemorrhage (OR: 4.76). No statistically significant impact of anemia was found on type of delivery, preterm birth, preeclampsia or gestational diabetes (p>0.05) (Table 3).

Table 3: Regression Analyses showing the relationship between maternal outcomes and anemia status in adolescent pregnant women

Maternal Outcome	OR	95% CI	p
Type of Delivery			
Anemic	0.82	0.66-1.03	0.093
Preterm Birth			
Anemic	1.03	0.73-1.45	0.859
Preeclampsia			
Anemic	0.62	0.25-1.54	0.305
Gestational Diabetes			
Anemic	1.12	0.90-1.40	0.294
Postpartum Transfusion			
Anemic	0.11	0.06-0.21	0.000
Postpartum Hemorrhage			
Anemic	0.21	0.08-0.60	0.003

NICU admission was significantly higher for the infants of anemic patients (OR:2.68). No statistically significant impact of anemia was found on birth weight, gestational age, small for gestational age (SGA) or Apgar scores of the infants (p>0.05) (Table 4).

Table 4: Regression Analyses showing the relationship between neonatal outcomes and anemia status in adolescent pregnant women

Neonatal Outcome	OR	95% CI	p
Birth weight <2500 gr			
Anemic	1.01	0.69-1.49	0.938
Gestational Age <37			
Anemic	1.03	0.73-1.45	0.859
Gestational Age <34			
Anemic	1.04	0.53-2.06	0.908
Small for gestational age			
Anemic	1.08	0.70-1.67	0.726
APGAR 5.minute <7			
Anemic	1.78	0.51-6.18	0.362
NICU			
Anemic	0.38	0.26-0.56	0.000

Discussion

This study shows the importance of anemia in adolescent pregnant women, especially in terms of maternal outcomes. We found that anemia significantly increases especially the postpartum maternal complications of postpartum transfusion and postpartum hemorrhage. Also, when analyzed in terms of fetal outcomes, we found that NICU admission was significantly higher for the infants of anemic patients.

Anemia is an important public health problem worldwide especially during the pregnancy period. It not only impairs maternal health and well-being, but also causes adverse outcomes for both the mother and the infant. According to WHO, anemia affects half a billion women of reproductive age (15-49 years); 29% of non-pregnant (496 million) and 38% of pregnant women (32.4 million) worldwide [16]. In our study group, the anemia frequency was 36%, which can be classified as a moderate public health problem according to the WHO classification of the public health significance of anemia. The WHO Global Database on anemia gives the anemia prevalence in pregnant women in Turkey as 40.2%, which is defined as a severe public health problem. The lower frequency determined in our study group may be due to the fact that our hospital is located in a developed city of Turkey where there is a relatively better socio-economic level compared to the entire country [14].

Adolescent pregnancy is one of the major health challenges of the 21st century. Not only the adverse health

effects on both the mother and the infant, but also the physical, mental and social difficulties experienced by adolescents makes it a multi-faceted problem worldwide. As most adolescents become pregnant before the completion of their physical, mental and emotional maturation, the social consequences of pregnancy in this age group can be severe, such as school dropout, low education and as a consequence a lack of opportunities for better employment and income [17]. In accordance with this information, most of the adolescents in our study group were found to have low education levels and low employment rates. According to the Turkey Demographic and Health Survey-2013, 18.9% of the adolescent age group [17-21] have a high school education level, which is similar to our results, and 16.9% are employed, which is a little bit higher than our results [5].

We found a significant correlation between low educational status and lack of civil marriage, health insurance and regular antepartum visits and anemia. Many studies in the literature showed significant associations between adolescent pregnancy and low education level, low socioeconomic status, being anemic and having few antenatal visits [18-22]. These results are not surprising since economic challenges due to low educational level and lack of health insurance may cause poor adherence to routine antenatal follow-ups and may prevent having a healthy pregnancy period. Antenatal care is not only essential for the health of the woman and her pregnancy but also presents opportunities to provide information to her about taking iron supplements, good nutrition, balanced diet and preventing anemia. In their study, Ikeanyi and Ibrahim aimed to determine the effect of antenatal care on preventing anemia in pregnancy at term and concluded that anemia was corrected in 69.9% of the women who received antenatal care [23]. It should be kept in mind that antenatal care is the most important way to detect problems in pregnancy so as to prevent unwanted outcomes.

Although no statistically significant impact of anemia was found on type of delivery, preterm birth, preeclampsia and gestational diabetes, a remarkable aspect of our results was the increased risk of the postpartum maternal complications of postpartum transfusion and hemorrhage. The results of the studies in the literature on anemia in terms of maternal complications are controversial. While some studies pointed out that maternal anemia in pregnancy is an important risk factor for preterm birth, preeclampsia, diabetes and increased maternal mortality [7-10], others did not find a correlation [11,12], as the case with our study. At the same time, our findings are consistent with the literature in terms of postpartum maternal results. In her study, Frass determined that postpartum hemorrhage is related to hemoglobin levels at labor and the severity of anemia is an important factor that causes greater blood loss and adverse maternal outcomes [23]. Similarly, in a study done in Scottish population which aimed to estimate the clinical outcomes of antenatal anemia, statistically significant relationship was found between anemia and hemorrhage, transfusion and postpartum infection [24]. Therefore, since adolescent pregnancy itself is a risk factor for life threatening complications such as postpartum hemorrhage [25,26], the negative effects of maternal anemia on the postpartum period, especially in this age group, should never be ignored.

In our study group, no statistically significant impact of anemia was found on birth weight, gestational age, SGA and Apgar scores of the infants. The association between maternal anemia and fetal outcomes remains equivocal with some [7,8,10,27] but no other studies [11,12] documenting an increased risk of low birth weight, SGA and low Apgar scores. Although no correlation between anemia and fetal outcomes were identifed in our study, the point to be noted is the significantly increased NICU admission of the infants born from anemic mothers. Similar to our results, Drukker et al. [27] in their study evaluated the effects of anemia on adverse neonatal outcomes and determined higher NICU admission forinfants of anemic mothers. They concluded that correction of hemoglobin concentrations even in late pregnancy is very important in preventing these adverse outcomes. Similarly, Raisanen et al. [28] found significant correlation between maternal anemia and increased admission to NICU for their infants and underscore that maternal anaemia is associated with several adverse perinatal outcomes. In addition to these results, most studies in the literature interpreted that teenage pregnant women had a significant number of complications in pregnancy, one of which is a higher percentage of NICU admissions of their infants [29,30]. Therefore, healthcare staff should be particularly careful about emergent complications that may arise in the newborns of adolescent pregnancies complicated by maternal anemia.

The present study has certain limitations. First of all, the retrospective nature of the study is a limitation. Also, since the patients were of similar socio-economic status, it is not possible to generalize the results. In addition, the low number of patients with severe anemia prevented an examination of the relationship between the severity of anemia and maternal-fetal outcomes. Although the effect of maternal anemia on outcomes of pregnancy in the literature is well-studied, despite the growing importance worldwide, adolescent studies of maternal anemia are still not so common. So despite the limitations, our work expands the understanding of the effect of antenatal anemia on both maternal and neonatal outcomes in the adolescent age group. Large, prospective studies with heterogeneous groups are needed to clarify the relationship between maternal anemia and its effect on teenage pregnant women and their infants.

In conclusion, although many health problems are particularly associated with negative outcomes of pregnancy during adolescence, due to its high frequency and adverse maternal and fetal outcomes, anemia should be carefully considered in adolescent girls, especially during the pregnancy period. As it seems hard to prevent adolescent marriages in our culture in the short term, making pregnancy safer for the youngest mothers and their babies must be a priority for our country to meet targets for improving basic health care. For this purpose, health care professionals should focus on education, nutritional support, and regular pre and antepartum control of the adolescent girls and try to create awareness in the community about the complications of both teenage pregnancy and anemia during this period.

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Comparison of VAS scores recorded by nurse vs surgeon: A case-control study

Hemşire ve cerrah tarafından kaydedilen VAS ağrı skorlarının karşılaştırılması: Vaka-kontrol çalışması

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Abstract

Aim: VAS (Visual Analogue Scale) is a scale that is frequently used, easily understood and applied especially in the assessment of postoperative pain. Many parameters are performed mainly by the nurses in the follow-up of the patient in the post-operative period, and follow-up of the pain from the major complaints is also performed by the nurses. The purpose of the study is to exhibit whether the identity of the questioner, i.e., the nurse in charge or surgeon in charge, causes a change in the VAS scale in questioning VAS pain scoring.

Methods: 120 patients who underwent elective laparoscopic cholecystectomy were included the study and the postoperative pain scores of the patients were evaluated with VAS (Visual Analogue Scale) at 1st, 6th and 24th hours. The pain questioning was first performed by the nurse in charge and also 15 minutes later by the physician in charge. No analgesic administration was performed to the patients between the two questioners. The difference between the pain scores was assessed statistically whether it had changed with the identity of the questioners.

Results: It was detected that VAS 1, VAS 6 and VAS 24 score averages were significantly different according to physicians and nurses ($p<0.05$). VAS average of the nurse in the 1st hour was 2.39±1.42 and VAS average of the physician was 1.19±0.79, VAS average of the nurse in the 6th hour was 2.15±1.73 and VAS average of the physician was 1.35± 1.25, VAS average of the nurse in the 24th hour was 1.23±0.96 and VAS average of the physician was 0.68±0.75. For each VAS score; it was detected that VAS scores given by the nurses were significantly higher than the VAS score averages given by the physician ($p<0.05$).

Conclusion: We think that the identity of the questioner is also influential on the pain score expressed by the patient in the assessment of the postoperative pain made by using the VAS pain score, who questions the pain in the pain palliation made by using this scale should also be evaluated.

Keywords: Postoperative pain, VAS, Pain follow-up

Öz

Amaç: VAS (Vısual Analog Scale); özellikle postop ağrının değerlendirilmesinde sık kullanılan, kolay anlaşılan ve uygulanan bir ölçektir. Hastanın ameliyat sonrası dönemde takibinde birçok parametre esas olarak hemşire tarafından gerçekleştirilmekte yine önemli şikayetlerden olan ağrının izlemi de yine hemşireler tarafından yapılmaktadır. Çalışmanın amacı VAS ağrı skorlamasının sorgulanmasında; sorgulayıcının kimliğinin yani sorumlu hemşire ya da cerrahı tarafından yapılmasının VAS ölçeğinde değişime neden olup olmadığını ortaya koymaktır.

Yöntemler: Elektif laparoskopik kolesistektomi yapılan 120 hastanın postoperatif ağrı skorları 1.,6. Ve 24. saatlerde VAS (Visual Analog Scale) ile değerlendirildi. Ağrı sorgulaması önce sorumlu hemşire tarafından, 15 dakika sonra da cerrahı tarafından gerçekleştirildi. Her iki sorgulayıcı arasında hastalara herhangi analjezik uygulaması yapılmadı. Ağrı skorları arasındaki farkın, sorgulayıcının kimliği ile değişip değişmediği istatistiksel olarak değerlendirildi.

Bulgular: VAS 1, VAS 6 ve VAS 24 skor ortalamalarının cerrah ve hemşirelere göre anlamlı düzeyde farklılık gösterdiği tespit edildi ($p<0,05$). 1.saatte hemşire için VAS ortalaması; 2,39±1,42, cerrah için VAS ortalaması; 1,19±0,79, 6.saatte hemşire VAS ortalaması; 2,15±1,73, cerrah VAS ortalaması; 1,35±1,25, 24.saat hemşire VAS ortalaması; 1,23±0,96, cerrah VAS ortalaması; 0,68±0,75 olarak bulundu. Her bir VAS skoru için hemşirelerin verdikleri VAS skorları, cerrahların verdiği VAS skoru ortalamalarından anlamlı derecede daha büyük olduğu tespit edildi ($p<0,05$).

Sonuç: VAS ağrı skoru kullanarak yapılan postoperatif ağrının değerlendirilmesinde sorgulayıcının kimliğinin de hasta tarafından ifade edilen ağrı skorunda etkili olduğu, bu skala kullanılarak yapılacak ağrı palyasyonunda ağrının kimin tarafından sorgulandığının da değerlendirilmesi gerektiğini düşünmekteyiz.

Anahtar kelimeler: Postoperative ağrı, VAS, Ağrı takibi

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Introduction

Pain is a multidimensional subjective experience that the human beings try to describe for centuries [1-3]. According to International Association for the Study of Pain (IASP, 1979) pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" and "a protection mechanism" [3,4].

Pain is actually a subjective concept, which means that it shows large differences from person to person, because many factors (such as gender, religion, language, race, socio-cultural environment) determine pain threshold and consequently response to the painful stimulant [5]. Therefore, both physical and non-physical components should be considered together when evaluating pain.

Pain measurements can be performed by "Direct Measurement" and "Indirect Measurement". Direct measurements are aimed at revealing the nature of the pain. Indirect measurements measure the effect of pain on the quality of life [6].

Another classification for pain measurements is classification as "Unidimensional Measurement" and "Multidimensional Measurement". LANSS (Leeds Assessment of Neuropathic Symptoms and Signs) Scale, Visual Analogue Scale (VAS), Numerical Rating Scale (NRS) and Verbal Rating Scale (VRS) are examples of unidimensional scales. Examples of multidimensional scales are the McGill Pain Questionnaire (MPQ), the Quality of Life Assessment and the Patient Diary [6].

Use of scale in pain assessment, transforms the severity and characteristic of pain into objective state and eliminates the difference between nurse and physician [7].

Visual Analogue Scale (VAS) is a reliable and valid pain measurement method for evaluating the severity of acute and chronic pain [8-10]. The scale consists of a horizontal line with a length of 10 cm. For pain severity according to VAS, “no pain” is generally rated as 0 points and “the worst imaginable pain” is rated as 10 points (10 cm scale) [11]. The patient is told to mark a point on the line that will reflect his pain correctly. The distance of the patient's mark to the left end is measured. This distance, which is usually measured in millimeters, is reported as "points".

Intervals for pain severity are specified as <3 mild pain, 3-6 moderate severe pain, >6 severe pain [11,12].

VAS is a valid and reliable measure used not only for acute pain but also for measurement of chronic pain severity, but it measures the severity of the pain in one dimension [8,9].

Despite all the improvements in pain management and treatment, postoperative pain is still an important clinical condition. Pain is tried to be minimized by a teamwork done by a team composed of physicians, nurses and other relevant health personnel. Pain palliation is one of the most important problems that can disturb patient comfort especially after surgery and sometimes cause prolongation of hospitalization. The aim of an effective pain management is not only to reduce physical discomfort, but also to provide early recovery and return to work, staying in the clinic shorter and minimizing health care costs. For many patients, pain palliation is not successful enough. One of the reasons for this is the fact that although pain is an old concept, pain science is a newly emerging science discipline and the other important reason is that physicians and nurses have inadequate knowledge about pain diagnosis and management [13,14]. Correct postoperative pain assessment is an important point for effective pain management [13,15]. Pain is a dynamic process and it is the responsibility of the nurse to understand it [15]. Nurses are ethically responsible for pain management and pain relief. Since the nurses spend the longest time with the painful patient, they have the opportunity to observe and evaluate the patient well. Therefore, the role of the nurse in approaching the painful patient is important and privileged [16,17]. Effective assessment of pain is a prerequisite for pain control and is one of the main components of nursing care.

There is a clinical study in the literature regarding the comparison of pain scores given by the relatives of the patient and nurses [18]. However, there are very few studies comparing the pain scores obtained by the nurse in charge and physician in charge. Our clinical observations tend in a direction that the patients express different scores to the nurse in charge and surgeon in charge, when they are questioned regarding their post-operative pain. Our aim in this study is to assess whether the patients express different pain scores to nurses and surgeons, when early postoperative pain assessment is performed in patients that underwent laparoscopic cholecystectomy, and whether this is significant or not.

Materials and methods

This was a case-control study and approval was granted by the Research Ethical Committee. 120 patients above the age of 18 who give written and oral approval, that are planned elective laparoscopic cholecystectomy, ASA I or II, that are operated between 2016 June and 2017 June.

In pre-operative meeting to the patients regarding VAS (Visual Analogue Scale) detailed information has been given. On the scale; it has been detailed explained to the patients and expected to be evaluated that 0 indicates the case without any pain, and 10 represents the highest rate of pain. Post-operative pain; is questioned by the responsible nurse and after 15 minutes by the responsible surgeon. Interrogators; were not informed regarding intra operative local anesthetic applications and insufflation pressure. To the nurses regarding VAS pain score interrogation and analgesic requirement application training has been given. In patients with the VAS pain score equals to or more than 4; Dexketoprofen (Arveles® 50 mg) has been applied. In case of requirement of analgesic intravenous dexketoprofen has been applied. Before the surgery following type of patients have been excluded from the study such as the ones to use psychotropic and opioid medication, ones to define psychiatric diseases stories, pregnants, the ones with alcohol addiction, the ones who define chronic pain not related to gall bladder stone, ones to use steroids, the ones who are sensitive to local anaesthetics, the ones to go under operations because of acute cholecystisis, because of the suspect of bleeding or surgery related suspects put drain. To none of the patients preemtive analgesic application has been done.

The postoperative pain scores of the patients were evaluated with VAS (Visual Analogue Scale) at 1st, 6th and 24th

hours. The pain questioning was first performed by the nurse in charge and also 15 minutes later by the physician in charge. No analgesic administration was performed to the patients between the two questioners. The difference between the pain scores was assessed statistically whether it had changed with the identity of the questioners.

Statistical Analysis

Kolmogorov-Smirnov and Shapiro Wilks test were used to determine whether VAS 1, VAS 6 and VAS 24 measurements obtained from the patients are appropriate to the normal distribution and it was observed that the data showed conformity to normal distribution. The t-test is used in independent groups to determine whether VAS 1, VAS 6 and VAS 24 measurements differed significantly between the nurses and the physicians; while the VAS values measured by the nurses and the physicians separately at different times were examined in dependent with the t-test. Analyzes were made at 95% confidence level in SPSS 20.0 software.

Results

The comparison of the VAS scores told by the patients to the physicians and the nurses is given in Table 1. According to this, the VAS 1, VAS 6 and VAS 24 score averages are significantly different according to the physicians and the nurses ($p<0.05$), and the VAS scores given by the nurses for each VAS score are significantly higher than the VAS score averages given by the physicians ($p>0.05$).

Table 1: VAS score comparison for surgeon vs. nurses

		n	Mean	Standard deviation	p
VAS 1	Nurse	120	2.39	1.42	<0.001*
	Surgeon	120	1.19	0.79	
VAS 6	Nurse	120	2.15	1.73	<0.001*
	Surgeon	120	1.35	1.25	
VAS 24	Nurse	120	1.23	0.96	<0.001*
	Surgeon	120	0.68	0.75	

* p<0,05

The comparison of the VAS scores that the patients told the nurses is given in Table 2. According to this, although there is no significant difference between VAS 1-VAS 6 score averages ($p>0.05$), there is a significant difference between VAS 1-VAS 24 and VAS 6 - VAS 24 score averages ($p<0.05$). VAS 1 score is significantly higher than VAS 24 score, and VAS 6 score is significantly higher than VAS 24 score.

Table 2: VAS scores for nurses

		n	Mean	Standard deviation	p
1	VAS 1	120	2.39	1.42	0.245
	VAS 6	120	2.15	1.73	
2	VAS 1	120	2.39	1.42	<0.001*
	VAS 24	120	1.23	0.96	
3	VAS 6	120	2.15	1.73	<0.001*
	VAS 24	120	1.23	0.96	

* p<0.05

The comparison of the VAS scores that the patients told the surgeons is given in Table 3. According to this, although there is no significant difference between VAS 1-VAS 6 score averages ($p>0.05$), there is a significant difference between VAS 1-VAS 24 and VAS 6 -VAS 24 score averages ($p<0.05$). VAS 1 score is significantly higher than VAS 24 score, and VAS 6 score is significantly higher than VAS 24 score.

Table 3: VAS scores for surgeons

		n	Mean	Standard deviation	p
1	VAS 1	120	1.19	0.79	0.265
	VAS 6	120	1.35	1.25	
2	VAS 1	120	1.19	0.79	<0.001*
	VAS 24	120	0.68	0.75	
3	VAS 6	120	1.35	1.25	<0.001*
	VAS 24	120	0.68	0.75	

* p<0.05

Discussion

The trauma occurred as a result of the surgical intervention causes direct damage to the neural structures and the stimulation of nociceptors. Pain arises as a result of this stimulation. Not only psychological, but also a number of pathophysiological changes occur as a result of pain [19].

The pain experience is dynamic and it is the responsibility of the nurse to understand it [15]. Nurses are the health care professionals, who spent most of time with the patients and their role in pain management is essential [17]. Sloman et al. found in their studies that nurses working in surgical departments underestimate the pain sensation of the patient and pain [13]. Most of the studies comparing the pain assessments of the patients by the nurses report that the nurses predict the pain scores lower [17,20-25].

Although the assessment of the patient's pain and the determination of the appropriate conditions for pain palliation are mainly the responsibility of the nurse performing follow-up during the period of hospitalization, physician in charge also questions pain, which is one of the most important complaints of the patient after surgery. However, follows the course of the pain scores during this time mostly from the nurse visits. The surgeon may detect different pain scores from the scores he or she receives from the nurse in the face-to-face interviews with the operated patient.

Although there are publications regarding the use of scale in the pain assessment eliminate the difference between the nurse and the physician by converting the severity and characteristic of the pain to an objective status [7], different scores appeared in the pain assessment using VAS between the nurse and the surgeon in our study. The pain scores recorded by the nurses are often low and this is associated with poor identification or ignorance of the pain [13]. However; pain scores given by nurses in our study in all of the 1st, 6th and 24th hours were significantly higher when compared with the surgeons. This finding was in contrary to the literature on nurse observation. Özer et al. [26] thought that the nurses had moderate knowledge and behavioral scoring related to pain and do not have sufficient knowledge about the pain physiology and pharmacological management of pain. In a study comparing the nurse and physician in terms of VAS score made by Martin et al. [27]; VAS scores expressed to the surgeons by the patients were found to be significantly higher compared to the nurses. We have obtained a finding on the contrary, meaning that the scores of the surgeons are significantly lower. We think that the fact that the scores of the physicians are much lower, when the surgeon and the nurse is compared, is based on making a more accurate assessment because they have much more knowledge about pain physiology and the patients express their pain scores to their surgeons more realistic because they have a higher level of

confidence. Therefore, we think that who performs the questioning is important in the treatment of pain that will be started by questioning VAS pain score.

Main limitation of this study was; the pain can vary between the two assessments in 15 minutes and the evaluation was not made by the doctor first and then by the nurse.

In conclusion, we think that the identity of the questioner is also influential on the pain score expressed by the patient in the assessment of the postoperative pain made by using the VAS pain score, who questions the pain in the pain palliation made by using this scale should also be evaluated.

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The effectiveness of whirlpool for patients with neuropathic pain due to knee osteoarthritis

Diz osteoartritine bağlı nöropatik ağrısı olan hastalarda whirlpool'un etkinliği

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Abstract

Aim: Both neuropathic and nociceptive mechanisms may contribute to the OA pain experience. The aim of this study is to determine the efficacy of warm whirlpool on pain, disability, quality of life (QoL) and sleep for patients with neuropathic pain.

Methods: This is a randomized, placebo controlled prospective study. Sixty patients with neuropathic pain due to knee OA were included and randomized into two groups. Group 1 (n=30) were treated with warm whirlpool and Group 2 (n=30) were treated with placebo for 20 minutes during 15 sessions. Patients were evaluated according to pain, knee range of motions (ROM), quality of life (QoL) and sleep quality. The primer outcome measure was pain severity and was assessed using a visual analogue scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). WOMAC disability and functional scores for functional ability, Short Form-36 Health Survey (SF-36) for QoL, Pittsburgh Sleep Quality Index (PSQI) for sleep, DN4 for neuropathic pain were used for assessments. Patients were evaluated at baseline and the end of the 15 day intervention.

Results: At the end of the therapy, there were statistically significant improvements in SF-36, PSQI, DN4 and knee ROM (active and passive) scores ($p<0.05$) for both groups. Also there were a statistically significant improvement for SF-36 scores except for general health score, PSQI and DN4 scores between groups ($p<0.05$);but this improvement was not statistically significant for VAS, WOMAC, SF-36 general health score and knee ROM between groups ($p>0.05$).

Conclusion: Whirlpool provided significant improvements in QoL, sleep, neuropathic pain and disability for patients with neuropathic pain due to knee OA.

Keywords: Neuropathic pain, Osteoarthritis, Sleep, Quality of life, Whirlpool

Öz

Amaç: Hem nöropatik hem de nosiseptif mekanizmalar osteoartritteki ağrıya neden olabilir. Bu çalışmanın amacı diz osteoartritine bağlı nöropatik ağrısı olan hastalarda whirlpool uygulamasının ağrı, dizabilite, yaşam kalitesi ve uyku üzerine olan etkinliğini değerlendirmektir.

Yöntemler: Bu çalışma randomize, placebo kontrollü prospektif bir çalışmadır. Diz osteoartritine bağlı nöropatik ağrısı olan 60 hasta çalışmaya alındı ve iki gruba randomize edildi. Grup 1'deki hastalar (n=30) sıcak whirlpool, Grup 2'deki hastalar (n=30) plasebo whirlpool ile 20 dakika süreyle 15 seans boyunca tedavi edildi. Primer sonuç ölçütü ağrı idi ve görsel analog skala (GAS) ve Western Ontario and McMaster Universities Osteoarthritis (WOMAC) indeksi ağrı skoru ile değerlendirildi. Fonksiyonel abilite için WOMAC dizabilite ve fiziksel fonksiyon skorları, yaşam kalitesi için Kısa-Form 36 (KF-36) ile; uyku, için Pittsburgh Uyku Kalitesi İndeksi (PUKİ) kullanıldı. Nöropatik ağrı varlığı DN4 anketi ile belirlendi. Değerlendirmeler tedavi öncesi ve sonrası yapıldı.

Bulgular: Tedavinin sonunda her iki grupta da KF-36, PUKİ ve DN4 skorları ile diz EHA değerlerindeki düzelme istatiksel olarak anlamlı bulundu ($p<0.05$). Gruplar arasında, KF-36'nın genel sağlık skoru dışındaki tüm alt bileşenleri, PUKİ ve DN4 skorlarındaki düzelme açısından istatiksel olarak anlamlı farklılık saptanırken ($p<0.05$); GAS, WOMAC indeksi ve KF-36 genel sağlık skoru ile diz EHA değerlerinde istatiksel olarak anlamlı farklılık saptanmadı ($p>0.05$).

Sonuç: Diz osteoartritine bağlı nöropatik ağrısı olan hastalarda whirlpool tedavisinin yaşam kalitesi, uyku, nöropatik ağrı ve dizabilite üzerine olumlu etkileri mevcuttur.

Anahtar kelimeler: Nöropatik ağrı, Osteoartrit, Uyku, Yaşam Kalitesi, Whirlpool

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Introduction

Osteoarthritis (OA) of the knee is the most common cause of knee pain in middle-aged and older persons and its known that prevalence of this condition is increasing [1,2]. OA-related pain has been attributed to local tissue injury and this injury can cause nociceptive pain [3]. However some studies showed that both neuropathic and nociceptive mechanisms may contribute to the OA pain experience [4-6].

Neuropathic pain may be caused by a lesion or a disease of the somatosensory system and the management of neuropathic pain is challenging because the response to most drugs remains unpredictable despite attempts to develop a more rational therapeutic approach [7-10]. So it has become the subject of research for alternative treatments of neuropathic pain for clinicians.

Hydrotherapy is a superficial heating or cooling process and it is an external application of water to the body parts for therapeutic purposes [11]. Whirlpool treatment method is used for medical and surgical conditions; also widely for musculoskeletal disorders [12]. This treatment is especially useful to decrease muscle spasm and pain [13-16]. In literature there are studies which recommend whirlpool therapy as a treatment for reducing pain in patients with osteoarthritis [16]. But we couldn't find any reports in the literature about the use of whirlpool for treatment of patients with neuropathic pain due to knee OA. The aim of this study was to determine the efficacy of warm whirlpool on pain, disability, quality of life (QoL) and sleep for patients with neuropathic pain.

Materials and methods

Study Design

This placebo randomized controlled trial was conducted in a university hospital. The study protocol was approved by the Institutional Review Board of the university ethics committee with 30112015-6 registry number. The Declaration of Helsinki protocols were followed. All participants were informed about the study and signed written informed consent before interventions. The study was carried out from December 2015 through March 2016.

Participants and Randomization

A total of 60 patients with neuropathic pain due to knee OA were randomized into either intervention (warm whirlpool) (n=30) or placebo (n=30) groups. Knee OA diagnosis was made based on American College of Rheumatology criteria [17]. Severity of knee OA was determined radiologically by Kellgren-Lawrence scoring system [18]. Neuropathic pain diagnosis was considered if Douleur Neuropathique 4 (DN4) score was ≥4. Individuals were included in the study if they were between 50-75 years and have been suffering from knee pain at least 3 months, whose radiological manifestations considering were consistent with grade 3 and 4 knee OA due to Kellgren and Lawrence criteria had DN4 scores ≥4. Individuals were excluded if they had lower extremity surgery history, knee infection, inflammatory disease like rheumatoid arthritis, back or pelvic pain related with knee pain, another cause of polyneuropathy (diabetes mellitus, vitamin B 12 deficiency, toxic or neurological disease like stroke, spinal cord injury), lumbar disc herniation, malignancy or active systemic disease.

After physical examination all patients received knee anteroposterior and lateral radiography; also full blood count, erythrocyte sedimentation rate (ESR), C- reactive protein (CRP) and biochemical markers were evaluated.

With numbered envelopes method participants were randomly assigned into two groups. All of the patients were blinded to treatment allocation but the physiotherapist who applied the therapy was aware of the procedure.

Intervention and control

Patients were asked to sit on an adjustable chair beside the whirlpool and submerse their legs in the water to mid-femoral level.

Intervention group (n=30) were treated with warm whirlpool. Warm whirlpool administered at temperatures between 30.0°C and 40.0°C.

Control group (n=30) were treated with warm water at temperatures between 30.0°C and 40.0°C when whirlpool machine was turned off. Both groups received 15 sessions for 20 minutes during 15 days.

A home-based exercise program including isometric-isotonic knee exercises and hip extensor stretching exercises were given to all patients every day during the treatment. No medications including analgesic drugs or non-steroidal anti-inflammatory drugs were allowed during the treatment process.

Outcome Measures

Patients were evaluated at baseline and the end of the 15 day intervention. The primary outcome measure of the study was pain intensity and the secondary outcome measures of the study were Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index, Short-Form 36 (SF-36) Survey, Pittsburgh Sleep Quality Index (PSQI), Douleur Neuropathique 4 scores and knee active and passive range of motion values.

Pain Intensity

Pain intensity was measured on visual analog scale (VAS), where 0 = no pain and 10 = worst possible pain. VAS revealed three mean scores for both knees; at rest, on movement and pain at night scores. This scale was completed by the patients.

Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index

WOMAC is a self-administered measure that assesses the dimensions of pain, stiffness and function in patients with OA of the hip or knee [19]. The 24-item WOMAC is divided into 3 subscales including pain (5 questions, score range: 0–20), joint stiffness (2 questions, score range: 0–8), and physical functionality (17 questions, score range: 0–68). It produces three subscale scores (pain, stiffness and physical function) and a total score (WOMAC index) that reflects disability overall. The reliability and validity study of the scale in the Turkish population was carried out by Tüzün et al. [20].

Short-Form 36 (SF-36) Survey

The health-related life quality of the patients in both groups was evaluated by SF-36 survey. SF-36 is composed of eight health subsections (physical function, physical role, pain, general health, vitality, social function, emotional role, and mental health). The scale is scored between "0" as the worst

score and "100" as the best score. The validity and reliability of the Turkish version of this survey has been reported by Kocyigit et al. [21].

Pittsburgh Sleep Quality Index (PSQI)

Sleep quality of the patients was evaluated with PSQI. The scale includes 24 questions; 19 questions answered by the person him/herself and the remaining 5 answered by his/her bed partner. The first 19 self-answered questions evaluate 7 subscales, i.e. subjective sleep quality, sleep latency, duration of sleep, routine sleep activity, sleep disorders, the use of drugs for sleeping, and daytime dysfunction. Each item in the scale is scored between 0 and 3 (no difficulty to severe difficulty) [22]. The sum of the 7 subscale scores give the overall PSQI scores [23]. Sleep quality is evaluated as fine in those with an overall score of 5 or lower. The reliability and validity study of the scale in the Turkish population was carried out by Ağargün et al. [23].

Douleur Neuropathique 4 (DN4) scores

The DN4 questionnaire (Douleur Neuropathique 4 questions) was originally developed and validated for neuropathic pain diagnosis [24]. DN4 is a clinician-administered questionnaire; consists seven items related to symptoms and three related to clinical examination. For each item, a score of ''1'' is given if the answer is ''yes'' and a score of ''0'' is given if it is ''no.''. The patient is defined to have neuropathic pain if the total score is calculated to be 4 or more. The reliability and validity study of Turkish version of DN4 was made by Cevik et al. [25].

Knee Range of Motion

The active and passive knee range of motion (ROM) (right–left) was measured using a goniometer when the patient was in neutral supine position and mean values for both knees were included.

Statistical analysis

The means and standard deviations were given as descriptive statistics. All data for normality was tested by using Kolmogorov-Smirnov test. Wilcoxon test was used to calculate the pre and post-treatment value differences. To compare the differences between two groups, Mann Whitney U was used. A level of significance of $p<0.05$ was accepted. All analyses were performed using the SPSS for Windows 18.0 software program.

Results

A total of 60 patients were included the study. All of the participants completed the study protocol and none of participants had any side effects.

The results of full blood count, ESR, CRP and biochemical markers were in normal ranges for all groups. 36 of patients had Kellgren- Lawrence grade 3 OA and 24 of patients had Kellgren- Lawrence grade 4 OA.

The demographic characteristics and baseline values of the outcome measures of the patients are presented in Table 1. No statistically significant differences were detected between the groups at baseline values ($p>0.05$) except age, weight and WOMAC total score values ($p<0.05$) (Table 1).

For both intervention and placebo groups, statistically significant improvement in VAS (p=0.00); WOMAC pain, stiffness, physical function and total scores (p=0.00) (Table 2); SF-36 physical function (p=0.00 and p=0.01 respectively), SF-36 role limitation (physical) (p=0.00 and p=0.01 respectively), SF-36 bodily pain (p=0.00 and p=0.01 respectively), SF-36 general health perceptions (p=0.00), SF-36 vitality (p=0.00), SF-36 social role function (p=0.00 and p=0.02 respectively), SF-36 role limitation (emotional) (p=0.00 and p=0.02 respectively) and SF-36 mental health (p=0.00 and p=0.03 respectively) scores, PSQI (p=0.00), DN4 score (p=0.00) and knee active and passive ROM (p=0.00) were found after 15 days of intervention (Table 3).

Table 1: Demographic characteristics and baseline values of the outcome measures

Variables	Intervention Group (n=30) mean±SD	Placebo Group (n=30) mean±SD	p
Age	67.77±7.70	66.40±8.13	0.20
Sex (Female/Male)	24/6	22/8	0.00*
Height (cm)	162.77±9.28	163.50±10.04	0.00*
Weight (kg)	75.17±10.39	74.33±6.60	0.09
Duration of disease	9.43±4.48	9.37±6.31	0.00*
VAS at rest	5.40±1.00	5.00±1.01	0.00*
VAS on movement	7.50±1.13	7.37±0.61	0.00*
VAS pain at night	4.43±1.13	4.10±1.06	0.00*
WOMAC pain	10.46±3.00	10.60±3.14	0.00*
WOMAC stiffness	2.83±1.20	2.06±1.38	0.00*
WOMAC physical function	33.86±8.76	34.06±8.48	0.00*
WOMAC total	47.16±11.62	46.73±11.97	0.10
SF-36 physical function	51.00±20.56	41.67±26.50	0.00*
SF-36 role limitation (physical)	30.00±36.78	30.00±35.59	0.00*
SF-36 bodily pain	39.70±10.63	41.40±15.81	0.00*
SF-36 general health perceptions	54.03±17.23	48.93±21.73	0.00*
SF-36 vitality	53.17±17.83	52.83±22.54	0.00*
SF-36 social role function	51.32±17.42	53.75±21.81	0.00*
SF-36 role limitation (emotional)	55.57±49.79	57.78±48.68	0.00*
SF-36 mental health	63.60±14.93	59.07±21.04	0.00*
PSQI score	12.93±3.52	12.10±3.49	0.00*
DN4 score	6.87±1.13	6.03±1.56	0.00*
Knee ROM (active)	115.67±5.97	123.33±11.84	0.00*
Knee ROM (passive)	122.17±6.65	127.33±10.64	0.01*

*p<0.05, mean±SD; mean±standard deviation, VAS; visual analog scale, WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index, SF-36;Short-Form 36, PSQI; Pittsburgh sleep quality index, DN4; Douleur Neuropathique 4, ROM; range of motion

Table 2: Comparison of the outcome measures in both groups and between the groups for VAS and WOMAC scores

Variable	Intervention Group (n=30) mean ±SD	Placebo Group (n=30) mean ±SD	p value
VAS at Rest			
Before treatment	5.40±1.00	5.00±1.01	0.34
After treatment	3.90±0.71	3.77±1.00	
p value	0.00*	0.00*	
VAS on Movement			
Before treatment	7.50±1.13	7.37±0.61	0.14
After treatment	5.60±1.00	5.93±0.94	
p value	0.00*	0.00*	
VAS Pain at Night			
Before treatment	4.43±1.13	4.10±1.06	0.34
After treatment	2.57±0.89	2.80±0.96	
p value	0.00*	0.00*	
WOMAC Pain			
Before treatment	10.46±3.00	10.60±3.14	0.20
After treatment	7.53±2.80	8.53±3.14	
p value	0.00*	0.00*	
WOMAC Stiffness			
Before treatment	2.83±1.20	2.06±1.38	0.38
After treatment	1.33±1.02	1.16±1.28	
p value	0.00*	0.00*	
WOMAC Physical Function			
Before treatment	33.86±8.76	34.06±8.48	0.15
After treatment	24.46±8.43	127.80±7.86	
p value	0.00*	0.00*	
WOMAC Total			
Before treatment	47.16±11.62	46.73±11.97	0.23
After treatment	33.33±10.91	37.5±11.28	
p value	0.00*	0.00*	

*p<0.05, mean±SD; mean±standard deviation, VAS; visual analog scale, WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index

Table 3: Comparison of the outcome measures in both groups and between the groups for SF-36, PSQI and DN4 scores and knee ROM (active and passive) values

Variable	Intervention Group (n=30) mean ±SD	Placebo Group (n=30) mean ±SD	p value
SF-36 Physical Function			
Before treatment	51.00±20.56	41.67±26.50	0.01*
After treatment	67.50±9.07	52.17±22.50	
p value	0.00*	0.00*	
SF-36 Role Limitation (Physical)			
Before treatment	30.00±36.78	30.00±35.59	0.00*
After treatment	74.17±24.10	45.83±37.76	
p value	0.00*	0.01*	
SF-36 Bodily Pain			
Before treatment	39.70±10.63	41.40±15.81	0.00*
After treatment	56.00±6.61	47.90±8.58	
p value	0.00*	0.01	
SF-36 General Health Perceptions			
Before treatment	54.03±17.23	48.93±21.73	0.06
After treatment	65.87±6.21	59.80±12.02	
p value	0.00*	0.00*	
SF-36 Vitality			
Before treatment	53.17±17.83	52.83±22.54	0.02*
After treatment	71.17±8.97	62.83±14.30	
p value	0.00*	0.00*	
SF-36 Social Role Function			
Before treatment	51.32±17.42	53.75±21.81	0.05*
After treatment	68.55±14.43	62.53±14.68	
p value	0.00*	0.02*	
SF-36 Role Limitation (Emotional)			
Before treatment	55.57±49.79	57.78±48.68	0.00*
After treatment	98.90±6.02	80.02±35.65	
p value	0.00*	0.02*	
SF-36 Mental Health			
Before treatment	63.60±14.93	59.07±21.04	0.04*
After treatment	74.27±6.36	65.67±15.77	
p value	0.00*	0.03*	
PSQI Score			
Before treatment	12.93±3.52	12.10±3.49	0.04*
After treatment	7.27±3.01	9.27±3.29	
p value	0.00*	0.00*	
DN4 Score			
Before treatment	6.87±1.13	6.03±1.56	0.01*
After treatment	4.37±0.85	5.00±1.31	
p value	0.00*	0.00*	
Knee ROM (active)			
Before treatment	115.67±5.97	123.33±11.84	0.49
After treatment	135.00±7.65	133.00±9.96	
p value	0.00*	0.00*	
Knee ROM (passive)			
Before treatment	122.17±6.65	127.33±10.64	0.24
After treatment	138.83±6.78	136.33±8.50	
p value	0.00*	0.00*	

*p<0.05, mean±SD; mean±standard deviation, SF-36; short form- 36, PSQI; Pittsburgh sleep quality index, DN4; Douleur Neuropathique 4, ROM; range of motion

After the treatment, statistical differences in SF-36 physical function (p=0.01), SF-36 role limitation (physical) (p=0.00), SF-36 bodily pain (p=0.00), SF-36 vitality (p=0.02), SF-36 social role function (p=0.05), SF-36 role limitation (emotional) (p=0.00) and SF-36 mental health (p=0.04) scores; PSQI (p=0.04) and DN4 scores (p=0.01) were found between the groups (Table 2). There were no statistical difference in VAS at rest (p=0.34), VAS on movement (p=0.14), VAS pain at night (p=0,34), WOMAC pain (p=0.20), WOMAC stiffness (p=0,38),WOMAC physical function (p=0,15), WOMAC total scores (p=0,23) (Table 2) and SF-36 general health perceptions scores (p=0,06) and knee active and passive ROM (p=0,498 and 0,245 respectively) between the groups at the end of the treatment (Table 3).

Discussion

Osteoarthritis (OA) of the knee is the most common cause of knee pain and OA-related pain both neuropathic and nociceptive mechanisms may contribute to the OA pain experience [4-6]. Chronic nociceptor stimulation leads modification of central neurons; also neuropathic pain mechanism can occur from different mechanisms like a damage to a nerve innervating an affected joint [26]. While nerve damage is not a recognized feature of OA, there may be sub-clinical damage to small peripheral nerves innervating OA joints increased ectopic activity can occur and contribute to pain intensity [27,28]. Studies with some animal OA models have shown that nerves re-innervating damaged tissues had similar characteristics to that seen in nerve-injury models, including abnormal morphology and an excess of neuropeptides involved in pain transmission [28]. Comorbid pain conditions, psychological and cognitive factors, subclinical neuropathies may further alter central pain processing [26,29,30]. These factors can be missed if evaluation for neuropathic pain is not a part of the standard OA assessment.

In this study we aimed to determine the efficacy of warm whirlpool on pain, disability, quality of life (QoL) and sleep for patients with neuropathic pain. To the best of our knowledge this is the first study which evaluates the effectiveness of whirlpool for patients with neuropathic pain due to knee osteoarthritis.

Hydrotherapy is a superficial heating or cooling process and it is an external application of water to the body parts for therapeutic purposes [11]. Whirlpool treatment was first started by the French army at the First World War years. This treatment method is widely used for medical and surgical conditions [12]. Whirlpool treatment is especially useful to decrease muscle spasm and pain [11,14,15]. This therapy is also recommended as a treatment for reducing pain in patients with osteoarthritis [16]. Hydrostatic immersion combined with warm temperature provides recovery of the blood circulation [31]. Also with heat treatment; capillary permeability, nerve conduction and collagen elasticity increases through vasodilation [16]. Therefore in this research we used warm whirlpool at temperatures between 30.0°C and 40.0°C.

Whirlpool has been found useful for various pain syndromes. In a study with 41 subjects who have myofascial pain syndrome, the patients were randomly assigned into two groups: the whirlpool therapy group whose bodies were immersed in a whirlpool bath at 34°C-36°C for 30 minutes; the hydrocollator group who took a 30-minute application of a standard hot hydrocollator pack [32]. At the end of the study the improvement on pain and anxiety was significantly greater in the whirlpool group, compared to the hydrocollator group [32]. This result was explained by the gate theory; Due to the pressure and thermal temperature of hydrotherapy on the skin pain is relieved [33]. On the other hand thermal waters with temperatures above 34oC are considered to relax muscles, increase tendon extensibility; also dilate blood vessels and facilitate blood circulation. So a wash out of pain mediators and elevation of pain threshold occurs [34]. In a study by Devrimsel et al. [35] 60 patients with complex regional pain syndrome received whirlpool therapy and neuromuscular electrical stimulation for 15 sessions. At the end of the study authors concluded that both whirlpool bath and neuromuscular electrical stimulation were effective in the treatment of complex regional pain syndrome, but the efficacy of the whirlpool bath treatment was better. In a study with 58 women with symptomatic hand OA, patients were randomized into whirpool and parafin treatment groups and at the end of the study it was found that the improvement in pain,

hand functions and quality of life in the whirlpool group was significantly better [36]. In these studies the effect of whirlpool was explained by that whirlpool bath treatment improves regional perfusion, and nutrition; with this the oxygenation to the tissues increases and the skin softens. So as a result, pain and edema reduces and range of motion improves [37,38]. In a study the effects of a warm whirlpool bath on pain and stiffness of 44 patients with chronic stroke induced knee OA were evaluated and whirlpool was found beneficial for patients with chronic stroke induced knee OA [39]. After intervention the stiffness of the whirlpool group was found significantly lower than control group. The results in the studies mentioned above were consistent with our study. Also we determined significant improvement for pain intensity and disability measures at the end of treatment for both groups; as a power of our work we evaluated QoL, sleep and neuropathic pain components and found significant differences between the groups for pain, disability, QoL and neuropathic pain.

There are a number of high-quality studies have recently been published that examine the association between neuropathic pain and health-related quality of life [40]. QoL and sleep are frequently impaired in patients with neuropathic pain [40,41]. So the management of neuropathic pain gains importance regarding QoL. In our study we determined significant improvements at QoL for both groups but this improvement was more significant in whirlpool group and there were statistically significant difference QoL measures except SF-36 general health score. Based on these results of our study, we can conclude that whirlpool therapy can be used as an alternative therapy method in patients with neuropathic pain due to knee OA for improving QoL.

The treatment of neuropathic pain is important because disturbed sleep is common in neuropathic pain and effects on daytime functioning and quality of life of the patient [42]. In our study the improvements at sleep quality was more significant in whirlpool group. So we can conclude that whirlpool therapy is effective for improvement of sleep in patients with neuropathic pain due to knee OA.

In the literature it was mentioned that whirlpool therapy also increases joint ROM [43]. In a study by Kuligowski, et al. [43] 56 subjects with delayed-onset muscle soreness were randomized into cold whirlpool, warm whirlpool and contrast therapy and it was found that cold whirlpool and contrast therapy are more effective than warm whirlpool in terms of improving ROM. They concluded that this effect can be due the effect of cold by decreasing response of muscle spindles to stretch and increasing firing rates of Golgi tendon organs and so muscle relaxation occurs. We determined significant improvement for knee active and passive ROM at the end of treatment for both groups; but there were no statistical significant difference between the groups. This result can be due the use of only warm whirlpool in our study.

Whirlpool therapy is cheap, available and has little or no side effects mostly rather than pharmacotherapy and other modalities. So in people who have neuropathic pain due to knee OA, whirlpool can be an ideal treatment modality.

In this study we have some limitations. We evaluated the effects of only warm whirlpool, but not cold. Heat treatment also contributes the positive effects in a significant manner. It is known that blood flow, capillary permeability, nerve conduction and collagen extensibility increases through vasodilation as a result of heat treatment [16]. So to prove the effects of whirlpool clearly there should be studies with both warm and non-warm whirlpool groups. On the other hand, patients were evaluated only immediately after therapy, long term effects are unknown. So with long term follow up further studies should investigate the effects of both warm and cold whirlpool for neuropathic pain in knee OA.

Warm whirlpool provided significant improvements in pain, disability, QoL, sleep and neuropathic pain and can be used as an additional therapy method in the treatment of patients with neuropathic pain due to knee OA. We think that these effects were mediated by the increase on tendon extensibility, improvement on blood circulation and oxygenation; but further studies with larger samples are needed to better explain the effects of this therapy modality.

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Antimicrobial resistance pattern of Klebsiella spp isolated from patients in Tehran, Iran

İran, Tahran'daki hastalarda izole edilen Klebsiella suşunun antimikrobiyal direnç paterni

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Abstract

Aim: The majority of clinical specimens infected can be by Klebsiella species. Furthermore the incidence of drug resistant Klebsiella is increasing, therefore drug resistance sensitivity test it seems necessary before prescribing antibiotics. The aim of this research was to determine the pattern of antimicrobial resistance of Klebsiella species from clinical.

Methods: The present research was performed on 300 specimens of Klebsiella collected from hospitalized patients between 2016 and 2017. Identification was carried out according to standard procedure, and drug sensitivity test was determined by Kirby-Bauer method.

Results: The frequency rates of the isolated Klebsiella species were: pneumonia (94%), oxytoca (4%), ozaenae (1%), and rhinoscleromatis (1%). The collected samples in order of frequency were: urine, sputum, vagina, scar, stool, and blood respectively. The percentage rates of resistance were as follows: Ampicillin (97%), amoxycillin (97%), cephalothin (39%), gentamicin (30%), colistin (55%), nalidixic acid (2%), chloramphenicol (26%), kanamycin (17%), tetracycline (28%), nitrofurantoin (44%), ceftazidime (2%), and amikacin (0%).

Conclusion: The lowest resistance rate obtained with amikacin in all tested Klebsiella; which can be recommended as the most effective antibiotic.

Keywords: Klebsiella, Infection, Antibiotic resistance

Öz

Amaç: Klinik örneklerin çoğu Klebsiella türleri ile enfekte olabilmektedir. Ayrıca ilaca dirençli Klebsiella insidansı artmaktadır, bu nedenle antibiyotik reçete edilmeden önce ilaç direnci duyarlılık testi gerekli görünmektedir. Bu araştırmanın amacı Klebsiella türlerinin antimikrobiyal direncini klinik olarak belirlemektir.

Yöntemler: Bu araştırma, 2016 ve 2017 yılları arasında hastanede yatan hastalardan toplanan 300 Klebsiella örneği üzerinde gerçekleştirilmiştir. Tanımlama standart yönteme göre gerçekleştirilmiş ve ilaç duyarlılık testi Kirby-Bauer yöntemi ile belirlenmiştir.

Bulgular: İzole Klebsiella türlerinin sıklık oranları: pnömoni (% 94), oksitoka (% 4), ozaenae (% 1) ve rinososikromatis (% 1). Sıklık sırasına göre toplanan örnekler: idrar, balgam, vajina, skar, dışkı ve kan idi. Rezistans yüzdesi şöyledir: Ampisilin (%97), amoksilin (%97), cefalotin (%39), gentamisin (%30), kolistin (%55), nalidiksik asit (%2), kloramfenikol (%26), kanamisin (%17), tetrasiklin (%28), nitrofurantoin (%44), seftazidim (%2) ve amikasin (%0).

Sonuç: Test edilen Klebsiella türlerinde en düşük direnç oranı Amikasin ile elde edilmiştir ve en etkili antibiyotik olarak önerilebilir.

Anahtar kelimeler: Klebsiella, Enfeksiyon, Antibiyotik direnci

Introduction

During the past decade given importance to nosocomial infections caused by Staphylococcus aureus. These days, gram-negative bacilli also were under consideration [1-3]. One of the major problems of small hospitals and large hospital were the large epidemics by these bacteria in recent years.

The positive (VP) gram-negative bacteria including Klebsiella are normal flora of the intestine and are known as Saprophytic in the digestive and respiratory tract of human and healthy infants [4]. In recent years it has become clear that Klebsiella have caused many infections in different cases. The importance of this group of organisms to cause a serious infections in patients admitted to hospital are well understood [5,6]. The ability of this organism to cause disease due to decreased host defenses from long and complex surgeries, as well as. Consumption of different drugs is growing [7,8].

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In a study in China during 1996 to 2002 the susceptibility of Klebsiella to imipenem from 94% to 100% has been reported [9]. In another study the susceptibility of Klebsiella to imipenem of 100% was reported [10]. There have been several reports in development of resistance to imipenem in gram negative pathogens in recent years [11]. There are not much information in distribution and the source of these bacteria in hospital infection. The epidemiological studies of Klebsiella infections did not had much success due to variation of methods and distribution of these bacteria as well as lack of generalized methods in all laboratories, due to the large number of antisera and difficulty in its preparation. These methods are applicable only a few research laboratories and capsular swelling (Quellung reaction) test are used for typing Klebsiella. To determine the type and evaluation of drug resistance of these gram-negative organisms isolated from clinical specimens are important in identification of virulence factors [12]. The aim of this study was to determine antibiotic susceptibility patterns of Klebsiella spp from hospitalized patients in Imam Khomeini Hospital between 2016 and 2017.

Materials and methods

This was a descriptive study carried out in 2016 on 1200 clinical samples, including urine, blood, feces, wounds, sputum and vaginal secretions. All the samples cultured on Hektone agar medium and incubated at 37°C for 24 hours. The suspected yellow colonies were cultured on Simon citrate, urease, Triple Sugar Iron Agar (TSI), Lysine Iron Agar, arginine, ornithine, and Lysine decarboxylase as well as Voges-Proskauer and Methyl Red (MRVP) test. The drug sensitivity test was determined for all of the 12 antibiotics as follow, imipenem, amoxicillin, colistin, nalidixic acid, cephalothin, chloramphenicol, kanamycin, gentamycin, tetracycline, nitrofurantoin, amikacin, and ceftazidime using standards disk diffusion by Kirby-Bauer method [13].

Results

Out of 1200 tested samples 300 samples (25%) were infected with Klebsiella types. The order of frequency include: Klebsiella pneumoniae, Klebsiella oxytoca, Klebsiella ozonae and Klebsiella rhinoscleromatis table 1.

Table 1: Frequency distribution of Klebsiella spp

Species	No. of Isolate	Percentage
Klebsiella pneumoniae	282	94
Klebsiella oxytoca	12	4
Klebsiella ozonae	3	1
Klebsiella rhinoscleromatis	3	1

The number of Klebsiella spp isolated from urine the most followed by sputum, vagina, wounds, feces, and blood respectively table 2. The results showed that the most effective antibiotic in treatment of Klebsiella spp was Imipenem as it shown in table 3.

Table 2: Frequency distribution of Klebsiella spp from different clinical sources

Clinical sources	Number of isolate	Percentage
Urine	219	73
Sputum	42	14
Vagina	18	6
Wounds	12	4
Feces	6	2
Blood	3	1

Table 3: Number and percentage of antimicrobial resistances to tested antibiotics

Antibiotics	R	I	S	Resistance
Imipenem	6	0	298	2
Amoxicillin	291	6	3	97
Colistin	165	18	117	55
Nalidixic acid	6	6	288	2
Cephalothin	117	120	63	39
Chloramphenicol	78	33	189	26
Kanamycin	51	90	159	17
gentamicin	9	11	177	30
Tetracycline	84	87	153	44
Nitrofurantoin	132	15	46	46.88
Amikacin	0	3	297	0
Ceftazidime	6	4	291	2

R: Resistance, I: Intermediate, S: Sensitive

Discussion

The genus Klebsiella species had various species based on biochemical classification. Exact identification of Klebsiella is necessary for epidemiological research in order to find the source and way of spreading of this microorganisms, is very important [13]. There are many reports of nosocomial infection and drug resistance caused by Klebsiella species. But the relationship between different species of Klebsiella for their pathologic properties is still unknown [14-17]. In this study out of 300 strains of Klebsiella isolates, 282 strains were Klebsiella pneumonia isolated from different parts of bodies with different clinical symptoms. This means that they did not targeted specific organ and in different circumstances could create variable infections. In this study apart from Klebsiella pneumoniae we isolated 12 strains of Klebsiella oxytoca, 3 strains of Klebsiella ozonae, and 3 strains of Klebsiella rhinoscleromatis. This means apart from Klebsiella pneumoniae, other Klebsiella` species also could cause serious infectious diseases.

The results of the antibiotic susceptibility test to 12 antibiotics showed high resistance to some used antibiotics, except to imipenem, amikacin, ceftazidime and nalidixic acid. In general 99% of isolates were sensitive to amikacin followed by 98% to imipenem, ceftazidime and nalidixic acid. In study carried out by Pakestan [18] 57.5% were found susceptible to nalidixic acid and 92.5% to imipenem. Other researchers reported of 38% of isolate were resistance to amikacin, 57% to ceftazidime and 33.6% to nalidixic acid although 90.9% of their Klebsiella pneumoniae isolate were sensitive to imipenem. These results apart from imipenem were in contradiction with our results, this might be due to variation of strains in their environments [19]. Considering the high percentage of strains Klebsiella resistant to the amoxicillin, therefore to use of this antibiotic in treatment of Klebsiella infections is not only useless, also it might prolong the treatments and increase the resistance strains [20]. In the case of gentamicin, the majority of species were sensitive; these results correlate with other results of other research workers [12]. The results of this study showed relatively high resistance of isolated strains to colistin, tetracycline, chloramphenicol and nitrofurantoin, and these results are in correlation with other researches [9,16,21]. The results of this study and comparison with other reports might be differences in some cases. This might to an error during testing. Factors such as such as disc, type and depth of culture medium play a major role and can changes the results. The standard depth of medium is 4 mm; thin depth can increase the sensitivity of antibiotic.

Resistant strains may occur due to geographic regions, climatic conditions, overuse of antibiotics [4,13,22]. The lowest

resistance rate is obtained with amikacin in Klebsiella spp, therefore it can be recommended as the most effective antibiotic.

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Is it easy to remove the bar fitted with Nuss procedure?

Nuss prosedürü ile takılan barların çıkarılması kolay mıdır?

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Abstract

Aim: Minimally invasive repair for pectus excavatum (PE) has become a popular approach since 1998. Convex bar is place into the substernal position to leverage the deformity and left for approximately 24 to 36 months. We have noticed difficulties during some of these bars at removal. So we presented difficulties during the bar removal in this study.

Methods: The medical files of 39 patients who removal of the bars at our clinic between June 2011 and March 2017 were reviewed retrospectively. The medical files were reviewed retrospectively and 9 cases involving difficulty removed the bar were included in this study. Patients were evaluated in terms of gender, age, the bar duration time on the body, duration of hospital stay, morbidity and mortality.

Results: Mean patients age was 24.1 (range, smallest 19 and greatest 36) years. The overall mean duration of pectus bar maintenance was 35.5 (range, minimum 34 and maximum 38) months. While the mean duration of surgery was 50 minutes (range 38-52) in the non-difficulty group, the mean duration was 90 (range 74-110) minutes in the difficulty group. The causes of difficulties are mostly fibrosis, ossification and displacement of the intrathoracic region.

Conclusion: Careful attention and multidisciplinary work are important for the removal of bars attached due to PE. Emerging difficulties can be overcome with the experience gained over time.

Keywords: Pectus excavatum, Nuss procedure, Bar removal

Öz

Amaç: Pektus Ekskavatum (PE)'un minimal invaziv yöntemle onarımı 1998'den beri popüler hale gelmiştir. Deformiteyi kaldırmak için substernal alana konveks şekil verilmiş bar yerleştirilir ve yaklaşık 24-36 ay arası kalır. Bu barların bazılarının çıkarılması esnasında zorluklarla karşılaştık. Bu nedenle çalışmamızda karşılaştığımız zorlukları sunmak istedik.

Yöntemler: Haziran 2011 ile Mart 2017 tarihleri arasında kliniğimizde barları çıkarılan 39 hastanın verileri retrospektif olarak incelendi ve 9 hastada bar çıkarılması esnasında zorluk tespit edildi. Hastalar cinsiyet, yaş, barın vücutta kalma süresi, hastanede yatış süreleri, morbidite ve mortaliteleri açısından değerlendirildi.

Bulgular: Ortalama hasta yaşı 24,1 (en küçük 19, en büyük 36) idi. Pektus barların ortalama kalış süresi 35,5 (en kısa 34, en uzun 38) aydı. Zorluk olmayan grupta ortalama ameliyat süresi 50 dakika iken, zorluk olan grupta 90 dakika idi. Zorluk sebepleri sıklıkla fibrozis, ossifikasyon ve barın intratorasik bölgeye yer değiştirmesi idi.

Sonuç: PE nedeniyle takılan barların çıkarılmasında dikkatli ve multidisipliner yaklaşım önemlidir. Görülen zorluklar zamanla kazanılan deneyimle aşılabilir.

Anahtar kelimeler: Pektus ekskavatum, Nuss prosedürü, Bar çıkarılması

Introduction

Minimally invasive repair of Pectus excavatum has been announced to the whole world by Nuss the first time in 1998 [1,2]. This technique is very successful with the length of the incisions, blood loss, operating time, recovery time, and the length of hospital stay [3,4]. The minimally invasive technique uses incisions in the lateral thoracic wall. Convex bar is placed into the substernal position to leverage the deformity. Stabilizers are placed on the end of the bar to keep the chest wall in the normal position [1,5]. The bar is left in place for 24 to 36 months. To remove bars are used replace the previous lateral incision [1]. Although we encountered some difficulties about bar removal, we didn't find more knowledge about this topic in the literature. So we presented difficulties during the bar removal in this study.

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Materials and methods

After obtaining approval Ethics Committee of University (Letter no 2016-05/25), the medical files of 39 patients who removal of the bars at our clinic between June 2011 and March 2017 were reviewed retrospectively. The medical files were reviewed retrospectively and 9 cases involving difficulty removed the bar were included in this study. Demographic data and reasons for the difficulties are shown in table 1.

Patients were evaluated in terms of gender, age, the bar duration time on the body, duration of hospital stay, morbidity and mortality. Nuss procedure was done by video thoracoscopically with double lumen intubation. We generally use shortest possible bar to avoid excessive postoperative pain and ossification of the curved bar's tip. For the placement of the bar in all cases used 2 symmetric lateral thoracic incisions. A pocket was done in either the submuscular (SM) or a subcutaneous (SC) tissue for placement of the bar ends. While in the first made cases inserted into the subcutaneous pocket, subsequent cases submuscular pocket was preferred due to more aesthetically. We followed the Nuss depiction in similar shape except the two differences. Firstly we preferred to create a SM pocket, whereas Dr Nuss' initial technique using an SC pocket. Secondly we prefer smaller bars contrary to what is described in the Nuss technique. We have fixed the bar to the chest wall with stabilizers to prevent bar migration.

For bar removal, incisions were made along previous incision scars, and skin and subcutaneous tissue dissection was done to uncover both bar tips and the stabilizer. Initial cases, as a standard approach, we exposed the bar tips in left side, whereas in later cases, we exposed bilaterally and straightened both ends before removal. In all difficult cases, bilateral incisions were made. All bar removal was done by the same surgeon. Bar removal was performed via subcutaneous tissue dissection in all patients without intrathoracic imaging. While there was no significant bleeding during surgery, there was significant prolongation of the operation. Only one patient needs to be taken to surgery twice. All patients were discharged within 24 hours after surgery.

Results

Mean patients age was 24.1 (range 19-36) years. The overall mean duration of pectus bar maintenance was 35.5 (range 34-38) months. All patients who participated in this study were male and over 18 years of age. The minimum stay of the implanted bars was 34 months. No significant hemorrhage occurred during the removal of the bars. While the mean duration of surgery was 50 minutes (range 38-52) in the non-difficulty group, the mean duration was 90 minutes (range 74-110) in the difficulty group. When investigating the reasons of difficulties, the most causes were fibrosis, ossification and displacing to the intrathoracic site (Figure 1). There was difficulty in finding the bar and stabilizer after excessive weight gaining and bodybuilding practices in two patients. Among the 9 troublesome patients, 3 (33.3%) required to use fluoroscopy to find the bar tip. In one case, we needed to perform surgery twice, because at the first surgery, the bar tip was out of reachable distance due to severe ossification on the right site and considering that the stick might be fixed in the pericardium, the surgery was terminated in order not to cause any complications. The subsequent thorax CT scan revealed that there was no retrosternal ossification and the patient underwent a second surgery and the bar was removed using fluoroscopy. All patients were discharged 24 hours after surgery. No morbidity or mortality was seen.

Table 1: Demographic data and reasons for the difficulties

	Age	Gender	Length of stay of the bar (month)	Difficulty Reason	S	Attachment
1	27	Male	38	Migration to the intrathoracic site	+	Removed in second surgery
2	26	Male	36	Migration to the intrathoracic site + fibrosis	-	Not necessary
3	21	Male	34	Fibrosis	-	Not necessary
4	22	Male	36	Weight gain, muscle hypertrophy	-	Not necessary
5	22	Male	34	Migration to the intrathoracic site + fibrosis + ossification	-	Not necessary
6	36	Male	36	Weight gain, muscle hypertrophy	+	Not necessary
7	26	Male	36	Fibrosis + ossification	-	Not necessary
8	18	Male	34	Migration to the intrathoracic site + ossification	-	Not necessary
9	19	Male	36	Ossification	+	Not necessary

S: Scopy

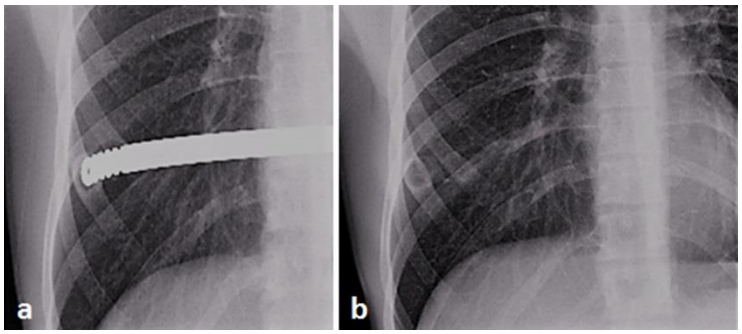

Figure 1: Image of the ossification on posteroanterior chest x-ray (a: preoperatif, b: postoperatif)

Discussion

The Nuss surgery which is performed for patients with pectus excavatum has been modified in time in order to improve the safety and cosmetic outcomes of the operation [6]. In the first described method by Nuss, SC tunnel for the molded bar tip was created. In the first Nuss operations of our clinic, SC tunnel was used, but later, SM tunnel was introduced due to better cosmetic outcomes. In Nuss surgery, a metal bar is placed under the sternum of the patients and the bar has to stay in the patient for at least 3 years [1,7]. This process usually coincides the rapid growth period and this might cause some unintentional effects. Some of these effects are fibrosis in the tissue around the bar, ossification of the fibrous tissue, displacement of the bar into the intrathoracic site and erosion on the ribs and/or the sternum [5].

These kinds of effects may lead to difficulties in removing the bars, as it was the case in our series of 9 cases.

When investigating the reasons of difficulty in removing the bars in the patients we included to this study, the most common reasons were fibrosis, ossification and displacing to the intrathoracic site (Table 1). In our cases with fibrosis, if ossification did not accompany, freeing was made through bilateral opening of the former incision without the need for scopy. Some authors suggest that a unilateral incision (site of the stabilizer) is sufficient for the bar removal and that the bar tip of the other site could be mobilized with a dissection on the incision site and flipper maneuvers [8]. In our clinic, previous approaches used unilateral incision in the first bar removal surgeries. However, in the case of severe fibrosis and ossification, there was difficulty in freeing the other site and considering that this would threaten the patient's life safety, we used bilateral incisions in our subsequent surgeries.

There are numerous publications in the literature suggesting that new bone development may occur around the implants due to trauma. In most cases, the implant is placed near the surface or the periost. This ossification is also an advantage in fixing the instrument [5,9]. While new bone development may be seen on the bar tips, some patients may develop a more aggressive ossification and ossification may also even be seen on the whole bar. This might also prevent the access to the bar [5]. In one case (No. 5) in our study, we could only reach the bar with scopy due to the density of the ossification (Figure 2). We established that patients whom we placed the bar SM developed a denser ossification.

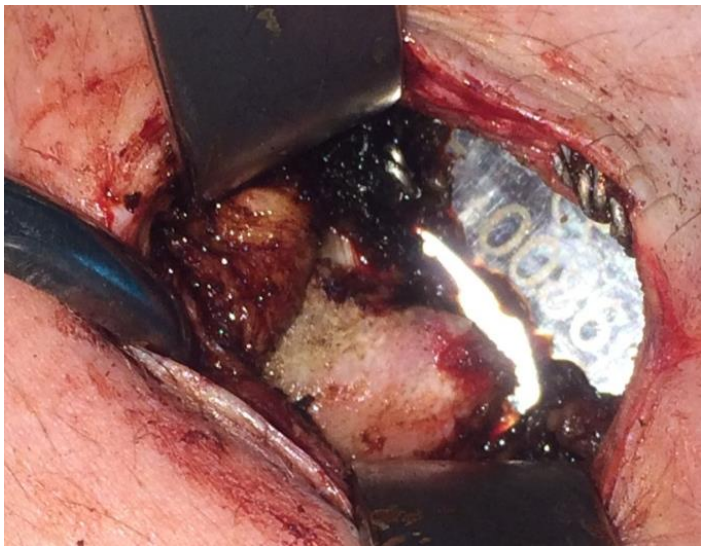

Figure 2: Intraoperation image of ossification

This ossification around the bar had a complicating affect in removing the bar; however, placing the bar carefully without damaging the fascia may decrease this ossification [5]. When there is suspect of ossification, a chest CT scan is indicated to assess the retrosternal ossification (that also may adhere on the pericardium) along the bar tract [10]. As so, we perform a thoracic CT scan to all patients that are suspicious of ossification in our clinic. Up to now, no retrosternal ossification was seen in any of our cases. Another common reason for difficulty during removal of the bar was the displacement of the bar tip or the stabilizer into the intrathoracic site. There are also some reports about the difficulty caused by the migration of the bar to the intrathoracic site [11-14]. After the bar has been placed over time, it can migrate to the intrathoracic area. Since the stabilizer is frequently placed on the left site, the migration to the intrathoracic site is more commonly seen on the right edge [10]. We required scopy in one patient (No. 1) who we had difficulty in removing the bar due to displacement to the intrathoracic site and the bar could only be removed two-staged. The other bars could be carefully dissected single-staged. Physical changes of the patient including weight gain, muscle hypertrophy, height increase rate may cause problems in bar removal. In our study group, there was difficulty in removing the bars in two (22.2%) cases due to excessive weight gain and body building. In one of these cases, the muscle hypertrophy was so severe that the bar could only be removed with scopy. We are in close contact with cardiac surgeons during bar removal procedures at our clinic. Plans are made together so they are prepared, if necessary. All of our preoperative patients were consulted since it is likely for unpredictive complications to occur during the process of bar removal by the nature of the Nuss procedure [15,16].

All together, these don't have a significant effect on pectus repairment; however, they may complicate the bar removal, leading to a requirement of a longer surgery duration. Emerging difficulties may be handled with multidisciplinary and experience achieved over time. Despite these types of complications, we consider that the Nuss procedure should be preferred as the most efficient and, according to patient satisfaction, the best surgery in patients with pectus excavatum.

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Review of 1078 tonsillectomy: Retrospective cohort study

1078 tonsillektominin gözden geçirilmesi: Retrospektif kohort çalışma

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Abstract

Aim: Tonsillectomy is one of the most frequently performed otolaryngologic surgical procedures. We represented our 5 years of experience in tonsillectomy and intended to compare our results with the current literature. We aimed to discuss our tonsillectomy outcomes, mainly giving emphasis on our post tonsillectomy infections and their possible relation with tonsillar pillar suturation, local anesthesia infiltration, comorbidities and presence of Actinomyces colonies in tonsil specimens.

Methods: This study was carried out retrospectively, in 1078 patients who underwent tonsillectomy operation in between December 2011 and December 2016. The demographic data of the patients, indications for tonsillectomy, suturation if applied, local anesthesia infiltration and its timing, histopathologic findings, co-morbid diseases, postoperative complications and re-hospitalizations were recorded. The association of suturation, infiltration of local anesthesia and it's timing (pre-incisional, post-dissectional), the histopathologic presentation of Actinomyces bacteria in tonsillar specimens and the presence of accompanying systemic disorders with post- tonsillectomy infections were statistically analyzed.

Results: Postoperative infection was seen in 5 (0.5%) patients. Among the suturation group, only 1 (0.5%) patient had infection (p=1). In the infection group 4 (80%) patients had post dissectional local anesthesia infiltration (p=0.574). None of the patients treated with preincisional local anesthesia infiltration, had postoperative infection (p=0.574). In 3 (0.3%) patients, Actinomyces was determined. None of these cases had post-tonsillectomy infections. 142 (13.2%) patients had various co-morbidities associated. Among them, 1 (0.7%) patient had postoperative infection (p=0.507).

Conclusion: According to our results, there is no statistically significant association between suturation of tonsillar pillars, local anesthesia infiltration, comorbidities and presence of Actinomyces and post tonsillectomy infections.

Keywords: Tonsillectomy, Tonsillectomy hemorrhage, Postoperative infection, Suturation, Local anesthesia, Actinomyces

Öz

Amaç: Tonsillektomi, en sık uygulanan otorinolaringolojik cerrahilerden biridir. Bu çalışmada, 5 yıllık tonsillektomi deneyimlerimiz sunulmuştur. Klinik sonuçlarımızın, güncel literatür ile karşılaştırılması; özellikle tonsillektomi sonrası gelişen enfeksiyonlar ile bu enfeksiyonların, tonsil pilika sütürasyonu, lokal anestezi uygulaması, komorbidite ve tonsil spesimenlerinde Aktinomiçes varlığı ile olan ilişkisi üzerinde durulması amaçlanmıştır.

Yöntemler: Aralık 2011 ve Aralık 2016 yılları arasında opere olmuş 1078 hasta retrospektif olarak değerlendirilmiştir. Hastaların demografik bilgileri, cerrahi endikasyonlar, tonsillar pilika sütürasyonu yapılan hastalar, lokal anestezi uygulandı ise zamanlaması, tonsil dokusunun histopatolojik değerlendirme sonuçları, eşlik eden sistemik patolojiler, post operatif komplikasyonlar ve rehospitalizasyon gereken durumlar belirlenmiştir. Tonsillektomi enfeksiyonları ile lokal anestezi uygulanması, sütürasyon, komorbid hastalıklar ve Aktinomiçes varlığı arasında ilişki araştırılmış, sonuçlar istatistiksel olarak değerlendirilmiştir.

Bulgular: Postoperatif enfeksiyon 5 (%0,5) hastada görülmüştür. Sütürasyon uygulanan 1 (%0,5) hastada enfeksiyon saptanmıştır (p=1). Enfeksiyon görülen 4 (%80) hastada disseksiyon sonrası lokal anestezi uygulanmıştır (p=0,574). İnsizyon öncesi lokal anestezi uygulanan hastaların hiçbirinde postoperatif enfeksiyon gelişmemiştir (p=0,574). Üç (%0,3) hastada Aktinomiçes saptanmıştır. Bu hastalarda tonsillektomi sonrası enfeksiyon gelişmemiştir. 142 (%13,2) hastada eşlik eden komorbiditeler mevcuttur. Bu grupta 1 (%0,7) hastada postoperatif enfeksiyon gelişmiştir (p=0,507).

Sonuç: Bulgularımıza göre, tonsillektomi sonrası enfeksiyonlar ile, tonsiller pilikaların sütürasyonu, lokal anestezi uygulanması, komobidite ve Actinomiçes varlığı arasında istatistiksel olarak anlamlı bir ilişki tespit edilmemiştir.

Anahtar kelimeler: Tonsillektomi, Tonsillektomi kanaması, Postoperatif enfeksiyon, Sütürasyon, Lokal anestezi, Actinomiçes

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Introduction

Tonsillectomy, with or without adenoidectomy is one of the most commonly performed surgical procedures, both in pediatric and adult patients. Cornelius Celsus performed the first dissection nearly 2000 years ago. Only in United States more than 530 000 procedures in childhood were reported in 2006 [1]. The most common indications for tonsillectomy are recurrent/chronical tonsil infections and sleep disordered breathing (SDB) [1,2].

Though it has been commonly performed for many years, complications are still encountered. The elective feature of the procedure and the surgical area in question, forces many scientists to search novel techniques, medications and devices to avoid the complications [3-5]. Besides giving the results of our 5 years' experience in tonsillectomy, we also aimed to investigate in detail, the post tonsillectomy infections (poorly mentioned in the literature so far) in our cohort and outline their relation with major factors, such as suturation of tonsillar pillars, local anesthesia infiltration, presence of Actinomyces in tonsil specimens and systemic co-morbidities.

Materials and methods

This research was designed as a retrospective cohort study. It was carried out in 1086 patients, who underwent tonsillectomy operation in our hospital between December 2011 and December 2016. This study was approved by the Institutional Review Board (Project no: KA17/117). The demographic data of the patients, indications for tonsillectomy, suturation if applied, local anesthesia infiltration and its timing, histopathologic findings, co-morbid diseases, postoperative complications and re-hospitalizations were recorded.

Patients with insufficient medical records, presence of malignancies in any site of the body, all the surgical techniques except conventional cold knife, patients over 70 years and hemorrhage in other surgical sites were excluded from the study. As a result 1078 patients were enrolled.

The association of suturation, infiltration of local anesthesia and it's timing (pre-incisional, post-dissectional), the histopathologic presentation of Actinomyces bacteria in tonsillar specimens and the presence of accompanying systemic disorders with post- tonsillectomy infections were statistically analyzed.

Statistical analysis

Statistical evaluation was performed with SPSS 22.0 (IBM Corporation, Armonk, New York, United States.) The relevance of the data's normal distribution was analyzed with Shapiro-Wilk test. The variance homogeneity was analyzed with Levene's test. The comparison of independent two groups according to quantitative data was achieved by Independent-Sample T test in accordance with Bootstrap results. Categorical variables were compared with Pearson Chi-Square and Fisher Exact tests using Monte Carlo Simulation technique. Quantitative variables were shown with ± standard deviation and median range (maximum-minimum). Categorical variables were shown as n (%). Variables were analyzed with 95% accuracy and p values less than 0.05 were considered as statistically significant.

Results

Among the patients, 628 (58.3%) were male, 450 (41.7%) were female. 925 (85.8%) patients were <18 years, 153 (14.2%) were >18 years (Table 1, 2). The primary indication for surgery was chronic/recurrent tonsillitis in 683 (53.6%), obstruction of the upper airway in 394 (36.5%) and spontaneous tonsillar hemorrhage in one (0.1%) patient. 235 (21.8%) cases undergone solely tonsillectomy, 599 (55.6%) patients had tonsillectomy and adenoidectomy (TA), 227 (21.1%) patients had tonsillectomy, adenoidectomy and ventilation tube application (TAT), 17 (1.6%) patients had tonsillectomy and ventilation tube application (TT).

Table 1: Age and sex distribution in the study group

Age	Mean±SD	Max	Min	p	<18 n (%)	18≤ n (%)	p
Female	10.09±10.57	59.0	2.0	0.156	380 (41.1)	70 (45.8)	0.289
Male	9.20±9.74	70.0	2.0		545 (58.9)	83 (54.2)	
Total	9.57±10.10	70.0	2.0		925 (100.0)	153 (100.0)	

Independent T test, Pearson Chi-Square Test, SD: Standard Deviation

Table 2: Demographic data of the participants

	n	%
Sex		
Female	450	41.7%
Male	628	58.3%
Age		
<18	925	85.8%
18≤	153	14.2%
Indication for surgery		
Chronic/recurrent infection	683	63.4%
Sleep disordered breathing	394	36.5%
Tonsillar hemorrhage	1	0.1%
Hemorrhage		
None	1054	97.8%
Present	24	2.2%
Infection		
None	1073	99.5%
Present	5	.5%
Suturation		
None	874	81.1%
Present	204	18.9%
Local anesthesia infiltration		
None	313	29.1%
Preincisional	141	13.1%
Post dissectional	623	57.8%
Co-morbidity		
None	930	86.3%
Present	148	13.7%
Surgical procedure		
Tonsillectomy	235	21.8%
Tonsillectomy + Adenoidectomy	599	55.6%
Tonsillectomy + Adenoidectomy + V Tube application	227	21.1%
Tonsillectomy +V Tube application	17	1.6%
	Mean±SD.	Median (Max.-Min.)
Day of onset of hemorrhage	4.9±2.99	6 (10-0)

SD: Standard Deviation

Hemorrhage was observed in 24 (2.2%) patients. Twenty two (91.6%) of them had secondary hemorrhage. Five (20.8%) patients underwent secondary surgery due to hemorrhage. Postoperative infection was seen in 5 (0.5%) patients. Pneumonia in one, acute lymphadenitis in one, acute bronchitis in one, Varicella Zoster infection in one, and non-specific upper respiratory system infection (URSI) in one patient was noted.

Re-hospitalization due to complications was recorded in 23 (2.1%) patients. Twenty patients (86.9%) were re-hospitalized due to hemorrhage. Among the patients with post tonsillectomy infections, one patient (4.34%) with acute lymphadenitis was re-hospitalized for 6 days. One patient (4.34%) was re-hospitalized due to dehydration, and another patient (4.34%) due to pain and poor oral uptake.

In 874 (81.1%) patients, tonsillar pillar suturation was not performed, while in 204 (18.9%) patients suturation was done. Among them, 199 (97.5%) patients did not have postoperative hemorrhage (p=0.793) (Table 3). Only one (0.5%) patient had infection (p=1) (Table 4).

Table 3: The hemorrhage rates compared as regards to suturation and local anesthesia infiltration

	Hemorrhage						
	Absent			Present			p
	n	Row n %	Column n %	n	Row n %	Column n %	
Suturation							
Absent	855	97.8%	81.1%	19	2.2%	79.2%	0.793
Present	199	97.5%	18.9%	5	2.5%	20.8%	
Local anesthesia							
None	311	99.4%	29.5%	2	0.6%	8.7%	0.075
Preincisional	138	97.9%	13.1%	3	2.1%	13.0%	
Post dissectional	605	97.1%	57.4%	18	2.9%	78.3%	

Pearson Chi-Square Test, Fisher Exact Test

To 313 (29.1%) patients, local anesthesia was not applied. Of the patients having local anesthesia infiltration, 141 (13.1%) had preincisional, 623 (%57.8) had post dissectional infiltration. Among the infection group 4 (80%) patients had post dissectional local anesthesia infiltration (p=0.574). One patient had pneumonia, one patient had acute lymphadenitis, one patient had acute bronchitis and one patient had non-specific URSI. None of the patients treated with preincisional local anesthesia infiltration, had postoperative infection (p=0.574) (Table 3). In non-infiltration group, only one (0.3%) patient had postoperative infection (Table 4).

Table 4: Infection rates and their relation with local anesthesia and suturation

	Infection						
	Absent			Present			p
	n	Row N %	Column N %	n	Row N %	Column N %	
Local anesthesia							
None	312	99.7%	29.1%	1	0.3%	20.0%	0.574
Preincisional	141	100.0%	13.2%	0	0.0%	0.0%	
Post dissectional	619	99.4%	57.7%	4	0.6%	80.0%	
Suturation							
Absent	870	99.5%	81.1%	4	0.5%	80.0%	1
Present	203	99.5%	18.9%	1	0.5%	20.0%	

Pearson Chi-Square Test, Fisher Exact Test

According to the histopathological evaluations, 1068 (99.3%) patients had chronic inflammation of the tonsil specimens. In three (0.3%) patients, Actinomyces was histopathologically determined. Two (0.2%) had chronic active inflammation characterized by erosion and cyrptitis, one (0.1%) had granulomatous inflammation, one (0.1%) had non-caseating granulomatous inflammation and one (0.1%) of them had foreign body reaction of tonsil specimens.

Cases with positive Actinomyces, did not have post tonsillectomy infections, however results were statistically insignificant. Of the study group, 142 (13.2%) patients had various co-morbidities. The most commonly encountered pathologies were asthma and hearth diseases (congenital and acquired hearth diseases) (Table 5). Among the cases with co-morbidities, postoperative infection was seen in 1 (0.7%) patient (p=0.507). He was a four years old boy with asthma who had acute non-specific URSI and required inpatient treatment (Table 6).

Four of the patients with post tonsillectomy infections had only 1 independent variable (they were treated only by local anesthesia, or suturation, and they don't have co-morbidities). Only one patient, a 4 years old male child, had two variables, including local anesthesia infiltration and asthma.

Table 5: The incidence of systemic co-morbidities

Systemic Disease	n	%	Systemic Disease	n	%
Absent	930	86.8%	Epilepsy, asthma	1	0.1%
Asthma	22	2.1%	Factor 7 deficiency. epilepsy	1	0.1%
Epilepsy	9	0.8%	Factor 7 &12 deficiency	1	0.1%
Down Syndrome	7	0.7%	FMF carrier	1	0.1%
PFAPA	7	0.7%	G6PD deficiency	1	0.1%
Hypothyroidism	5	0.5%	Goldenhar Syndrome	1	0.1%
VSD	5	0.5%	Hodgkin Lymphoma	1	0.1%
Hypertension	4	0.4%	Hepatitis B infection	1	0.1%
Operated VSD	4	0.4%	Hepatitis C infection	1	0.1%
ASD	3	0.3%	Hypercholesterolemia	1	0.1%
Liver Transplantation	3	0.3%	Hyperthyroidism	1	0.1%
Autism	3	0.3%	Hypertrophic Cardiomyopathy	1	0.1%
Diabetes Mellitus	2	0.2%	Idiopathic thrombocytopenic purpura (ITP)	1	0.1%
Factor 5 & 8 deficiency	2	0.2%	Cardiac failure	1	0.1%
Tetralogy of Fallot	2	0.2%	Congenital hypothyroidism	1	0.1%
FMF	2	0.2%	Men 1 Syndrome	1	0.1%
Renal Transplantation	2	0.2%	Mental Retardation	1	0.1%
Cerebral Palsy (CP)	2	0.2%	Mucopolysaccharidosis	1	0.1%
ADEM	1	0.1%	Mitral valve prolapses (MVP)	1	0.1%
Aortic stenosis	1	0.1%	MVP. Mitral valve insufficiency (MVI)	1	0.1%
Acute rheumatoid fever (ARF)	1	0.1%	MVI	1	0.1%
ARF, MVI, MVP	1	0.1%	Myocarditis (twice)	1	0.1%
ARF.MVI	1	0.1%	Nephrectomy, Pacemaker application. Hypertension	1	0.1%
Transposition of great arteries (TGA)	1	0.1%	Nephrotic syndrome	1	0.1%
ASD, Pulmonary hypertension	1	0.1%	Obesity	1	0.1%
ASD,VSD	2	0.2%	Operated chronic otitis media (tympanoplasty)	1	0.1%
Asthma. Graves Syndrome	1	0.1%	Autism. epilepsy	1	0.1%
Asthma, Hypertension	1	0.1%	Ovarian Carcinoma, Hypothyroidism	1	0.1%
Asthma. Renal Pelvic obstruction (RPO)	1	0.1%	Patent foramen ovale (PFO)	1	0.1%
Asthma, epilepsy	1	0.1%	Allergy	1	0.1%
Atrial valve insufficiency (AVI)	1	0,1%	Situs in versus	1	0.1%
CP, epilepsy	1	0.1%	Systemic Lupus Erythematosus (SLE)	1	0.1%
Depression	1	0.1%	Thalassemia carrier	1	0.1%
Di George Syndrome	1	0.1%	TGA. Mitral - tricuspid valve insufficiency	1	0.1%
Down Syndrome, AVSD	2	0.2%	TGA. AVSD	1	0.1%
Down Syndrome, Hypothyroidism	1	0.1%	Tourette Syndrome	1	0.1%
Cleft lip-palate repair	1	0.1%	Pulmonary stenosis	1	0.1%

Table 6: The statistical analysis of the relation between co-morbidity and postoperative infection

	Systemic Diseases						p
	Absent			Present			
	n	Row N %	Column N %	n	Row N %	Column N %	
Infection							
None	932	86.9%	99.6%	141	13.1%	99.3%	0.507
Present	4	80%	0.4%	1	20%	0.7%	

Fisher Exact Test

Discussion

There was a male predominance in our study group which is consistent with the literature [6]. Similarly, the most common indications for tonsillectomy were chronic recurrent infections and upper airway obstruction causing SDB [2]. Seshamani and colleagues [3] observed 3.56% and 6.17% of hemorrhage rates within 7 and 14 days respectively. However in pediatric cases it ranges between 0.1% and 3.3%. Hemorrhage rate in this study was 2.2%, lower than Seshamani's reports.

Tonsillectomy is implemented under general anesthesia using endotracheal intubation. It is initiated with a mucosal incision overlying anterior tonsillar pillar and blunt dissection is hold along the tonsillar fossae in the peri-tonsillar plane, excising the tonsils with their capsules. Hemostasis is achieved by pressure packing, suture ligations, electrocautery devices and suturation of pillars. Consequently -if suturation of the pillars is

not performed-, an open wound is produced which exposes the tonsillar fossae to the oropharyngeal area. Following the injury, the tissue robustness and integrity should be constituted promptly in order to re-establish homeostatic mechanisms, prevent infection and minimize fluid loss [4]. Acute wound healing is composed of 4 phases known as hemostasis, inflammation, cellular proliferation and remodeling [4-5]. Following the surgery open tonsillar fossae is quickly covered with inflammatory mediators which initiate the proliferative phase 3-4 days after wound injury, leading to extracellular matrix (ECM) and granulation tissue formation. ECM, which is a scaffold for cellular adhesions and, migration is constituted by fibroblastic proliferation. Angiogenesis is crucial for reconstructing the new blood vessels to supply oxygen, blood constituents and nutrients to restore normoxia and promote fibroplasia [4]. After the formation, ECM undergoes a remodeling process and reaches a stable state 21 days after surgery. Any intervening factor disrupting this process may cause improper wound healing and infection.

Tonsillectomy is performed in a surgical field which is colonized by both saprophytic and pathogenic bacteria; hence it is associated with a risk of both local and systemic complications [5]. Local complications (1% of postoperative morbidity) are commonly related to surgical wound infections, whilst systemic complications which correspond to 0.2% of postoperative morbidity are associated with pneumonia, meningitis, sepsis etc. Precisely, our postoperative infection rate was 0.5%, and, in all cases systemic infections (pneumonia, bronchitis, URSI, Varicella Zoster infection and lymphadenitis) were observed.

The most commonly performed technique in our clinic is ‘gold standard’ cold knife tonsillectomy. Electrocautery is commonly preferred for hemostasis if necessary. According to Sinha et al. [6], steel scalpel has few disadvantages; 1) lack of hemostasis, undesired blood loss, 2) indistinct tissue planes, 3) increased operative time, 4) use of foreign material (ligature) in the wound causing infection risk, 5) possibility of accidental injury to the operative personnel, leading to intraoperative transmission of blood-borne diseases, 6) potential for tumor metastasis via lymphatic channels. Thus novel techniques have been investigated since the beginning of 20th century. However these techniques were analyzed especially for postoperative hemorrhage and pain. Infections are still a matter of debate. Additionally, electrocautery is also commonly associated with thermal tissue injury causing improper healing [6-10].

If suturation is preferred, the posterior tonsillar pillar is laid over the tonsillar fossa and clinched to the anterior tonsillar mucosa with 4-5/0 absorbable sutures. Genç et al. [11] reported in their randomized single blinded study, that the edema in the suturation side was significantly higher, but they found no correlation with suturation and deteriorated wound healing or development of infection. However they found a significant pain control after 3 days of the surgery. To reduce the risk of surgical site infections, small rather than large, suture bites are recommended. It is also suggested that the use of sutures with antimicrobial coating reduces the incidence of surgical site infections [12]. We, similarly, found no significant relation between suturation and post tonsillectomy infections in this current study.

Perioperative local anesthesia is a relatively new attempt to avoid postoperative pain and hemorrhage. In our clinic many surgeons prefer a preincisional local anesthesia infiltration, however only one senior surgeon applies a post dissectional infiltration, in order to avoid the masking effect of the vasoconstructing agent on the potential hemorrhagic loci. The local anesthetic agent of choice was a mixture of 2cc Jetocaine® (Adeka, Istanbul, Turkey) and 2cc Marcaine® (AstraZeneca, Istanbul, Turkey) buffered in a 4 cc physiologic saline for the surgeon performing post-dissectional infiltration; while 2cc Jetocaine® buffered in 2 cc physiologic saline was prefered by the rest of the surgeons in the clinic, who were performing pre-incisional infiltrations. Local anesthesia was introduced submucosally into upper, middle and lower parts of the anterior pillars, and into the middle and inferior parts of the posterior tonsillar pillars. Jetocaine® includes lidocaine and 1:100.000 epinephrine, while Marcaine® includes bupivacaine as the local anesthetic agent. Both agents are commonly preferred [13-15]. However a study by Ozkırıs et al. [16] suggested that there was no significant difference in postoperative hemorrhage rates of bupivacaine and lidocaine, but bupivacaine had significantly higher postoperative analgesia scores.

Numerous studies have been conducted so far, regarding the pain control effect of local anesthesia in tonsillectomy. Naja et al. reported significantly increased rates of pain control, oral uptake, jaw opening, surgeon and parent satisfaction following preincisional local anesthesia infiltration, compared to the controls [13].

Grainger J et al. [14] outlined the use of local anesthesia in post-tonsillectomy pain control. They also suggested that the use of topical local anesthetics have similar level of analgesia, and provides a safer method.

Adverse effects of local anesthesia in post tonsillectomy period was previously outlined in the literature, that, it can be associated with Horner’s syndrome, facial nerve paralysis, atlanto-axial subluxation or osteomyelitis [14,17,18].

Fradis et al. [19] reported a case with deep cervical abscess following the infiltration of the tonsillar bed with bupivacaine in 1998. They suggested that the bupivacaine infiltration contributed to the penetration of bacteria in the tonsillar fossae through the deeper neck planes, leading to deep cervical abscess. According to our results, in 4 of the 5 patients with post tonsillectomy infections, post- dissectional local anesthesia infiltrations were performed.

Allareddy and colleagues [20] studied 141.599 hospitalized tonsillectomy patients and reported that comorbidity was an important independent predictor of complications in their cohort. There are several factors, known to increase surgical site infections (SSI) are, obesity, smoking, diabetes, chronic obstructive pulmonary disease (COPD) and immunodeficiency [12,21].

Thyroid hormone deficiency cause, derangements in cardiovascular, pulmonary, renal and central nervous system functions, and alters drug metabolism and predispose to surgical complications. Ekmektzoglu et al. [22] concluded in their report that both Diabetes Mellitus and hypothyroidism have negative impact on wound healing.

In this current study, the most commonly seen pathologies were asthma, congenital or acquired hearth diseases, epilepsy and Down syndrome. However, we observed post-tonsillectomy infection in only one patient with co-morbidities.

Actinomyces are slow growing, gram positive non-acid fast, anaerobic, filamentous commensal bacteria. It has been histologically observed in tonsillar specimens since 1896. There is a great variability in the literature regarding the rates of Actinomyces detected in tonsillar tissues. The occurrence rate differs between 1.3% and 37% [23]. It seems to be related to the features of the study groups and differences in histopathological evaluation. This bacterium is commonly associated with tonsillar hypertrophy, and it is believed to be a saprophyte of the normal tonsil. They became invasive when they gain access to the subcutaneous tissue, through a mucosal lesion [24]. We found no correlation between postoperative infections and the presence of Actinomyces in tonsillar tissue. Results were insignificant due to very low prevalence of this bacterium in this cohort.

The limitations of this study were primarily due to its retrospective nature. It was observed that the infection rates were higher in the post dissectional local anesthesia infiltration group, however the results were insignificant. Our results were insufficient to hypothesize any pathogenetic mechanisms. Also there were no statistically significant contributions of systemic pathologies and the presence of Actinomyces in tonsil specimens in the development of post tonsillectomy infections.

In conclusion, tonsillectomy infections can be troublesome and worth investigating. In this study we presented our tonsillectomy outcomes; however we found no significant relation between post tonsillectomy infections and suturation, local anesthesia infiltration, positive Actinomyces in tonsillar tissue and co-morbidities. Further investigations are essential.

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The role of lactate clearance on deciding discharge in exacerbation of chronic obstructive pulmonary disease: Retrospective cohort study

Kronik obstruktif akciğer hastalığı alevlenmesinde taburculuk kararı verilmesinde laktat klirensinin rolü: Retrospektif kohort çalışma

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Abstract

Aim: Patients presenting with chronic obstructive pulmonary disease (COPD) exacerbation in crowded emergency departments are often discharged with symptomatic treatment. This situation increases the number of patients admitted to the hospital and the number of attacks. It is very important to be able to predict hospitalization with cheap and easy blood parameters to be looked at the time of application. In our study, we aimed to investigate the relationship between lactate Clearance and admission or discharge decision in patients presenting with acute exacerbation of COPD.

Methods: In this study, patients over 18 years old who were admitted to Batman Regional State Hospital Emergency Department with COPD attack between January 1, 2014 and January 1, 2018 were retrospectively studied. The patients were divided into 2 groups. Group 1 included the patients who discharged after treatment in emergency, group 2 included the patients who hospitalized. Both groups were compared in terms of lactate clearance values.

Results: We studied 117 patients who met the criteria for inclusion in the study. Of these, 65 were discharged and 52 were hospitalized. Six of the hospitalized patients were hospitalized in the intensive care unit. Forty-one patients were female and 76 were male. We did not find any difference between the first and last lactate values of patients who were admitted and discharged (p=0.345 and 0.829). However, the lactate clearances of the discharged patients were higher, while the lactate clearances of patients with hospitalization indications were lower (p<0.001).

Conclusion: We think that lactate clearance can be used as a marker in patients presenting emergency services with COPD exacerbation without deciding on discharge or admission.

Keywords: Chronic obstructive pulmonary disease, Lactate clearance, Prediction

Öz

Amaç: Kalabalık acil servislerde kronik obstruktif akciğer hastalığı (KOAH) alevlenmesi ile başvuran hastalar sıklıkla semptomatik tedavi ile taburcu edilmektedir. Bu durum hastaların hastaneye başvuru ve atak sayısını arttırmaktadır. Başvuru anında bakılacak ucuz ve kolay kan parametreleri ile yatış öngörüsü yapabilmek oldukça önemlidir. Bizde çalışmamızda, acil servise KOAH akut alevlenmesi ile başvuran hastalarda, yatış veya taburculuk kararı verilmesi ile laktat klirensi arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Bu çalışmada, 1 Ocak 2014 ile 1 Ocak 2018 tarihleri arasında Batman Bölge Devlet Hastanesi Acil Servisi'ne KOAH atak nedeniyle başvuran 18 yaş üstü hastalar retrospektif olarak incelendi. Hastalar 2 gruba ayrıldı. Grup 1, acil olarak tedaviden sonra taburcu olan hastaları, grup 2'yi hastaneye yatırılan hastaları kapsamaktadır. Her iki grup laktat klirens değerleri açısından karşılaştırıldı.

Bulgular: Çalışmaya 117 hasta dahil edildi. Bunlardan 65'i taburcu olurken; 52'si hastaneye yatırıldı. Hastanede yatan hastalardan 6'sı yoğun bakım ünitesine yatırıldı. Hastaların 41'i kadın, 76'sı erkek idi. Başvuran ve taburcu edilen hastaların ilk ve son laktat değerleri arasında bir fark bulamadık (p=0,345 ve 0,829). Bununla birlikte, taburcu olan hastaların laktat açıklıkları daha yüksek iken, hastaneye yatırılan hastaların laktat klirensi daha düşük bulundu (p<0,001).

Sonuç: KOAH atak nedeni ile acil servise başvuran hastalarda taburculuk veya yatış kararı vermede, laktat klirensinin, bir belirteç olarak kullanılabileceğini düşünmekteyiz.

Anahtar kelimeler: Kronik obstruktif akciğer hastalığı, Laktat klirensi, Ön görmek

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Introduction

Chronic obstructive pulmonary disease (COPD); is a preventable and treatable disease state characterized by complete non-reversible airflow restriction [1]. COPD is an important and increasing cause of morbidity and mortality worldwide [2]. According to the World Health Organization, COPD is the fourth most common cause of death worldwide and is predicted to be the third most common cause in 2020 [3]. Ministry of Health Global Burden of Disease (Global Burden of Study) using the method in the study aims to estimate the causes of death in Turkey, cause of death among the most common COPD 's been reported to be the third cause of death [4,5].

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COPD exacerbations are defined as an acute deterioration of respiratory symptoms, resulting in the need for additional treatment of stabilized periodic treatments. Exacerbations; are important events that should be considered in the management of COPD treatment because the health status of patients, re-admission and hospitalization rates to the hospital, and therefore the progression of the disease, are adversely affected [6,7]. Indications for admission to hospital during COPD exacerbations Exacerbation of dyspnea at rest, increase in respiratory rate, low oxygen saturation, confusion and drowsiness, acute respiratory insufficiency, lack of response to medical treatment, presence of serious comorbidities (egg heart failure, newly developed arrhythmia etc.) such as medical care [8].

The lactate in the human body is produced by the reduction of pyruvate by the lactate dehydrogenase enzyme [9,10]. In the normal physiological state, the reaction does not support the formation of lactate, which only accounts for one-tenth of the total pyruvate metabolism [11]. However, in critical situations such as hypo perfusion and hypoxia, pyruvate accumulates rapidly and shifts to lactate production, the metabolic anaerobic pathway [12,13]. As a result, intracellular lactate begins to multiply and pass into the bloodstream [14]. The single lactate level measured in the application is thought to be a marker of organ dysfunction and mortality. However, a single measurement of lactate may exhibit static variability. In order to be more clinically useful, it is necessary to define the relationship between lactate clearance (LK) and clinical outcome, which is a measure of the change in lactate levels during treatment [14]. There are studies showing that there is a relationship between high lactate clearance and high survival in sepsis and septic shock patients admitted to emergency services [15,16].

Patients presenting with COPD exacerbation in crowded emergency departments are often discharged with symptomatic treatment. This situation increases the number of patients admitted to the hospital and the number of attacks. It is very important to be able to predict hospitalization with cheap and easy blood parameters to be looked at time of application. In our study, we aimed to investigate the relationship between lactate clearance and admission or discharge decision in patients presenting with acute exacerbation of COPD.

Materials and methods

This retrospective cohort study was conducted on patients over 18 years old who were admitted to Batman Regional State Hospital Emergency Department with COPD attack between January 1, 2014 and January 1, 2018. This study includes patients who were admitted emergency service with exacerbation of COPD and have at least 2 blood gases at 6 hour intervals and older 18 years. Ethical approval was taken from a local ethic committee. Patients' age, gender, O_2 saturation, respiratory rate, blood pressure, fever, pulse and blood gas values at the time of admission and arterial blood gas values measured after 6 hours were recorded. The patients were divided into 2 groups. Group 1 included the patients who discharged after treatment in emergency, group 2 included the patients who hospitalized. Patients who did not have at least 2 arterial blood gases at 6 hour intervals, those younger than 18 years, those with acute hepatic insufficiency, and those who could not obtain information from the hospital automation system were excluded from the study. We compared the lactate clearance values of two groups in our study and investigate the place of lactate clearance giving discharge decision.

Lactate Clearance is calculated as explained; LC = Lactate Measured in Emergency Service Addition - Lactate Measured at 6^{th} hour x 100 / Lactate Measured in Emergency Service Addition. A negative result indicates an increase in lactate value relative to the reference after 6 hours, while the positive result of the addition indicates lactate reduction or clearance.

Statistical analysis

Univariate statistical analyzes were performed using Chi-Square test for categorical variables, Wilcoxon T test for dependent variables. T-test was used for comparison of descriptive variables with normal distribution and Mann-Whitney U without normal distribution. Numerical variables were given as n (%), mean (SD) and median (Inter quartile range (IQR) 25-75). P <0.05 was considered statistically significant.

Results

We studied 117 patients who met the criteria for inclusion in the study. Of these, 65 were discharged and 52 were hospitalized. Six of the hospitalized patients were hospitalized in the intensive care unit. 41 of the patients were female and 76 were male. Patients who were hospitalized and discharged were comparable in terms of demographic characteristics and vital findings and did not show any statistically significant difference between the groups (Table 1). In total, 78 (66%) of the patients who applied were smoking.

Table 1: Demographic features and vital findings

	All patients (n=117)	Group 1 (n=52)	Group 2 (n=65)	p
Age (years) mean±SD	66±10	67±10	66±10	0.324
Gender				
Female n (%)	41 (35)	18 (35)	22 (34)	0.421
Male n (%)	76 (65)	34 (65)	43 (66)	
	median (IQR)	median (IQR)	median (IQR)	
Body temperature (° C)	36.5 (36.3-36.9)	36.5 (36.3-36.9)	36.7 (36.4-37.0)	0.892
Heart rate (beats / min)	106 (101-116)	110 (102-118)	104 (98-112)	0.125
Systolic blood pressure (mmHg)	136 (126-152)	132 (122-148)	143(133-156)	0.257
Oxygen saturation (% SaO2)	91(84-94)	87(82-93)	90(84-95)	0.823
Respiration rate (/ min)	28(21-35)	31(23-38)	27(20-34)	0.645

SD: Standard deviation, IQR: Inter quartile range

When we examined according to the time of admission, the most frequent emergency services were seen in the winter (n=79, 67%) and autumn (n=42, 35%) seasons. The most common complaints of the patients were dyspnea (86%) followed by chest pain. In total, no lung graphs were taken in 5 of the cases that were not studied. Pneumonic infiltration was present in 11 of 112 cases with chest X-ray. In total, 83 (71%) of the patients had a history of hospitalization.

Patients who were hospitalized and discharged compared blood gas parameters at the time of admission to the hospital with blood gas parameters taken at least 3 hours later. We did not statistically distinguish between the blood gas parameters taken at the time of application. We found a significant elevation in the CO_2 values of the blood gas parameters taken after at least 3 hours (p=0.035) (Table 2).

Table 2: Blood gas parameters of patients at the time of application and after 6 hours

Blood gas parameters		All patients (n=117)	Group 1 (n=52) median (IQR)	Group 2 (n=65) median (IQR)	p
admission	pO2 (mmHg)	67.6 (63.6-71.8)	63.2 (60.4-66.1)	69.4 (65.4-73.0)	0.679
	pCO2 (mmHg)	41.5 (37.8-46.7)	42.5 (37.3-47.2)	39.6 (34.2-43.8)	0.195
	pH	7.37 (7.13-7.51)	7.37 (7.12-7.50)	7.37 (7.13-7.52)	0.521
6th hour	pO2 (mmHg)	76.4 (74.2-80.8)	73.5 (70.9-77.3)	81.4 (77.9-85.6)	0.129
	pCO2 (mmHg)	40.7 (36.1-45.2)	44.5 (40.3-48.2)	38.6 (34.3-43.2)	0.035
	pH	7.39 (7.19-7.53)	7.38 (7.18-7.51)	7.41 (7.20-7.58)	0.201

IQR: Inter quartile range

We compared the lactate levels in the first and second blood gases of patients who were admitted and discharged. We did not find any statistically significant difference between the first and last lactate values of patients who were admitted and discharged (p=0.345 and 0.829). However, we found a statistically significant difference between the two groups in terms of lactate clearances. The lactate clearances of the discharged patients were higher whereas the lactate clearances of the patients who were hospitalized were found to be lower (p<0.001) (Table 3).

Table 3: Lactate and lactate clearance values at the time of application and after 6 hours

	Group 1 (n=52) median (IQR)	Group 2 (n=65) median (IQR)	p
First blood gas - lactate value (mg/dL)	12 (9-15)	15 (12-17)	0.621
Second blood gas - lactate value (mg/dL)	13 (10-17)	11 (9-13)	0.21
Lactate clearances	–10.6%	%15.3	<0.001

IQR: Inter quartile range

Discussion

In our study, the rate of lactate values (lactate clearances) in the first and last arterial blood gases was investigated in the emergency department of patients who applied with COPD exacerbation. According to this, it was determined that the clearances of the patients discharged within the 6-hour follow-up period were higher.

The GOLD guidelines in 2017 aimed to set a standard in COPD patient management, but nevertheless made it difficult for physicians to provide a standard [6], since the protocols applied indicated that the protocol would vary by patient, hospital and country. For this reason, we think that it would be useful to have easy and cheap parameters in the decision of hospitalization of patients with COPD in hospitals with crowded emergency services such as our country.

In disease states with hypo perfusion and hypoxia, pyruvate accumulates rapidly and its metabolism shifts to lactate production, and lactate increases and then passes into the bloodstream [12]. There are studies showing that tissue hypoxia increases blood lactate level [17]. Accordingly, it can be predicted that COPD exacerbations requiring hospitalization will not be able to clear the lactate canal due to prolonged tissue hypoxia. Lactate level measurement is thought to be a strong indicator of organ dysfunction and mortality.

However, lactate is a static variant. Therefore, in order for lactate measurement to be clinically useful, it is necessary to identify the lactate clearance to be measured during treatment and its relation to the clinical outcome. In previous studies, lactate clearance was found to be associated with all-cause mortality in various critical patient groups, such as sepsis followed in emergency care or intensive care units [14].

In our study lactate and lactate levels measured at 6th hour and lactate clearance of patients were calculated. There was a statistically significant difference between the lactate clearances and the first measured and second measured lactate values between the patient groups who were admitted and discharged by looking at these values. In our study group, lactate clearance was calculated as 15.3% in the patient group and -10.6% in the inpatient group and statistical difference was found between them. In other words, the negative lactate clearance that we found in the hospitalized group indicates to us that lactate cannot be cleaned after treatment.

This study has some limitations. Our study is not multicenter and the size of the sample is limited. There is a need for prospective study on this issue. We cannot reach all information about the patients due to our crowded emergency service the patient files aren't recorded. And also the comorbid disease may be affected the lactate clearance value.

In conclusion, we found that lactate clearance may be useful in patients with COPD exacerbation at deciding on discharge or admission.

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Resistance patterns of gram negative bacteria in urinary tract infections and efficacy of empirical treatment in noncomplicated cases: Retrospective cohort study of 2180 women

Üriner sistem enfeksiyonlarında gram negatif bakterilerin direnç paternleri ve komplike olmayan hastalarda ampirik tedavinin uygunluğu: 2180 kadın hastada retrospektif kohort çalışma

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Abstract

Aim: Community and hospital acquired urinary tract infections (UTI) are the most common bacterial infections in all age groups. In this study, the women diagnosed UTI, which complicated and uncomplicated, were referred to outpatient clinics between 2011 and 2015 were selected. The suitability of empirical antimicrobial therapy prescribed with resistance patterns of Gram negative bacteria isolated from these patients was investigated.

Methods: UTI complaining and urine culture $\geq 10^5$ cfu / ml of bacteria that women aged 18-65 were comprised the study group. HIS (Hospital Information System Software) was scanned for these patients and uncomplicated and complicated UTI distinction was made according to the criteria set by Infectious Diseases Society of America (IDSA, 2016). Of the 2180 patients studied, 836 were complicated and 896 were noncomplicated. Identification of Gram negative isolates in urine culture; Conventional methods and Matrix-Assisted Laser Desorption and Ionization Time-Of-Flight Mass Spectrometry (MALDI-TOF MS), (Biotyper, Bruker, Germany) systems were used. The antimicrobial susceptibilities of the isolated strains from 2011 to 2014 were determined according to the Clinical Laboratory Standards Institute (CLSI) and the isolated strains in 2015 were determined according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Results: The distribution of 2180 female patients (18 to 65 years old) was urology polyclinic (68%), family medicine, infectious disease and physical medicine and rehabilitation polyclinics (19.1%), and emergency medicine polyclinic (12.6%). E. coli (84%), K. pneumonia / oxytoca (7%) and Enterobacter spp (2.6%) were the most frequently detected agents in the uncomplicated UTIs, while complicated UTI E. coli (91%), K. pneumonia / oxytoca (5.7%) and P. aeruginosa (1%) were found to be the first, second and third in the patients. Quinolones were prescribed 18.2%, phosphomycin 16.7%, nitrofurantoin 15.6%, nitrofurantoin and phosphomycin combined 16.3%, second generation oral cephalosporins 9.6% and third generation oral cephalosporins 10.7%. Resistance to quinolones, the most commonly prescribed antibiotic, was found in 19% of E. coli, 21% of Klebsiella spp., 13% of Enterobacter spp. and 9% of Proteus spp.

Conclusion: When these prescriptions were compared with the results of antimicrobial susceptibility, it was observed that 38 (14%) were incompatible with the sensitivity results. It was found that 42% of cefuroxime prescriptions, 28% of quinolone prescriptions and 17% of ceftriaxone prescriptions were incompatible with the antibiogram results.

Keywords: Urinary tract infections, Antimicrobial resistance, Empirical therapy, Escherichia coli, Klebsiella spp

Öz

Amaç: Toplum ve hastane kaynaklı üriner sistem enfeksiyonları (ÜSE), tüm yaş gruplarında en sık karşılaşılan bakteriyel enfeksiyonlardır. Bu çalışmada 2011-2015 yılları arasında polikliniklere ÜSE şikayetiyle başvuran hastalardan izole edilen Gram negatif bakterilerin direnç paternleri ile bu hastalara reçetelenen ampirik antimikrobiyal tedavinin uygunluğunun araştırıldı.

Yöntemler: ÜSE şikayetiyle başvuran ve idrar kültüründe $\geq 10^5$ kob/ml bakteri üremesi olan 18-65 yaş arası kadın hastalar çalışma grubunu oluşturdu. HBYS (Hastane Bilgi Yazılım Sistemi)'nden bu hastaların dosyası taranarak Infectious Diseases Society of America (IDSA, 2016) tarafından belirlenen kriterler doğrultusunda komplike olmayan ve komplike ÜSE ayrımları yapıldı. Buna göre 2180 hastanın 836'sı komplike ÜSE tanısı alırken, 896'sının nonkomplike ÜSE tanısı aldığı tespit edildi. İdrar kültüründe izole edilen Gram negatif izolatların identifikasyonu; konvansiyonel yöntemler ve Matrix-Assisted Laser Desorption and İonization Time-Of-Flight Mass Spectrometry (MALDI-TOF MS), (Biotyper, Bruker, Almanya) sistemleri ile yapıldı. İzole edilen suşların antimikrobiyal duyarlılıkları 2011-2014 yılları için Clinical Laboratory Standards Institute (CLSI), 2015 yılı için ise The European Committee on Antimicrobial Susceptibility Testing (EUCAST) önerilerine göre belirlendi.

Bulgular: ÜSE şikayetiyle çalışmaya alınan 18-65 yaş arası 2180 kadın hastanın poliklinik dağılımı; %68 Üroloji, %19,1 Aile Hekimliği pol., Enfeksiyon pol ve Fizik Tedavi ve Rehabilitasyon pol. ve %12,6 Acil pol. idi. Komplike olmayan ÜSE'lerde 1., 2. ve 3. sırada en çok tespit edilen etken sırasıyla E. coli (%84), K. pneumoni/oxytoca (%7) ve Enterobacter spp (%2,6) iken, komplike ÜSE'li hastalarda 1., 2. ve 3. sırada E. coli (%91), K. pneumoni/oxytoca (%5,7) ve P. aeruginosa (%1) tespit edildi. Hastalara reçete edilen antimikrobiyallere bakıldığında; kinolonların %18,2 oranında, fosfomisin %16,7, nitrofurantoin %15,6, nitrofurantoin ve fosfomisin kombine olarak %16,3 oranında, 2. kuşak oral sefalosporinlerin %9,6 ve 3. kuşak oral sefalosporinlerin ise %10,7 oranında reçetelendiği saptandı. Ayaktan tedavi edilen hastalara en sık reçete edilen antibiyotik olan kinolonlara direnç, E.coli'de %19, Klebsiella spp.'de %21, Enterobacter spp.'de %13, Proteus spp.'de %9 olarak bulundu.

Sonuç: Bu reçetelerin antimikrobiyal duyarlılık sonuçları ile uyumuna bakıldığında ise, 38 (%14)'inin duyarlılık sonuçları ile uyumsuz olduğu gözlendi. Sefuroksim reçetelerinin %42, kinolon reçetelerinin %28, seftriakson reçetelerinin ise %17 oranında antibiyogram sonucu ile uyumsuz olduğu saptandı.

Anahtar kelimeler: Üriner sistem enfeksiyonu, Antimikrobiyal direnç, Ampirik tedavi, Escherichia coli, Klebsiella spp

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Introduction

Urinary tract infections are the most common bacterial infections in our country as well as all over the world [1]. It has been reported that every year, eight million people visit emergency services or outpatient clinics with the symptoms of urinary tract infection (UTI) in the United States, and that 100,000 of them have been hospitalized [2]. In our country also about 5 million cystitis cases have been reported every year [3]. Uncomplicated UTIs are the most important reason for the use of antibiotics under outpatient conditions. The use of unnecessary and inappropriate antibiotics is gradually increasing the prevalence of antibiotic-resistant uropathogens. Therefore, it is very important to choose an appropriate antibiotic in the empirical treatment of UTIs. Determining an effective treatment with systematic follow-up of the antibiotic resistance status according to regions is important in terms of preventing the development of bacterial resistance and time loss [4,5]. During the selection of empirical treatment, patient's antibiotic use and/or hospitalization history within the last 6 months should also be taken into consideration by questioning.

The aim of this study was to investigate the resistance patterns of Gram negative bacteria isolated from patients by analyzing the patients, who were admitted to policlinics with the complaints of UTI and received the pre-diagnosis of complicated and uncomplicated UTI, and to investigate the suitability of the empirical antimicrobial therapy prescribed for patients with uncomplicated UTI.

Materials and methods

Acute uncomplicated UTI is often categorized in women by Infectious Diseases Society of America (IDSA, 2016) and European Society for Microbiology and Infectious Diseases (ESCMID) as they are frequently seen in women. Therefore this study group included women between the ages of 18-65 who were admitted to polyclinics of our hospital between 2011 and 2015 and diagnosed with UTI. The files of these patients were scanned retrospectively from HBYS (Hospital Information Software System). The distinction between complicated and uncomplicated UTI was carried out according to the criteria set by the Infectious Diseases Society of America (IDSA, 2016). According to that, symptoms as frequent urination without fever, dysuria, and sensation of urinary urgency were defined as uncomplicated UTI. Fever, history of hospital visit with the complaints of UTI, functional or structural urinary system anomalies, catheterization, kidney and ureter stones, malignancy, transplantation, chronic renal disease, benign prostatic hypertrophy, hydronephrosis, neurogenic bladder, presence of double J catheter, chronic heart failure, diabetes, immunosuppression status, use of antibiotics in the last three months, and hospitalization history due to any cause in the last year were considered as the criteria of complicated UTI. Demographic information, risk factors, the polyclinic admitted, the cause of infection identified as a result of urinary culture, antibiotic susceptibility results of causative microorganism, and empirically initiated antibiotics of patients were recorded.

In Microbiology Laboratory of our hospital, the urine samples are incubated with 10 µl volumes in sheep blood and EMB agar media for 18-24 hours at 37 °C; all isolates that grow by counts of ≥105 cfu/ml at the end of this time are considered to be significant bacteriuria. Urine cultures identified to have a Gram negative growth of ≥105 cfu/ml were included in the study. Identification of isolates was carried out using conventional techniques and MALDI-TOF MS (Biotyper, Bruker, Germany) system.

Antimicrobial susceptibilities of isolated Gram negative bacteria were studied using the disc diffusion technique according to the recommendations of the Clinical Laboratory Standards Institute (CLSI) for 2011-2014 and according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for 2015; identification of ESBL was studied using combined disc synergy technique.

Statistical analysis

SPSS 23 (SPSS Inc. Chicago, IL, USA) program was used to analyze the data. The chi-square test was used to investigate the relationship between the changes in antimicrobial resistance over years and patient groups.

Results

It was found that there were 2180 female patients between the ages of 18-65 years who received a pre-diagnosis of UTI after admitting to polyclinics of our hospital between 2011 and 2015. Sixty-eight percent of the patients were admitted to Urology and 12.6% to Emergency Polyclinic, whereas 19% of them were admitted to different policlinics such as Family Medicine, Infectious Diseases and Clinical Microbiology and Physical Therapy and Rehabilitation. It was found that 836 of 2180 patients, who were included in the study according to the determined criteria, received the diagnosis of complicated UTI and 896 of them received the diagnosis of uncomplicated UTI.

The most common complicating factor was found to be a history of kidney/ureter stones (n:261, 31%), hydronephrosis and malignancy (n:188, 22%) in the case of complicated UTI . These were followed by a history of diabetes and hypertension (n: 96, 11%), neuromuscular dysfunction of bladder (n: 71, 9%) and a history of pregnancy (n: 51, 6%), respectively. There was a history of antibiotic use and hospitalization in 21% of patients (n:169).

The determinants of UTI in uncomplicated cases were E. coli (84%), K. pneumonia/oxytoca (7%), Enterobacter spp (2.6%), Proteus spp (2.4%), P. aeuginosa (2.2%), C. freundii (0.8%) and Salmonella spp (0.2%). In complicated UTI, the determinants were isolated to be E. coli (91%), K. pneumonia/oxytoca (5.7%), Enterobacter spp (0.5%), Proteus spp. (0.3%), P. aeuginosa (1%) and C. freundi (0.1%).

During this period, E. coli has been found to have ranked first as a determinant of complicated and uncomplicated UTI with n (%) values of 768 (91%) and 756 (84%), respectively. While K. pneumonia/oxytoca found to have ranked second in both groups with n values of 47 (5.7%) and 62 (7%), respectively, Enterobacter spp. ranked third in uncomplicated patients with n value of 24 (2.6%), and P. aeruginosa ranked third in complicated patients with n value of 8 (1%).

Considering the most common 5 microorganisms, ampicillin (AMP) (55%) was observed to have the highest resistance rate in both groups of patients in the case of E. coli,

whereas Trimetoprim-Sulfomethoxazole resistance (SXT) was 44%, ciprofloxacin (CIP) resistance was 27%, ceftriaxone (CRO) resistance was 20%, Extended Spectrum Betalactamase (ESBL) resistance was 9%, Nitrofurantoine (NT) resistance was 5% and Piperacillin Tazobactam (TPZ) resistance was 6%. Imipenem (IMP) 0%, phosfomycin (FF) 1% and amikacin (AK) 2% were found to have the lowest resistance rates (Table 1).

Table 1: Changes in the antimicrobial resistance of *E. coli* strains isolated from complicated and uncomplicated UTI's over the years

	2011 UC-C n(%)-n(%)	2012 UC-C n(%)-n(%)	2013 UC-C n(%)-n(%)	2014 UC-C n(%)-n(%)	2015 UC-C n(%)-n(%)
AMP	61(46)-84(61)	80(44)-187(65)	118(50)- 100(58)	28 (49)-25(51)	89 (58)-73(60)
SAM	15(11)-40(29)	24(13)-57(20)	46 (26)-53(30)	13 (23)-17(32)	32(21)-39(33)
AMC	8(6)-33(24)	19(11)-69(24)	39(7)-43(25)	11(19)-12(25)	31(20)-36(30)
GN	15(11)-26(18)	10(6)-47(16)	17(8)-31(28)	5(9)-9(18)	21(13)-22(18)
LEV	26(19)-38(28)	29(16)-99(34)	36(16)-58(34)	10(18)-18(36)	29(18)-42(35)
CIP	28(21)-42(30)	33(18)-107(37)	40(17)-61(36)	11(19)-19(38)	30(20)-40(34)
NOR	30(23)-41(31)	33(18)-110(38)	41(18)-63(37)	12(21)- 19(38)	28(18)-3(36)
AK	3(2)-5(4)	3(2)-10(4)	3(1)-6(4)	0-1(2)	0-4(3)
FF	0-4(3)	1(0.5)-0	1(0.4)-3(2)	0-1(2)	0-6(6)
NT	20(2)-10(7)	8(3)-8(3)	5(2)-11(6)	0-4(8)	4(2)-10(8)
CRO	24(18)-29(21)	27(16)-60(20)	44(19)-32(19)	12(21)-12(24)	27(18)-35(29)
SXT	50(38)-65(47)	67(37)-171(58)	93(40)-84(49)	20(35)-22(45)	46(30)-48(40)
TPZ	2(2)-13(10)	3(2)-21(7)	16(7)-13(8)	3(5)-3(6)	10(7)
IMP	0	0	0	0	0-0
ESBL	8(6)-8(7)	10(6)-19(7)	23(10)-17(10)	6(11)-6(12)	17(11)-18(15)

UC: Uncomplicated, C: Complicated, AMP: Ampicillin, SAM: Ampicillin-Sulbactam, AMC: Amoxicillin clavulanic acid, GN: Gentamicin, LEV: Levofloxacin, CIP: Ciprofloxacin, NOR: Norfloxacin, AK: Amikacin, FF: Phosphomycin, NT: nitrofurantoine, CRO: Ceftriaxone, SXT: Trimetoprim-Sulfomethoxazole TPZ: Piperacillin-Tazobactam, IMP: Imipenem ESBL: Extended Spectrum Betalactamase *The figures after the conviction are rounded

In the case of Klebsiella spp., AMP resistance was 92%, SXT resistance was 43%, CIP resistance was 19%, NT resistance was 21%, CRO resistance was 22%, TPZ resistance was 15% and AK resistance was 4% (Table 2). 21% of the strains were found to have ESBL.

Table 2: The antimicrobial resistance of K. pneumonia / oxytoca strains isolated from complicated and noncomplicated UTI's over the years

	2011 UC-C n(%)-n(%)	2012 UC-C n(%)-n(%)	2013 UC-C n(%)-n(%)	2014 UC-C n(%)-n(%)	2015 UC-C n(%)-n(%)
AMP	7 (87)-4(80)	9 (80)-12(100)	16 (80)-15(100)	5(100)-7(100)	13 (72)-12(100)
SAM	1 (13)-2(40)	3 (27)-3(33)	5 (25)-5(33)	1 (20)-2(28)	3 (17)-5(41)
AMC	1 (13)-2(40)	2 (18)-4(44)	5 (25)-4(26)	1 (20)-3(42)	6 (33)- 5(41)
GN	0 -0	1 (9) -1(11)	3 (15)-2(13)	0 -1(14)	2 (11)-2(16)
CIP	2 (25)-1(20)	2 (18)- 1(11)	4 (20)-2(13)	1 (20)	4 (22)- 2(16)
AK	0 -0	0-0	1 (5)-1(6.6)	0 -0	1 (5.5)-1(8)
NT	0 - 3(60)	1 (9)- 4(44)	2 (10)-5(33)	0 (0)- 1(14)	2 (11)-5(41)
CRO	1 (13)-1(20)	2 (18)-2(22)	4 (20)-3(20)	1 (20)-2(28)	4 (22)-4(33)
SXT	3 (37)-2(40)	5 (45)-5(55)	9 (45)-9(60)	2 (40)-4(57)	4 (22)-4(33)
TPZ	1 (13)-1(20)	2 (18)- 2(22)	1 (20)- 2(13)	1 (20)-2(28)	1 (5.5)-3(25)
ESBL	1 (12)- 1(20)	2 (18)- 2(22)	4 (20)-3(20)	1 (20)-2(28)	4 (22)- 3(25)

UC: Uncomplicated, C: Complicated, AMP: Ampicillin, SAM: Ampicillin-Sulbactam, AMC: Amoxicillin clavulanic acid, GN: Gentamicin, CIP: Ciprofloxacin, AK: Amikacin, NT: Nitrofurantoine, CRO: Ceftriaxone , SXT: Trimetoprim-Sulfomethoxazole TPZ: Piperacillin-Tazobactam, ESBL: Extended Spectrum Betalactamase, *The figures after the conviction are rounded

In the cases of Enterobacter spp. and P. aeruginosa, the resistance rates were found to be 14% and 25 % of CIP resistance, 21% and 25 % of Gentamycin (GN) resistance, 0% and 13% of AK resistance, 10% and 13% of TPZ resistance, respectively.

While an increase has been observed in STX and AK resistance of E.coli, which is a determinant of complicated and uncomplicated UTI, a partial increase has been observed in NT, CRO, TPZ resistance and ESBL rates (Table 1). A statistically significant correlation was found between the resistance increases of TPZ, AMC and NT antibiotics when the resistance correlation between the same antibiotics was investigated in E. coli strains isolated from uncomplicated UTIs according to years ($p<0.05$). When the correlation between antibiotic resistances of E. coli strains isolated from complicated UTI was investigated according to years, a statistically significant increase was identified in Sulbactam-ampicillin (SAM), FF and ESBL resistance, whereas a statistically significant decrease in SXT resistance ($p<0.05$).

While the prevalence of quinolone (LEV, CIP and NOR) resistance in patients with uncomplicated UTI decreased between 2011 and 2013, it displayed an increase between 2014 and 2015. While in patients with complicated UTIs, it increased between 2011 and 2014, a decrease was observed in 2015. The antimicrobial resistance rates of patients with complicated UTI were significantly higher than those with uncomplicated UTI ($p<0.05$).

Over the years, an increase was observed in NT, CRO, TPZ and GSBL resistance rates in the case of uncomplicated UTI with K. pneumonia/oxytoca determinant, and in AK, GN, CRO, TPZ, CIP and ESBL resistance rates in the case of complicated UTI. However, no statistically significant difference was found ($p>0.05$). The antibiotics to which Enterobacter spp was most resistant were found to be AMP (100%) and SAM (100%), whereas the antibiotics to which it is most susceptible were found to be AK, FF and NT in both groups. While no carbapenem resistance was observed in Pseudomonas spp, the highest resistance was observed in GN (25%), CIP (25%) and TIM (25%).

The prescriptions of 269 patients, for whom an empirical treatment was initiated, were reached. It was found that quinolones (18.2%), phosphomicine (16.7%), nitrofurantoin (15.6%), the combined use of nitrofurantane and phosphomycin (16.3%), 2nd generation oral cephalosporins (9.6%) and 3rd generation oral cephalosporins (10.7%) have been prescribed before urine culture (Figure 1). It was observed that 38 (14%) of these prescriptions were incompatible with the susceptibility results (Table 3). Forty-two percent of cefuroxime prescriptions, 28% of fluoroquinolone prescriptions and 17% of ceftriaxone prescriptions were resistant according to antibiogram results. When these prescriptions were analyzed, it was observed that only 4 (10%) of them were changed according to the antimicrobial susceptibility result, and that most of the prescription changes were made in FF and NT patients.

Table 3: Resistance rates according to culture results of empirically given antimicrobials in patients with uncomplicated UTI between 2011 and 2015

Empirical Prescription Antimicrobials	n(%)
Quinolone	14(28)
Phosphomycine	1(2.2)
Nitrofurantoine	2(6.6)
Cefuroxime	11(42)
Ceftriaxone	5(17.2)
Nitrofurantoine and Phoshomycine	0(0)
Ampicillin-Sulbactam and Amoxicillin clavulanic acid	5(15)

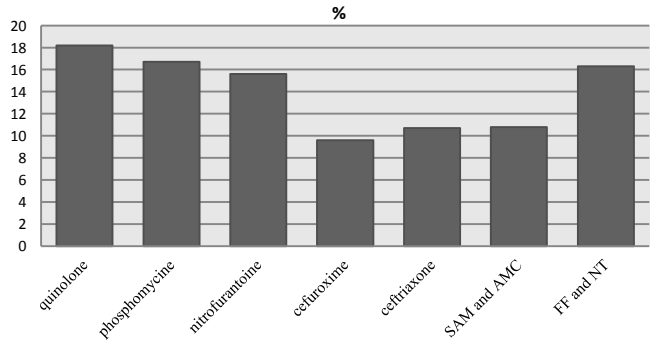

Figure 1: Percent distribution of empirically prescribed antimicrobials in patients with uncomplicated UTI

Discussion

It is mostly recommended that empirical treatment of uncomplicated UTI should be initiated because the diagnosis of UTI can usually be made based on the patient's symptoms and complete urinalysis [6]. First recommended medications according to various guidelines in the empirical treatment of uncomplicated UTI include nitrofurantoin and phosphomycin, alternatively quinolone and in cases where the resistance rate is below 20% trimethoprim/sulfamethoxazole (TMP-SXT) [6,7]. As in many studies conducted in our country, E. coli ranked first and Klebsiella spp. ranked second in the cases of complicated and uncomplicated UTIs [8,9].

When studies on antimicrobials prescribed in empirical treatments of UTIs were analyzed, it seemed that 77% quinolones, 10% TMP-SXT, 2% NT and 9% FF have been prescribed [10]. TMP-SXT (25.8%) is the most commonly prescribed medication for the empirical treatment of UTIs in Israel, followed by quinolones (22.8%) and nitrofurantoin (14.7%) [11]. In Germany, TMP-SXT (60%) and quinolones (21%) are the most commonly prescribed medications. Due to their high resistance rates, ampicillin is no longer found in empirical prescriptions.

Despite the resistance problem, perhaps because of the ease of oral use, TMP-SXT and quinolones still appear to be at the top on empirical prescriptions in several countries [12]. In our country, TMP-SXT resistance varies from 20% to 60% for E. coli strains isolated from community-acquired urinary tract infections (Table 4) [8,9,13-16]. Because of the high TMP-SXT resistance, it seems that TMP-SXT has not been included in the prescriptions arranged by our polyclinics in accordance with the recommendations of guidelines. In our study, TMP-SXT resistance was also found to be quite high in E. coli. However, there was a significant decrease in the resistance of TMP-SXT over the years in both groups, especially more evidently in patients with complicated UTI ($p<0.05$). This can be explained by the fact that TMP-SXT is not included in prescriptions arranged empirically.

Table 4: Antibiotic resistance rates of *E. coli* strains detected in uncomplicated UTI in studies conducted in Turkey (%).

	Province	Year	AMC	CRO	GN	AMP	AK	FEP	CIP	SXT	NT
Gözüküçük et al [13]	Istanbul	2012	36.6	19.2	10.2	63.7	1.1	6.4	19.8	40	12.4
Gül et al [8]	Kırıkkale	2014	182	3	-	-	-	-	18.2	21.2	-
DurmuşG et al [14]	Edirne	2009	11.1	10	0	60	0	-	30	60	0
Zengin et al [9]	Van	2014	42	18	10	55	5	-	33	45	-
Duman Y et al [15]	Maraş	2014	35	18	11	62	0	16	20	36	5
Yılmaz N et al [16]	Izmir	2016	37	28	24	67	0.3	12	50	20	0.9

AMC: Amoxicillin-Clavulanic acid, CRO: Ceftriaxone, GN: Gentamicin, AMP: Ampicillin, AK: Amikacin, FEP: Cefepime, CIP: Ciprofloxasin, SXT: Trimethoprime-Sulfametoxazole, NT: Nitrofurantoine

Ciprofloxacin (CIP) resistance rates of E.coli range from 3.2% to 22% in the world [17]. When we look at the studies on quinolone resistance in UTI conducted in our country, it seems that the (CIP) resistance rate was between 18.2% and 50% in uncomplicated urinary tract infections, showing an increase over the years (Table 4). According to a multi-centered study included 6 different geographical regions of Turkey, CIP resistance of patients with community-acquired complicated and uncomplicated UTI were found to be lowest in the Marmara Region (23%) [18]. In our study, CIP resistance was found to be higher in ESBL (+) E. coli strains isolated from patients with complicated urinary tract infections ($p<0.05$). Our study data is consistent with the studies conducted in our country, and quinolone resistance is higher in patients with complicated UTI and since CIP is a commonly preferred antimicrobial agent in the empirical treatment, care should be exercised while arranging prescriptions in polyclinics, especially for patients with complicated risk factors.

It was observed that the microorganism grew in 28% of the patients for whom empirical quinolone was prescribed for the treatment of uncomplicated UTI in our polyclinics was quinolone-resistant, and that prescription modification according to the antibiogram result was performed only in 4% of the cases.

Ceftriaxone (CRO) resistance in E. coli strains that are the determining factors for UTI ranges from 3% to 28% in Turkey (Table 4). CRO resistance in hospital-acquired E. coli strains is significantly higher than in community-acquired strains [19]. We also found a similarly high resistance in patients with complicated UTI.

NT resistance of E. coli ranges between 0% and 12.5% in studies conducted in our country (Table-4). A meta-analysis including the period between 1996 and 2012 reported that NT resistance has declined from 24% to 8.5%. The researchers argue that this is due to the fact that NT is less preferred in the treatment and accordingly not reported in antibiogram results because of its reduced use in recent years [20]. In our study, NT resistance of E. coli was also found to be below 10% in both complicated and uncomplicated cases, suggesting that NT may still be a preferred agent in the empirical treatment of patients with UTI. However, the increase in resistance of E.coli observed in uncomplicated cases over the years is significant ($p<0.05$). Therefore, the compatibility of initiated treatments should absolutely be confirmed by antibiogram results.

Phosphomycin is a preferred antibiotic in the empirical treatment because of its ease of use, which can be effective even in ESBL (+) cases. FF resistance is low in studies conducted in our country and FF resistance of E. coli strains isolated from community-acquired urinary system infections was found to be 4.3% in İzmir between the years of 2008-2014 [21,22]. In another study, resistance rates were reported to be 10% in ESBL (+) E. coli strains and 5% in ESBL (-) E. coli strains [18,23]. However, as drug use increases, resistance rates are also gradually increasing, as we have observed.

The prevalence of ESBL in E. coli strains ranges between 6%-25% in our country [24,25]. Over the years, ESBL positivity has increased in E.coli, which was a determinant of complicated and uncomplicated UTI in our study, and was found to be significant in patients with uncomplicated UTI ($p<0.05$). This demonstrates that resistant strains have also increased in our hospital, similar to the studies conducted, suggesting that phosphomicine may still be a suitable option in empirical treatment.

TMP-SXT resistance has been reported to be 14.3-30.2% in Klebsiella spp. strains isolated from patients with UTI in our country [8,18,26,27]. However, this rate was found to be even higher (22-60%) in our study (Table-2). The identified

resistance rates suggest that this antibiotic should be prescribed according to TMP-SXT culture antibiogram result in Klebsiella spp. When empirical prescriptions were analyzed, this antibiotic was found not to have been preferred empirically at all since TMP-SXT resistance was found to be greater than 20%.

Quinolone resistance of Klebsiella spp. is also increasing throughout the world (19-27%) [28,29]. Quinolone resistance rates range between 10-50% in Turkey. [8,18,26,27]. Our results are also parallel to this data, and antimicrobial resistance has increased significantly over the years ($p<0.05$). ESBL production in Klebsiella spp. is also increasing over the years, particularly more significantly in complicated UTI cases. It is also natural to see an increase in cephalosporin resistance rate in connection with that (24). CRO resistance rate in Klebsiella spp. strains isolated from patients with UTI in our country was found to be between 14.3-27%. [8,18,26,27]. Over the years, a linear increase was observed in CRO resistance rates (13-33%) of patients with uncomplicated UTI in our study, but this increase was not found to be statistically significant ($p>0.05$).

Our study found that third generation oral cephalosporins have been empirically prescribed at a rate of 10.7% and second generation oral cephalosporins have been empirically prescribed at a rate of 9,6%, and that 42% of cefuroxime prescriptions and 17% of cefixime prescriptions were incompatible with antibiogram results. The results suggest that these antimicrobials should be prescribed according to the antibiotic susceptibility result. On the other hand, NT resistance was found to be low, especially in uncomplicated cases. It may be a suitable option in the empirical treatment.

Similar resistance problems also exist in other microorganisms. However, since the number of these microorganisms was small in our study, these results were not included in the discussion.

Conclusion

Consequently, the problem of resistance is gradually increasing in UTI. As seen in other countries in which inappropriate use of antibiotic is high, other antibiotics that may be prescribed to outpatients in the cases of uncomplicated UTI also have a high resistance. Therefore, empirically initiated treatments are often ineffective. Considering all the prescriptions in our study, 38 (14%) of these empirically initiated prescriptions were found to be incompatible with antimicrobial susceptibility results. When these prescriptions were analyzed, it was found that only 4 (10%) of them were changed according to the antimicrobial susceptibility result, and that that most of the prescription changes were made in FF and NT patients because the susceptibility was found to be high in patients to whom FF and NT were prescribed. These results support the usability of FF and NT, which have good efficacy in uncomplicated UTIs, in the empirical treatment. However, it is considered that antimicrobials other than NT should be prescribed according to culture/antibiogram results in the case of complicated UTIs.

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Burnout syndrome, job satisfaction and associated factors among primary health care doctors in Erzurum, Turkey

Türkiye, Erzurum ili birinci basamak sağlık kurumlarında görev yapan hekimlerin tükenmişlik sendromu, iş doyumu düzeyleri ve ilişkili faktörler

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Abstract

Aim: The aim of this study was to determine burnout and job satisfaction levels and related factors among general practitioners in Erzurum province.

Methods: 246 out of the 253 physicians working in primary health institutions in Erzurum in 2012 were included in the study. Data were collected using a Personal Information Form, the Maslach Burnout Inventory (MBI), and the Minnesota Satisfaction Questionnaire (MSQ).

Results: Males represented 72.8% (n=179) of the participating physicians, and 70.7% (n=174) were married. The mean age of the participants was 34.0±5.7 years, and 92.7% (n=228) believed that the profession was not valued as it deserved in the community. We found higher depersonalization scores and lower personal accomplishment scores in physicians aged 29 or less compared to those aged 40 or over (OR: 2.28, 95% 1.50 – 4.92, p=0.03). Job satisfaction and personal accomplishment scores were higher among physicians taking regular vacations, while emotional exhaustion was higher among those not taking regular vacations. (p<0.05). MBI subscale scores of emotional exhaustion, depersonalization, and personal accomplishment were low, at 69.1%, 75.6%, and 70.3%, respectively. The general job satisfaction score was moderate, at 70.6%.

Conclusion: Both burnout and job satisfaction were high in 1/3 of the general practitioners working in primary health care services. Activities to combat physician burnout and motivate health are needed.

Keywords: Burnout, Job satisfaction, Physician, Erzurum

Öz

Amaç: Bu çalışmanın amacı, Erzurum ilindeki pratisyen hekimler arasında tükenmişlik ve iş doyumu düzeylerini ve ilişkili faktörleri belirlemektir.

Yöntemler: Erzurum'da 2012 yılında birinci basamakta çalışan 253 doktordan, 246 tanesi çalışmaya dahil edilmiştir. Veriler Kişisel Bilgi Formu, Maslach Tükenmişlik Ölçeği (MTÖ) ve Minnesota İş Doyumu Ölçeği (MİDÖ) kullanılarak toplanmıştır.

Bulgular: Çalışmaya katılan hekimlerin %72,8'i erkek, %70,7'si evli ve yaş ortalamaları 34,0±5,7 şeklindedir. Mesleğinin toplumda hak ettiği değeri bulduğuna inanmayanlar %92,5 olduğu saptanmıştır. 40 yaş üstü hekimlerin kişisel başarı puanları 29 yaş altındaki doktorlara göre daha düşük bulunmuştur (OR: 2,28, %95 1,50 – 4,92, p=0,03). Düzenli tatil yapmayan hekimlerin düzenli tatil yapmayan hekimlere göre iş doyumu ve kişisel başarı puanları daha yüksektir (p<0,05).

Hekimlerin, MTÖ alt boyutları olan duygusal tükenmişlik, duyarsızlaşma, kişisel başarı puanları sırasıyla %69,1'inde, %75,6'sında ve %79,3'ünda düşük saptanmıştır. Genel iş doyumu puan ortalaması ise %70,6'sında orta düzeyde bulunmuştur.

Sonuç: Birinci basamak sağlık kurumlarında görev yapan hekimlerin 1/3'ünde tükenmişlik ve iş doyumu yüksek bulunmuştur. Bu durum göz önüne alınarak, hekimlerin tükenmişlik düzeylerini azaltmaya, iş doyumu düzeylerini arttırmaya yönelik öneriler yapılmıştır.

Anahtar kelimeler: Tükenmişlik, İş memnuniyeti, Doktor, Erzurum

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Introduction

Burnout is a syndrome, in which emotional exhaustion, depersonalization, and low personal accomplishment may occur among workers in jobs requiring interpersonal contact [1]. Emotional exhaustion manifests with a feeling of lack of energy and consumed emotional resources. Depersonalization exhibits with workers treating the individuals whom they serve as if they were objects rather than human beings. Low personal accomplishment manifests with a decrease in feelings of success and sufficiency in association with work and relations with people encountered in the context of work. Burnout results in losing creativity and not striving for improvement [2]. The characteristic that distinguishes burnout from other reactions is that it emerges as a result of frequent and intense interactions other people encountered in the work context.

People spend a significant part of their day-to-day lives working. Hence, work is not only important in economic terms but also performs an important psychological role. Job satisfaction is defined as a positive emotional state emerging as a result of the value the individual attaches to his work. Job satisfaction is evaluated as a measure of the presence of a sound working environment in an institution and is defined as the satisfaction or dissatisfaction that people feel with their jobs [3].

An individual's dissatisfaction with his job can be due to burnout. Job dissatisfaction associated with work deficiencies, the individual's own deficiencies and exhaustion associated with work deficiencies all result in poor performance. The concepts of both burnout and job dissatisfaction are especially important in medicine, a profession involving intensive face-to-face contact with people. These two phenomena are inter-related, one increasing or decreasing together with the other [4].

The health system in Turkey was changed in 2004 with the replacement of the 'Law No. 224 on the Socialization of Health Services', dated 1961 by the 'Family Medicine Pilot Implementation Law No. 5258,' leading to the adoption of the 'Family Medicine Model' [5,6]. The Family Medicine Model was first implemented in the province of Düzce in 2005. In Erzurum, the model was adopted in 2008. Under the Directive on Family Medicine Implementation (FMI), primary health care services are mainly provided in Family Health Centers and Public Health Centers [6].

In addition to the difficulty involved in serving sick individuals, a particularly sensitive group, primary care physicians also have to make decisions regarding clinically uncertain situations face the consequences of those decisions. Fear of malpractice makes medicine a particularly stressful profession. Family physicians encounter undifferentiated patients, as mentioned under the core competencies by WONCA (World Organization of National Colleges). One of the most significant difficulties in family medicine is the management of patients with clinically undifferentiated symptoms [7]. Besides, deficiencies deriving from the health system and unbalanced distribution of services and personnel can create disappointment and tension in family physicians. Work-related pressures can cause psychological effects such as anxiety, hopelessness, depression, and somatic effects including headache, muscular tension, and sleeplessness. The result is a decrease in employee productivity, poor timekeeping, and absenteeism without valid justification; even entire abandonment of the job comes into question. Studies have shown that burnout syndrome affects personal and professional productivity in 30-40% of physicians [8].

Until the FMI in 2010, primary care physicians were known as 'general practitioners' who were subsequently referred to as 'family physicians'. Family physicians began providing preventative, therapeutic and rehabilitative health services in family health centers.

There is a substantial probability that this change in the health system in Turkey will have a positive or adverse impact on job satisfaction and burnout levels among physicians working in primary health services. Hence, regular monitoring of employee satisfaction and burnout bears critical importance in the sense of judging the changes in the health system. With this study, we aimed to determine burnout and job satisfaction levels and associated factors among general practitioners in the Erzurum province.

Materials and methods

The study was conducted in the Erzurum province, an eastern province of Turkey with around 600,000 inhabitants. During the study period, 253 physicians were working in the primary health institutions in Erzurum. Our cross-sectional study between March and June 2012, included 246 (97.2%) physicians from the study population. Since the survey aimed to cover all study population, we did not make a sample size calculation.

Following ethical and official permissions and verbal consent from physicians, the participants were asked to complete the study questionnaire. Data collection was done during working hours, at time slots when physicians were least busy. A personal information form intended to elicit physicians' sociodemographic characteristics. Also, the Maslach Burnout Inventory (MBI) developed to measure burnout levels, and the Minnesota Satisfaction Questionnaire (MSQ) short form intended to measure job satisfaction were applied to all participants.

Data Collection

1. Sociodemographic information form: After seeking expert opinion, these questions concerning various personal and professional characteristics and physicians' views regarding their working conditions were prepared by the researchers.

2. Minnesota Satisfaction Questionnaire (MSQ): The MSQ consists of 20 questions. Two forms of this scale are available; long and short. The short form was employed in this study.

The MSQ was developed in 1967 by Weiss et al. to determine job satisfaction levels [9]. The scale was translated into Turkish by Baycan, and its validity and reliability were established [10]. The general satisfaction score is obtained by dividing the total scores from the 20 items by 20. Means of all scores are calculated as values between 1.0 and 5.0. In percentage terms, values of 25% or below indicate low job satisfaction, values of 26-74% indicate moderate job satisfaction and values of 75% or more indicate good job satisfaction.

3. Maslach Burnout Inventory (MBI): This scale was validated by Ergin [11] for Turkish and consists of 22 questions

on a 5-point Likert scale. It contains three subdimensions: emotional exhaustion, depersonalization, and personal accomplishment. The emotional exhaustion and depersonalization subdimensions consist of negative statements while the personal accomplishment subdimension has positive items. The scores for each subdimension are therefore evaluated separately. Higher emotional exhaustion and depersonalization scores or lower personal accomplishment scores indicate burnout. Scores of 28 or more for emotional exhaustion are assessed as high, scores of 21-27 as moderate and of 21 or less as low, while for depersonalization, scores 13 or above are regarded as high, scores of 9-12 as moderate and of 8 or less as low, and for personal accomplishment, scores of 0-23 are considered to be low, scores of 24-26 as moderate and scores of 27 or more as high [11].

Data were entered into the computer and analyzed on the SPSS for Windows 18.00 software. Normal distribution of data was assessed using the Kolmogorov-Smirnov test. The parametric one-way analysis of variance (ANOVA) and t-test, and the non-parametric Kruskal Wallis and Mann Whitney U tests were used for analysis. Post-hoc Bonferroni correction was used to determine the variable representing the source of variation for parametric variables and Bonferroni corrected Kruskal Wallis and Mann Whitney U tests for non-parametric variables. $p<0.05$ was considered as statistically significant.

The MBI and MSQ subdimension scores were grouped into binary variables based on their median values. The effects of independent variables were measured using binary logistic regression analysis where lower categories were regarded as reference values.

Results

A total of 246 physicians were enrolled, of which 72.8% (n=179) were males, and 70.7% were married. The mean age of the physicians was 34.0 ± 5.7 years. Distribution of other sociodemographic characteristics of the participants is shown in Table 1.

Regarding the total length of service, 49.6% (n=122) of physicians had been in the profession for six years or less and 7.7% (n=19) for 18 years or more. On the other hand, 62.2% (n=153) stated that their expectations were partially met and 46.7% (n=115) that the physical conditions in the workplace were partly adequate. Besides, while 82.9% (n=204) of physicians had received in-service training in the previous year, 29.7% (n=73) had attended no congress, course or seminar, but 78.8% (n=n=194) reported reading medical publications from time to time. Other professional characteristics of the physicians in the study are shown in Table 2.

The mean MBI scores of the participants were 17.14 ± 7.5 for emotional exhaustion, 5.85 ± 3.8 for depersonalization, and 20.0 ± 4.34 for personal accomplishment. The mean job satisfaction score from the MSQ was 3.22 ± 0.63.

Mean depersonalization and general job satisfaction scores were significantly higher among physicians aged 29 or more ($p<0.05$). Job satisfaction and personal accomplishment scores were higher among physicians taking regular vacations, while emotional exhaustion was higher among those not taking regular vacations ($p< 0.05$). On the other hand, mean job satisfaction scores were lower among physicians who believed they had chosen the wrong profession ($p<0.05$). Various physician characteristics and mean MBI subscale and general job satisfaction scores are shown in Table 3.

Table 1: Distribution of participant characteristics (n=246)

	n	%
Age group		
<29	60	24.4
30-39	138	56.1
>40	48	19.5
Sex		
Male	179	72.8
Female	67	27.2
Marital Status		
Married	174	70.7
Single	69	28.0
Widowed/Divorced	3	1.2
Exercise activity		
Yes	51	20.7
No	195	79.3
Vacation within last year		
Taken	104	42.3
Not Taken	142	57.7
Chronic disease status		
Yes	29	11.8
No	217	88.2
Smoking status		
Current smoker	80	32.5
Ex-smoker	56	22.8
Never smoker	110	44.7
Alcohol consumption		
Yes	25	10.2
No	221	89.8
Place of residence		
Provincial center	117	47.6
District center	103	41.9
Township/Village	26	10.6

Table 2: Distribution of the physicians' professional characteristics (n=246)

	n	%
Is the profession valued as it deserves in the community?		
Yes	18	7.5
No	228	92.5
Opinions concerning selection of the profession		
Correct Choice	78	31.7
Partially Wrong Choice	121	49.2
Wrong Choice	47	19.1
Are professional expectations met?		
Yes	35	14.2
Partly	153	62.2
No	58	23.6
Physical conditions in the workplace		
Adequate	57	23.2
Partially Adequate	115	46.7
Inadequate	74	30.1

Table 3: Relationship between various physician characteristics and burnout and general job satisfaction scores

	MBI-EE Mean ± SD	MBI-D Mean ± SD	MBI-PA Mean ± SD	General job satisfaction Mean ± SD
Sex				
Male	17.62 ± 7.7	6.3 ± 3.9	20.2 ± 4.39	3.16 ± 0.65
Female	15.8 ± 6.9	4.5 ± 3.2	19.3 ± 4.1	3.38 ± 0.57
	P^1=0.10	P^1<0.01	P^1= 0.14	P^1=0.01
Marital status				
Married	16.9± 7.5	5.4 ± 3.5	20.0 ± 4.3	3.19 ± 0.64
Single	17.5 ± 7.4	6.7 ± 4.27	19.8 ± 4.3	3.32 ± 0.62
	P^1=0.65	P^1=0.00	P^1=0.74	P^1=0.16
Is the profession valued as it deserves in the community?				
Yes	8.9 ± 5.2	3.1 ± 2.7	21.9 ± 4.7	3.83 ± 0.40
No	17.7 ± 7.3	6.0 ± 3.8	19.8 ± 4.2	3.18 ± 0.63
	P^1=0.00	P^1=0.00	P^1=0.04	P^2=0.00

[1] Student–t Test, [2] Mann Whitney U test

MBI-EE= Maslach Burnout Inventory - emotional exhaustion; MBI-D= Maslach Burnout Inventory – depersonalization; MBI-PA= Maslach Burnout Inventory - personal accomplishment

According to the logistic regression model findings, the risk of emotional exhaustion was 2.63-fold higher in the subjects not taking a vacation every year, 5.65-fold higher among physicians discontent with the family medicine system, and 10.95-fold higher among physicians thinking that their

expectations from the job were not met (p<0.05). The risk of depersonalization, personal accomplishment and general job satisfaction by various sociodemographic and professional characteristics is shown in tables 4, 5 and 6.

Table 4: Binary logistic regression analysis results concerning physician depersonalization.

Category	OR (95.0% C.I.)	p
Sex		
Female	1.00 (Ref.)	
Male	2.20 (1.03 – 4.66)	0.04
Age group		
40 or over	1.00 (Ref.)	
30-39	3.18 (1.45 – 7.01)	<0.01
29 or below	7.71 (2.79– 21.30)	0.01
Total professional experience		
18 years or more	1.00 (Ref.)	
11-17 years	1.81 (0.52 – 6.25)	0.34
7-10 years	3,73 (1,18 – 11,56)	0.02
6 years or less	4.99 (1,52 – 16.34)	<0.01
Opinions regarding choice of profession		
Correct choice	1.00 (Ref.)	
Partially wrong choice	2.02 (1.09 – 3.74)	0.02
Wrong choice	2.50 (1.11 – 5.61)	0.02

Binary logistic regression analysis, OR=Odds ratio.

Table 5: Binary logistic regression analysis results concerning the physician personal accomplishment subdimension

	OR (95.0% C.I.)	p
Age group		
29 or below	1.00 (Ref.)	
30-39	1.15 (0.62 – 2.13)	0.64
40 years and above	2.28 (1.50 – 4.92)	0.03
Total professional experience		
6 years or less	1.00 (Ref.)	
7 -10 years	0.70 (0.36 – 1,34)	0.28
11 -17 years	0.91 (0.43 – 1.91)	0.80
18 years or more	3.97 (1.30 – 12.1)	0.01
Opinions concerning choice of profession		
Wrong choice	1.00 (Ref.)	
Correct choice	2.97 (1.19 – 7.39)	0.01
Prtially wrong choice	1.70 (0.80 – 3.63)	0.16

Binary logistic regression analysis, OR=Odds ratio.

Table 6: Binary Logistic regression analysis results concerning the physician general job satisfaction dimension

	OR (95.0% C.I.)	p
Sex		
Male	1.00 (Ref.)	
Female	1.79 (1.30 – 3.20)	0.04
Place of residence		
Provincial center	1.00 (Ref.)	
District	2.24 (1.14 – 4.40)	0.01
Township/village	2.91 (1.70 – 7.95)	0.03
Opinions concerning choice of profession		
Wrong choice	1.00 (Ref.)	
Correct choice	5.66 (2.18 – 14.71)	<0.01
Partially wrong choice	3.95 (1.62 – 9.58)	<0.01

Binary logistic regression analysis, OR=Odds ratio.

Discussion

Our study determined low mean emotional exhaustion, depersonalization, and personal accomplishment scores in physicians working in primary health care institutions in Erzurum. Similar results to ours were reported in a study of family physicians in Sakarya [12]. Baykan et al. [13] reported lower mean emotional exhaustion and depersonalization and higher personal accomplishment scores compared to our findings in their study involving family physicians. In another study of burnout among health workers employed in the FHI, Elbi et al. [14] reported lower emotional exhaustion scores but higher personal accomplishment scores compared to ours. The differences between the studies may derive from study settings and regional or sociocultural factors.

Studies of primary care physicians in Portugal, Sweden, and Italy have determined similar mean emotional exhaustion and depersonalization scores to ours, but higher personal accomplishment scores [15–17]. Variations in pre- and post-graduation medical training, the lack of a gate control in Turkey, patient preferences to skip the referral stage and directly access to the secondary/tertiary health care institutions and limited number of applications to primary care physicians seeking treatment, physicians' self-perception of incompetency, all may be contributing to the low personal accomplishment scores.

General job satisfaction levels among the physicians in our study were moderate. Tekin [18] reported similar mean general job satisfaction levels among family physicians to those in our study. Mean general job satisfaction levels are known to rise in line with socioeconomic conditions conferred by the job. Studies from Eskisehir and Adana provinces in Turkey have reported higher job satisfaction levels [19,20]. This difference was attributed to the regional living conditions. Indeed, socioeconomic conditions in those two provinces are more advanced than Erzurum [21].

We found higher depersonalization scores and lower personal accomplishment scores in physicians aged 29 or less compared to those aged 40 or over. Increased professional experience, better ability to take independent decisions, possession of a certain status, and familiarity in coping with difficulties may have played a role in this. Our findings are similar to those of Baykan's study [13] of family physicians and Üner's study [22] of primary care physicians. No correlation was observed in our study between the age of family physicians and the job satisfaction scores. International [23,24] and Turkish [20,25–27] studies compatible with our own research have been published in the literature. Further studies are now needed in terms of demographic data capable of impacting on job satisfaction.

Male physicians had higher depersonalization scores than females. This is compatible with Baykan, Elbi, and Özyurt's studies [13,14,28]. On the other hand, general job satisfaction was higher among women, which is consistent with Ataoğlu's physician-based study [29]. This difference may be attributed to women being more sensing (particularly in face-to-face communication), and selfless. Women also find it easier to discuss problems than men, which may also contribute to experiencing fewer issues in the workplace [30].

Comparison of mean scores by place of the residence revealed no significant variation concerning mean burnout subdimension scores. However, Koşan [31] reported higher emotional exhaustion among workers in rural areas. In contrast to previous years, family physicians are allowed to choose their own places of work. Hence, this variation may derive from differences in the system. Subjects living in the provincial center in our study had lower general job satisfaction scores. Similarly, a study involving practicing physicians in Australia reported higher job satisfaction among physicians living in rural areas compared to those living in cities [32]. In a study including physicians from all levels of care in Erzurum, Sevimli [33] observed lower job satisfaction among doctors in rural areas compared to those living in the city center. Physicians choosing to work in rural areas on their own volition and doctors in rural areas receiving higher salaries than those in the city center may account for this variation.

Single subjects in our study scored higher regarding depersonalization than married participants. Şerik et al. [12] reported similar findings to ours. We may, therefore, conclude that positive, mutual sharing among married subjects means that they are less exposed to depersonalization. Marital status did not affect physicians' job satisfaction in our study. Several other studies from Turkey have also reported no effect of marital status on job satisfaction [34,35].

The risk of depersonalization was higher, and personal accomplishment scores were lower among physicians with professional experience of 6 years or less compared to those with 18 years or more. We think that this may be due to higher professional expertise associated with better problem-solving skills and an improved ability to combat burnout. More extensive professional experience may increase the physician's self-confidence and personal accomplishment. Our findings are compatible with those of Kaya's study [36] of primary care physicians. While we determined no relationship between physicians' length of experience and mean general job satisfaction scores, Sevimli's study [33] of physicians working in all levels of care in our region reported that job satisfaction increased with numbers of years worked.

Physicians who thought they had chosen the wrong profession had higher emotional exhaustion and depersonalization scores and lower personal accomplishment scores. Our results are comparable to those of another study in our region, reporting an increased risk of emotional exhaustion [31]. Physicians may think that their material and other professional expectations after a long and arduous training period are not being met. In addition, we determined higher general job satisfaction among physicians who believed they had made the right choice of profession. In Sevimli's study [33], job satisfaction was also higher among subjects who thought they had selected the right occupation.

Emotional exhaustion and depersonalization scores in our study were higher, and personal accomplishment and job satisfaction were lower among physicians who did not believe that the profession was not valued by society as much as it deserves. Increasing violence in the health sector in the recent years may have resulted in physicians' expectations failing to be met. Mean emotional exhaustion and depersonalization scores were higher and job satisfaction was lower among physicians who considered their working conditions to be inadequate. Previous studies have also shown that physical conditions in the workplace have a similar effect on physicians' burnout and job satisfaction levels [20,28,31]. Inadequate physical conditions in the workplace cause a decrease in the job satisfaction, impacting on work productivity, health, and social life. Working conditions are important in terms of personal comfort and of doing one's job well.

Our study reflects burnout and job satisfaction levels only among primary care physicians in the province of Erzurum, and these findings cannot be generalized to all general practitioners in Turkey. However, the principal strength of this study is that it is the first in our region since the transformation to the FMI.

In conclusion, job satisfaction and burnout levels among physicians working in primary health care services should be measured at specific intervals. Measures aimed at matters resulting in dissatisfaction should be introduced, and social activities designed at motivating all health workers should be arranged. Deficiencies in the existing system need to be overcome to reduce burnout and increase job satisfaction. Further research is needed into the relationship between physicians' professional perceptions, the esteem they enjoy in the society, and their job satisfaction.

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Intensity-modulated radiation therapy reduces late salivary toxicity and mandibular osteoradionecrosis in the treatment of oral cavity cancer: Retrospective study

Şiddet modülasyonlu radyasyon tedavisi, oral kavite kanseri tedavisinde geç tükrük toksisitesini ve mandibular osteoradionekrozu azaltır: Retrospektif çalışma

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Abstract

Aim: It is increasingly being recognized that oral cavity cancer incidences are rising globally. Irradiation using 3D conformal radiotherapy results in high incidence of late radiation side-effects. Xerostomia and manibudlar osteoradionecrosis result in most significant effects on patients quality of life. Intensive modulated radiotherapy (IMRT) is an advanced approach to 3D treatment planning and conformal radiotherapy. It optimizes the delivery of irradiation to irregularly-shaped volumes and has the ability to spare normal tissue while delivering adequate doses to the tumor volumes. In present retrospective analysis, we aimed to analyze the clinical and dosimetric characteristics with the dose constraints in patients followed for oral cavity cancer and treated by IMRT.

Methods: 19 patients followed for non-metastatic oral cavity cancer who were treated with IMRT, were retrospectively analyzed at the radiotherapy department Hassan II University hospital, Fes, Morocco between January 2016 and December 2016.

Results: The mean age was 58.5 years. The predominant histological type was epidermoid carcinoma. RCC was received in 79% of cases versus 15.8% of exclusive radiotherapy. 68.4% of cases received 70Gy for HR PTV, the mean dose delivered to the homolateral and controlateral parotid glands was 36Gy and 22Gy respectively, the average dose delivered to the mandible was 51.9Gy.

Conclusion: IMRT of oral cavity tumors offers reduces the risks of xerostomia and ORN through parotid and mandibular sparing, without compromising on target volume coverage.

Keywords: Intensive modulated radiotherapy, Oral cavity cancer, Xerostomia, Mandibular osteoradionecrosis

Öz

Amaç: Dünyada oral kavite kanseri vakalarının giderek arttığı artan bir şekilde bilinmektedir. 3D konformal radyoterapi kullanılarak ışınlama, geç radyasyon yan etkilerinin yüksek insidansına neden olur. Xerostomia ve manibudlar osteoradiyonekroz, hastaların yaşam kalitesi üzerinde en önemli etkilerle sonuçlanır. Yoğun modüle radyoterapi (IMRT), 3D tedavi planlaması ve konformal radyoterapiye ileri bir yaklaşımdır. İrradyasyonun düzensiz şekilli hacimlere ulaştırılmasını optimize eder ve tümör hacimlerine yeterli dozları verirken normal dokuları yedekleme özelliğine sahiptir. Bu retrospektif analizde, oral kavite kanseri için takip edilen ve IMRT ile tedavi edilen hastalarda doz kısıtları ile klinik ve dozimetrik özellikleri analiz etmeyi amaçladık.

Yöntemler: IMRT ile tedavi edilen metastatik olmayan oral kavite kanseri nedeniyle takip edilen 19 hasta retrospektif olarak Ocak 2016-Aralık 2016 tarihleri arasında Fes, Fas'taki radyoterapi bölümü II'de kayıt edildi.

Bulgular: Ortalama yaş 58,5 idi. Baskın histolojik tip epidermoid karsinomdu. Olguların %79'unda RCC, %15.8'inde özel radyoterapi görüldü. Olguların %68,4'ünde HR PTV için 70Gy, homolateral ve kontrolateral parotis bezlerine verilen ortalama doz sırasıyla 36Gy ve 22Gy, mandibula verilen ortalama doz 51,9Gy idi.

Sonuç: Oral kavite tümörlerinin IMRT'si, hedef hacim kapsamından ödün vermeden, parotis ve mandibular koruma ile kserostomi ve ORN riskini azaltmaktadır.

Anahtar kelimeler: Yoğun modüle radyoterapi, Oral kavite kanseri, Kserostomi, Mandibular osteoradionekroz

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Introduction

Oral cavity cancer is the sixth most common cancer worldwide [1]. Incidences very wildely across geographical areas with the UK demonstrating a relatively low incidende of 3500 cases per year, [2] compared to parts of South East Asia where a third of all male cancers in India originate in the oral cavity [3]. Etiological factors for some squamous cell oral cavity cancer such as high tobacco and alcohol consumption, and betel quid chewing, may account for these geographical variations [4]. Recently infection with human papilloma virus had been identified as a casual factor for the rising incidence of oropharyngeal cancers in non-smokers. However, the relationship with oral cavity cancer is not yet established.

Treatments of oral cavity cancer

External beam radiotherapy is used in the treatment of OCC, primarily in the post-operative setting but also as first definitive treatment when surgery is felt to be inappropriate [5]. In these early stage patients, risk stratification is based on thickness and grade of tumor [6]. Patients with oral tongue tumors or floor of mouth tumors with a clinically node-negative neck require surgical resection of the primary lesion and elective neck dissection at the very least. In 1972, a study by Lindberg demonstrated that the lymph node groups most frequently involved in patients with carcinoma of the oral cavity are the jugulodigastric and midjugular nodes (levels II and III). In patients with carcinoma of the floor of the mouth, anterior oral tongue, and buccal mucosa, the nodes most frequently involved are in the submandibular triangle (level I). Lindberg also noted that cancers frequently metastasize to both sides of the neck and can skip the submandibular and jugulodigastric nodes, metastasizing first to the midjugular region. Supra-omohyoid neck dissection (dissection of nodal compartments level I to III) offers similar rates of locoregional control and survival as a modified radical neck dissection [7]. Most surgical groups advocate the use of an extended supraomohyoid dissection in oral tongue tumors and deem it compulsory for the node positive patient due to the risk of skip metastasis to nodal compartment level IV while some groups will recommend the extended supra-omohyoid dissection for floor of mouth tumors in addition to tongue tumors [8]. Tumors approaching the midline require dissection of the contralateral neck. Post-operative radiotherapy is administered in selected high risk groups [9].

Radiotherapy for oral cavity cancers

Stage III and IV tumors of the oral cavity generally require bilateral oral cavity and neck irradiation following surgery. The acute toxicity from bilateral oral cavity irradiation is severe, and the majority of patients develop grade 2/3 oral mucositis and dysphagia. However, these acute effects are self-limiting and it is the permanent nature of the late effects which become more problematic. Sixty-six percent of patients with stage III disease and 58% patients with stage IV undergoing appropriate surgical management and postoperative radiotherapy will survive five years or longer and are deemed cured beyond this point. They are therefore susceptible to lifelong consequences of irradiation.

Intensity modulated radiotherapy

Intensity modulated radiotherapy (IMRT) is an advanced approach to 3-D treatment planning and conformal therapy (3D-CRT). It optimizes the delivery of irradiation to irregularly shaped volumes and has the ability to produce concavities in radiation treatment volumes. Typically for head and neck cancer the clinical target volume 1 (CTV1), which includes the primary tumor and the involved nodes receives a higher radiation dose as compared to the clinical target volume 2 (CTV2). The different doses to CTV1 and 2 can be delivered simultaneously, while sparing the parotid salivary glands and the spinal cord. In the head and neck region, IMRT has a number of potential advantages:

- it allows for greater sparing of normal structures such as salivary glands, esophagus, optic nerves, brain stem, and spinal cord; [10,11]

- it allows treatment to be delivered in a single treatment phase without the requirement for matching additional fields to provide tumor boosts and eliminates the need for electron fields to the posterior (level II, V) neck nodes;

- it offers the possibility of simultaneously delivering higher radiation doses to regions of gross disease and lower doses to areas of microscopic disease, the so-called simultaneous integrated boost (SIB-IMRT) [12].

IMRT is the gold standard in the treatment of upper aerodigestive cancers. One of the goals is the protection of risk organs such as salivary glands and the mandible. The risks of hyposialism, trismus and osteoradionecrosis must be reduced.

The objective of our retrospective study, carried out at the radiotherapy department Hassan II University hospital, Fes, Morocco between January 2016 and December 2016, is to analyze the clinical and dosimetric characteristics with the dose constraints in patients followed for oral cavity cancer and treated by IMRT.

Materials and methods

We collected 19 patients followed for non-metastatic oral cavity cancer who were treated with IMRT, including 9 cases of tongue cancer (47.3%), 4 cases of lip cancer (21%), 3 cases of cheek cancer (15.7%), 2 cases of the palate cancer (10.5%), and one case of the retro-molar trine cancer (5.2%).

Statistical analysis was obtained using Excel and SPSS computer software. The significance level of all observed differences was set for all statistical tests at a probability value $p \leq 0.05$.

Results

The mean age was 58.5 years, with a female predominance (sex ratio at 1.71). The predominant histological type was epidermoid carcinoma in 84.2% of cases; there was only one case of underwent adenocarcinoma, one case of basal cell carcinoma and one case of sarcomatoid mycoepithelial carcinoma. The number of patients with stage I, II, III and IV disease were 1, 3, 8, and 7 respectively. 8 patients underwent tumor excision (42.1%) against 57.8% of non-operated patients. RCC was received in 79% of cases versus 15.8% of exclusive radiotherapy.

68.4% of cases received 70Gy for HR PTV, 21% of cases received 66Gy, 5.2% of cases received 60Gy and 5.2% of cases received 46Gy. The mean dose delivered to the homolateral and controlateral parotid glands was 36Gy and 22Gy respectively.

The average dose delivered to the mandible was 51.9Gy. The mean dose delivered to the homolateral and contralateral TMJ was 23.2Gy and 19.3Gy respectively.

Discussion

Our study demonstrates the benefit of IMRT to reduce the risk of xerostomia by delivering a mean dose less than 22Gy to the parotide which concord perfectly with the data of literature. Eisbruch and al. Proposed an average contralateral parotid dose <26Gy as a parotid sparing goal to recover the initial salivary flow at 12 months [13]. In a recent analysis of a multicentric phase III trial (PARSPORT) compared the occurrence of a xerostomy in case of IMRT and 3D conformal radiotherapy in ENT cancers, a contralateral parotid constraint was defined with a mean dose <24Gy and which was concluded that there is a clear reduction in the risk of xerostomia with IMRT with no difference in overall survival or locoregional control [14].

No specific prospective study has been done to precisely define the exact doses to be received by the mandible and it is through the analysis of dosimetric data that proposals can be made. The average dose delivered to the mandible in our study was 51.9Gy and the radionecrosis risk is significantly reduced. In a review by Maignon et al. [15], he have evoked a notion of average dose less than 60 to 65Gy if the patient is toothless, with a radionecrosis risk of 5% at 5 years, or less than 60Gy if the patient is not edentulous, with a risk of radionecrosis from 5% to 5 years.

With regard to temporomandibular joints, the data are missing in the literature to be very reliable. A maximum dose below 65Gy (or D2% <65Gy), or even 60Gy seems advisable [16]. The results of our study are in perfect accord with the data from the literature.

In conclusion, IMRT of advanced oral cavity tumors offers the potential to reduce the risks of xerostomia and ORN through parotid and mandibular sparing. This can be performed without compromising on target volume coverage and hence treatment outcomes.

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The effect of insulin resistance on House-Brackmann grade of facial paralysis in patients with Bell's palsy

İnsülin direncinin Bell's palsy hastalarında House-Brackman evrelemesi üzerine etkisi

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Abstract

Aim: Bell's palsy is the most common cause of facial nerve lesion and is frequently observed in diabetic patients and the duration of healing is delayed in diabetic patients. To investigate the effect of insulin resistance on the facial paralysis as graded by the House-Brackmann classification in patients with Bell's palsy and to determine the importance of insulin resistance assessed primarily prior to treatment planning.

Methods: Patients admitting to our emergency department and outpatient neurology clinic with suspected facial paralysis who were not administered steroid therapy within the first 24 hours were studied. Demographic data were collected for patients with Bell's palsy from different age groups with a normal body mass index (BMI) and no chronic endocrine disease. The House-Brackmann (HB) grading scale was used to assess the clinical severity of the facial paralysis. In addition to routine laboratory tests, fasting insulin level was obtained to estimate HOMA-IR (Homeostatic model assessment for insulin resistance) for all patients.

Results: Of 19 patients enrolled, 10 were female (52.6%). Patients had a mean age of 33 years, mean glucose value of 106 mg/dL, mean insulin value of 15.9 µU/mL and mean HOMA-IR value of 4.1. A moderate positive correlation and a statistically significant association were found between mean glucose values and HOMA-IR values (r=0.548; p=0.015) Age and glucose values were not statistically significantly associated with insulin and HOMA-IR values (p=0.858 and p=0.015, respectively).

Conclusion: Higher blood glucose and average insulin levels were found in patients with facial nerve paralysis in comparison to general population. Most of the patients were IR-positive. Therefore, assessment of insulin resistance would be beneficial for both treatment planning and taking proactive measures against future development of diabetes in all patients presenting with Bell's palsy.

Keywords: Insulin resistance, House-Brackmann, Facial paralysis

Öz

Amaç: Bell's palsi fasial sinir lezyonun en sık nedenidir ve diyabetli hastalarda sık izlenir ve iyileşme süresi diyabetli hastalarda gecikmiştir. Bell's palys geçiren hastalarda insulin resistansının House – Brackman evrelemesi üzerine etkisini araştırmak ve bu araştırma sonucunda Bell' palsi tedavisi planlamadan önce öncelikli olarak insulin direncinin bakılmasının önemini araştırmak.

Yöntemler: Çalışmaya fasial paralizi şüphesiyle ilk 24 saat içinde acile veya polikliniğe başvuran ve bu nedenle steroid almamış hastalar dahil edildi. Bell's palys'li hastaların demografik verileri toplanıldı. Endokrin hastalığı olmayan çeşitli yaş gruplarında normal vücut kitle endexi olan hastalar çalışmaya alındı. Fasia paralizinin derecesinin değerlendirilmesi için House-Brackman klinik skalası kullanıldı. Tüm hastaların rutin laboratuar testlerine ek olarak açlık insülin seviyeleri bakıldı ve HOMA-IR değeri hesaplandı.

Sonuçlar: Çalışmaya alınan 19 hastanın 10'u kadın (%52,6) diğeri erkekti. Çalışmaya katılan hastaların ortlama yaşı 33 glukoz değeri ise 106 (mg/dL), ortalama insulin değeri 15,9 (µU/mL) ve ortalama HOMA-IR değeri ise 4,1 idi. Ortalama glucose değeri ile HOMA-IR değeri arasında istatistiksel olarak pozitif yönde orta şiddette anlamlı korelasyon saptanmıştır (r=0,548; p=0,015) Yaş ve glucose değerleri ile insülin ve HOMA-IR değerleri arasında istatistiksel olarak anlamlı bir ilişkiye rastlanmamıştır (sırasıyla p=0,858, p=0,015).

Tartışma: Fasial sinir felci ilen başvuran hastaların çoğunun kan şekeri yüksek ve ortlama insulin değerleri toplumdan daha fazla izlendi. Hastaların büyük çoğunluğunda IR pozitifliğine rastlanıldı. Bu yüzden Bell's palsi ile başvuran tüm hastlarda insulin rezsitansına bakıklmasını ve tedavi planın ve gelecekte hastada gelişebilecek bir diyabet açısından dikkatli olunmasını önermekteyiz.

Anahtar kelimeler: İnsülin resistansı, House-Brackman, Fasial paralizi

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Introduction

Bell's palsy (BP) is the most common cause of facial nerve paralysis. In this condition, the muscles on one side of the face suddenly become weak or paralyzed due to malfunction of the 7th cranial nerve. This causes drooping of the affected side of the face and inability to keep one eye closed, and the face is drawn across to the opposite side on smiling. For most people, Bell's palsy is temporary. Symptoms usually start to improve within a few weeks, with complete recovery in about six months. A small number of people continue to have some Bell's palsy symptoms for life. Rarely, Bell's palsy can recur. Globally, approximately 11–40/100,000 people are affected by BP every year [1,2]. It has been found that there are no sex-related differences in its prevalence. Viral infections, vascular ischemia, disorder of the autonomic regulation and inflammation have been implicated in BP [3]. Controversies still exist about the incidence and exact cause of BP. Some authors reported increased incidence of BP among people who are aged between 30 and 39 years and a tendency for BP to occur more frequently during the colder seasons (autumn and winter) [4, 5]. However, other researchers showed an increased rate of BP during warmer spring months [6,7].

Insulin resistance (IR) is a condition in which the body's cells become resistant to the effects of insulin in the blood circulation. As a result, the normal response to a given amount of insulin is reduced. IR may develop in obese, non-diabetic individuals as well as patients with type 2 diabetes mellitus [8]. A transient IR state occurs physiologically during puberty as part of normal development and pregnancy to maintain adaptation and homeostasis. IR may be present without comorbidities such as obesity or hypertension. It was shown that IR may also occur in non-obese individuals with normal glucose tolerance. Abnormalities in the concentration or affinity of the insulin receptors or both result in impaired insulin effectiveness [9].

In the present study, clinical grading of BP patients was performed using the House-Brackmann (HB) Facial Nerve Grading System (Table 1) and IR was estimated by HOMA-IR (Homeostatic model assessment for IR) to assess whether IR affected HB grading of the patients [10].

Materials and methods

Non-diabetic patients with Bell's palsy and a normal BMI who admitted to Gaziantep Sanko University Medical Faculty in 2017 were included in the study. A retrospective chart review was conducted. Patients admitting to our emergency department and outpatient neurology clinic with suspected facial paralysis who were not administered steroid therapy within the first 24 hours were studied. Patients were mostly enrolled in the fall season.

Patients with paralysis, secondary to trauma, zoster oticus, hypertensive cerebral hemorrhage, diabetes and cerebellopontine angle tumors were excluded. Data including gender, age, month of disease onset and clinical features were recorded. The House-Brackmann (HB) grading scale was used to assess the clinical severity of the facial palsy (Table 1).

Table 1: House-Brackmann scale ranges between I (normal) and VI (no movement)

Grade	Explanation
I	Normal symmetrical function
II	Slight weakness noticeable only on close inspection
	Complete eye closure with minimal effort
	Slight asymmetry of smile with maximal effort
	Synkinesis barely noticeable, contracture, or spasm absent
III	Obvious weakness, but not disfigurment
	May not be able to lift eyebrows
	Complete eye closure and strong but asymmetrical mouth movement
	Obvious, but not disfiguring synkinesis, mass movement, or spasm
IV	Obvious disfiguring weakness
	Inability to lift eyebrows
	Incomplete eye closure and asymmetry of mouth with maximal effort
	Severe synkinesis, mass movement, or spasm
V	Motion barely perceptible
	Incomplete eye closure, slight movement at mouth corner
	Synkinesis, contracture, and spasm usually absent
VI	No movement, loss of tone, no synkinesis, contracture, or spasm

Medical history, age, and gender data were recorded by an expert neurologist. Height and body weight were measured to obtain body mass index (BMI; kg/m2) and age- and sex-specific BMI percentiles. Associations between average doses of study medications and blood glucose, insulin and HOMA-IR values were examined in relation to age and gender. IR was calculated using the HOMA-IR formula of fasting insulin (μU/mL) x fasting glucose (mmol/L) / 405 using a cut-off value of 2.5. The homeostasis model assessment of IR (HOMA-IR) is a non-invasive and effective alternative method to evaluate insulin sensitivity based on the glucose level and the level of serum insulin measured in fasting conditions. HOMA-IR is considered a standard method of measuring IR in epidemiological studies [11].

Statistical Analysis

Normality of numerical data was tested by Shapiro-Wilk test. For normally distributed numerical data, one-way analysis of variance (ANOVA) and LSD (least significant difference) multiple comparison tests were used to compare 2 independent groups. Kruskal-Wallis test and all pairwise multiple comparison tests were used for non-normally distributed data. Relationships between independent categorical variables were tested by Chi-square test and relationships between numerical variables were tested by Spearman's rank correlation coefficient. For descriptive statistics, mean ±standard deviation and median (Inter quartile range 25%-75%) values were presented for numerical variables and number and percentage (%) for categorical variables. All analyses were performed using SPSS for Windows, version 24.0 and a p value equal and smaller than 0.05 was considered significant.

Results

Of 19 patients enrolled, 10 were female (52.6%). Patients had a mean age of 33 years, mean glucose value of 106 mg/dL, mean insulin value of 15.9 μU/mL and mean HOMA-IR value of 4.1 (Table 2). HOMA-IR was greater than 2.5 in 14 (73.7%) patients, all of whom were found to have insulin resistance. The remaining five patients did not have insulin resistance. Based on HB grading, moderate dysfunction of the facial nerve was found in 9 (47.4) patients and 4 (%21.1) patients had moderately severe dysfunction (Table 3). A moderate positive correlation and a statistically significant association were found between mean glucose value and HOMA-IR value ($r=0.548$; $p=0.015$). Age and glucose values were not statistically significantly associated with insulin and HOMA-IR values

(p=0.858 and p=0.015, respectively, Table 4). Comparison of HBS classes in terms of age, glucose, insulin and HOMA-IR values did not yield any statistically significantly differences between these variables (p=0.791, p=0.715, p=0.405 and p=0.693, respectively; Table 5). HB grade was not significantly associated with sex (p=0.454). Similarly, HB grade was not associated with IR either (p=0.710; Table 6).

Table 2: General identifier for numeric variables

Variable (n=19)	M [Q_1 Q_3]	Mean±SD
Age	33.00 [30.00 50.00]	37.000±18.00
Glucose (mg/dL)	106.00 [95.00 118.00]	112.74±33.52
Insulin (µU/mL)	15.90 [10.00 51.00]	30.25±30.33
HOMA-IR	4.10 [2.32 11.00]	6.90±6.38

Q_1: First quartile (25%), Q_3: Third quertile (75%), M: Median, SD: Standard deviation, HOMA-IR: Homeostatic model assessment for insulin resistance

Table 3: Demographic characteristics of patients

Variable		n	%
Gender	Male	9	47.4
	Female	10	52.6
HOMA-IR	IR+	14	73.7
	IR-	5	26.3
HBS	Slight Dysfunction	3	15.8
	Moderate Dysfunction	9	47.4
	Moderately Severe Dysfunction	4	21.1
	Severe Dysfunction	3	15.8

HOMA-IR: Homeostatic model assessment for insulin resistance, HBS: House-Brackmann Scale

Table 4: Relationship between age, glucose insulin and HOMA-IR

		Insulin	HOMA-IR
Age (years)	r	0.018	-0.044
	p	0.941	0.858
	n	19	19
Glucose (mg/dL)	r	0.301	0.548*
	p	0.211	0.015
	n	19	19

*(p<0.05), HOMA-IR: Homeostatic model assessment for insulin resistance

Table 5: Comparison of HBS classes in terms of age, glucose, insulin and HOMA-IR

Variable		n	Mean±SD	Test Statistics	p
Age	Slight Dysfunction	3	32.33±2.52	F=0.348	0.791
	Moderate Dysfunction	9	41.67±17.18		
	Moderately Severe Dysfunction	4	33.25±15.19		
	Severe Dysfunction	3	33.00±33.05		
	Total	19	37.05±17.67		
Glucose (mg/dL)	Slight Dysfunction	3	100.00±6.25	F=0.458	0.715
	Moderate Dysfunction	9	122.33±37.98		
	Moderately Severe Dysfunction	4	103.50±10.38		
	Severe Dysfunction	3	109.00±57.38		
	Total	19	112.74±33.52		
Insulin (µU/mL)	Slight Dysfunction	3	16.66±1.60	x^2= 2.917	0.405
	Moderate Dysfunction	9	42.39±36.51		
	Moderately Severe Dysfunction	4	27.03±31.23		
	Severe Dysfunction	3	11.70±2.07		
	Total	19	30.25±30.33		
HOMA-IR	Slight Dysfunction	3	4.88±1.65	x^2=1.454	0.693
	Moderate Dysfunction	9	8.80±7.28		
	Moderately Severe Dysfunction	4	7.08±8.35		
	Severe Dysfunction	3	2.93±1.04		
	Total	19	6.89±6.38		

F: ANOVA test, x^2: Kruskal-Wallis Test, HOMA-IR: Homeostatic model assessment for insulin resistance

Table 6: Comparison of categorical variables

		HBE			
		Slight Dysfunction	Moderate Dysfunction	Moderately Severe Dysfunction	Severe Dysfunction
		Count	Count	Count	Count
Gender	Male	2	3	3	1
	Female	1	6	1	2
		x^2= 2.621 P=0.454			
HOMA-IR	Yes	3	6	3	2
	None	0	3	1	1
		x^2= 1.380 P=0.710			

HOMA-IR: Homeostatic model assessment for insulin resistance, HBS: House-Brackmann Scale

Discussion

IR is a pathogenic factor for type 2 diabetes mellitus (DM) [12]. Increased insulin secretion and chronic hyperinsulinemia can develop when pancreatic beta cells can no longer compensate and maintain glucose homeostasis, leading to the development of type 2 DM [13]. In adults, a cut-off value of 2.5 is generally used for HOMA-IR. Another study in 691 apparently healthy Indian adolescents (aged 10–17 years) established a HOMA-IR cut-off of 2.5 [14]. In a prevalence study, IR was positive in 28.9% of females and 25.1% of males [15]. In one study, on average, 25% of overweight individuals had insulin resistance; however, in the present study, 52.5% of the total study sample tested positive for IR although our patients had normal body weight [16]. In contrast to previous studies, 73.7% of our patients tested positive for insulin resistance. IR coexists with neurodegenerative and infectious diseases, and metabolic abnormalities such as obesity and type 2 diabetes are frequently associated with underlying immune disorders. A higher prevalence of neurodegenerative diseases was shown in individuals with IR [17]. Vascular endothelium maintains the balance between vasodilation and vasoconstriction and IR may cause hypertension by disrupting the balance of active endocrine functions of the vascular endothelium [18]. Animal and human studies demonstrated inhibition of insulin signaling after exposure to oxidative stress at the cellular level [19] and established the link between IR and oxidative stress. In insulin resistance, plasminogen activator inhibitor-1 increases the risk for macrovascular disease by elevating Factor VII, Factor VIII, von-Willebrand factor and fibrinogen levels [20]. A study found a greater incidence of infection among patients with IR [21]. Previous studies have reported that HSV (herpes simplex virus), as an opportunistic infection agent, may cause BP in IR-positive patients and it seems likely that BP might be a manifestation of prediabetes. In one study, recovery from Bell's palsy in a diabetic group was found to be delayed in comparison to a nondiabetic group and the authors stated that more aggressive treatments might be considered in diabetic patients with severe Bell's palsy [22]. In another study, the recovery rate of BP was significantly lower in the group with metabolic syndrome (MS) than in the non-MS group and was particularly affected by diabetes mellitus obesity and high triglycerides [23]. Consistently, a separate study showed a tendency for incomplete recovery from BP among diabetic patients [24]. Aforementioned three studies also a statistically non-significant effect of high blood glucose on BP and HB grade in the diabetic group compared to the non-diabetic group, supporting our finding. In a review study involving 372 cases; it was found that patients with facial palsy most commonly presented with HB grades III and IV [25]. Similarly, in the present study, our patients presented mostly with HB grades III and IV. In the review study mentioned above, the highest incidence of BP was identified in patients between 39 and 50 years of age.

Consistently, the mean age of our BP patients was 33 years. Limitations of our study include lack of follow-up of patients during the treatment process and the failure to investigate the effect of IR on the duration of treatment. Other limitation of this study is that the number of patients is low, patients are not followed for a long time and therefore the recovery period of patients with IR is not monitored. In this sense there is a need for further study.

IR is a metabolic disorder which is closely related to obesity and abdominal adipose tissue mass. Further studies are needed to clarify the pathogenesis of insulin resistance. Polygenic etiology of IR should be investigated by genetic research. Prevention of IR might be possible in the future if its

mechanisms are fully described through molecular studies. Increasing evidence demonstrate the strong relation between insulin signaling pathways and complications of insulin resistance. It is crucial to prevent and reduce obesity in order to be able to overcome insulin resistance. IR may be present in apparently healthy individuals. Screening targeted to individuals at risk for IR may allow early detection of the condition. IR may be easily diagnosed using HOMA-IR formula based on fasting insulin and fasting glucose levels. Potentially severe complications of IR might be prevented by early diagnosis and lifestyle changes including dietary modification, regular exercise, and weight loss. Longstanding IR accompanied by obesity will inevitably lead to single or multiple manifestations of type 2 diabetes mellitus, cardiovascular diseases, hypertension and cancer. Estimation of pretreatment HOMA-IR value would be beneficial for both treatments planning and taking proactive measures against future development of diabetes in patients presenting with facial paralysis.

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Reliability and validity of the Turkish version of the foot function index in patients with calcaneal heel spur

Topuk dikeni olan hastalarda ayak fonksiyon indeksinin Türkçe geçerlik ve güvenirlik çalışması

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Abstract

Aim: One of the most extensively used questionnaires in studies and clinical trials is the Foot Function Index (FFI). The aim of our study was to evaluate the reliability and the validity of the FFI in Turkish patients with calcaneal heel spur.

Methods: A cross-sectional study was performed in 20014-2015 in Ankara, Turkey with 146 patients with calcaneal heel spur. Statistical analyses were performed using the SPSS software version 20. Intra-class correlation coefficients (ICC) and Cronbach alpha coefficients were used to determine test-retest reliability and internal consistency of FFI. Construct validity was tested by Pearson correlation coefficient approach comparing the correlation of the Visual Analogue Pain Scale (VAS-pain), foot and ankle outcome score (FAOS) and The Short Form-36 (SF-36) questionnaire with FFI.

Results: A hundred and forty six patients (125 women, 21 men) were enrolled in the study. The mean age of the patients were 46,4±10,3 years. The random ICC for the total FFI and three subscales ranged from 0.74 to 0.99. The Cronbach's alpha coefficient ranged from 0.78 to 0.83. In terms of validity, there was a significant correlation between the Turkish version of FFI, VAS, some of the sub-scales of FAOS and SF-36 scores ($p<0.05$).

Conclusion: The Turkish version of FFI was valid and reliable to assess the foot disease in patients with heel spur. It can be used for both in clinic and research studies in the assessment of pain, disability and limitation of the function of the foot.

Keywords: Foot function index, Reliability and validity, Foot diseases

Öz

Amaç: Ayak Fonksiyon İndeksi (Foot Function Index: FFI) klinik uygulamalar ve araştırmalarda yaygın kullanılan ölçeklerden biridir. Bu araştırmanın amacı FFI'in, topuk dikeni tanısı olan hastalarda Türkçe geçerlik ve güvenirliğini çalışmaktır.

Yöntemler: Verilerin İstatistiksel analizleri SPSS 20 paket programı kullanılarak analiz edilmiştir. Test-tekrar test güvenirliğini ve FFI iç tutarlılığını belirlemek için sınıf içi korelasyon katsayıları (ICC) ve Cronbach alfa katsayıları kullanılmıştır. Yapı geçerliği, vizüel analog skalası (VAS-ağrı), ayak ve ayak bileği sonuç skoru (FAOS) ve Kısa Form-36 (SF-36) ile FFI arasındaki ilişki Pearson korelasyon katsayısı ile test edilmiştir.

Bulgular: Çalışmamıza 125'i kadın 21'i erkek olmak üzere 146 hasta dahil edilmiştir. Hastaların yaş ortalaması 46,4± 10,3 yıl idi. Toplam FFI ve üç alt ölçek olan VAS, FAOS ve

SF-36 için rastgele ICC, 0,74 ile 0,99 arasında bulunmuştur. Cronbach'ın alfa güvenirlik katsayısı en düşük 0,78 ve en büyük 0,83 olarak hesaplanmıştır. Geçerlik açısından ise FFI ile VAS, FAOS ve SF-36 puanlarının bazı alt ölçekleri arasında anlamlı ilişki bulunmuştur ($p<0.05$).

Sonuç: Bu çalışmada, topuk dikeni tanısı olan hastaları değerlendirmek için kullandığımız FFI'nın Türkçe versiyonun geçerli ve güvenilir olduğu gösterilmiştir. Bu ölçeğin, klinik ve araştırmalarda ayak ağrıları, yetersizlik ve ayak fonksiyonlarını değerlendirmek için hastalara uygulanabileceğini düşünmekteyiz.

Anahtar kelimeler: Ayak fonksiyon indeksi, Geçerlik ve güvenirlik, Ayak hastalıkları

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Introduction

Foot pain has been shown to have a damaging impact on health-related quality of life across a spectrum of age groups [1]. Heel spur, is the most frequent reason of the calcaneal pain and is a common problem among adults [2]. Although the etiological mechanism of heel spur is not clearly known, it was suggested that repetitive traction of the insertion of the plantar fascia into the calcaneus and repetitive compression causes heel spurs [3].

Self-reported outcome scales have been used by clinicians and investigators to evaluate the effect of treatments directed at patients with foot problems and following impairments [4]. The use of valid, reliable, and responsive outcomes measures is important for successful clinical outcomes research. The American Orthopedic Foot and Ankle Society (AOFAS) scale is the most widely used one, in published studies to evaluate the outcomes of foot and ankle surgery [5]. Comparisons are difficult to make with these studies as a range of different measurement approaches have been used. One of the most extensively used questionnaires in studies and clinical trials is the Foot Function Index (FFI) [6-9]. This questionnaire has been developed and validated in 1991, and it has been compared and validated with other foot health questionnaires [10-14]. Previously, the adaptation of the FFI to Turkish in patients with plantar fasciitis was performed but the validity and reliability of FFI was not studied in patients with calcaneal heel spur [15]. The purpose of this study is to evaluate the reliability and validity of FFI in Turkish patients with foot pain related with calcaneal heel spur.

Materials and methods

The cross-sectional study was conducted in 20014-2015 in Ankara, Turkey. All patients gave their written informed consent to participate in this trial before enrolment and the study was approved by Ethics Committee at Ankara Training and Research Hospital. Permission to validate in Turkish the original version of the FFI was asked to the developer.

The included patients were adults >18 years old, duration of symptoms over 3 months, heel spur was diagnosed with localized tenderness at the tuberosity of calcaneus with typical radiological appearance. Patients were excluded in case of age less than 18 years, inflammatory or septic arthritis, and amputation of a limb, cancer, cognitive disorders, foot surgery and pregnancy. Also the patients with pain in the dorsiflexion of toes and patients with tenderness on the plantar fascia area indicating plantar fasciitis were excluded. The demographic properties including age, gender, occupation and body mass index (BMI) were recorded.

FFI was translated into Turkish by two Turkish physiatrists and an interpreter. After that they met in order to review the translations and inconsistencies in the translations were resolved by discussions among the translators. Independent back translation was performed by two native English speakers fluent in Turkish and with medical background. A second consensus meeting of all involved translators was held in order to check for any problems, and to establish the pre-final Turkish version of the FFI. During the translation stage of questionnaire, only one cultural adaptation was necessary regarding distance evaluation represented in the English version by “four blocks”. We have chosed to use numeric scale of distance to improve the understanding of patients. We have changed “four blocks” to 200 meters in Turkish form.

The final Turkish version was obtained after testing it on twenty patients with foot pain to determine the ease of understanding the questions. The feed-back from the pretest study group did not identify any concerns. The Turkish version of FFI was answered by the patients themselves. One physiatrist was in the interview room in order to help the patients in case they needed assistance, which was the case only in a few patients with difficulty in reading. The scale was completed by each patient twice with 10 days interval.

The FFI is a self-questionnaire made of 23 items and it is divided into three subscales: pain, disability and activity limitations for assessing patients with foot diseases [10,16]. Each item is rated on a 0-10 numeric scale and the scores of all items are summed separately for three subscales, divided by the maximum score achievable of all rated items, and finally multiplied by 100. Although all the various published translations of the FFI [17-18], included 18 items we have used the original questionnaire with 23 items.

We have used the foot and ankle outcome score (FAOS), the Short Form-36 (SF-36) questionnaire and visual analogue scale (VAS) to compare the FFI for reliability in Turkish patients with calcaneal heel spur.

The foot pain was assessed by the VAS that consisted of 0-10 cm line; 0 equal to ”no pain” and 10 equal to “worst possible pain” [19].

The FAOS has been validated for use in Turkey and consists of 42 items assessing five separate patient-relevant dimensions: Pain (nine items); other symptoms like stiffness, swelling, and range of motion (seven items); activities of daily living (ADL) (17 items); sport and recreational activities (Sport/Rec) (five items; and lower limb-related quality of life (QoL) (four items). To answer each question, five Likert boxes were used (no, mild, moderate, severe, extreme) and all items was scored from zero to four. Each of the five subscale scores were calculated as the sum of the items included. Raw scores were then transformed to a scale from zero to 100. The higher total value indicates the lesser problems and/or functional limitations [20].

SF-36 has been validated for use in Turkey21. This questionnaire provides eight separate subscales: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (EV), social functioning (SF), role emotional (RM), mental health (MH) which are then aggregated into two main scores: the physical composite score (PCS) and the mental composite score (MCS). The higher the score, the better was the perceived health level [21].

Statistical analyses

Data were analyzed using SPSS 20 (IBM SPSS Incorporated, Chicago, IL, USA). Descriptive analyses were applied to calculate means and standard deviations of the demographic variables. No factor analysis was performed because the factors were determined in the study of Budiman-Mak [10].

Reliability

For test-retest reliability, all patients completed the questionnaires at the same time of day, during a non-treatment period [22]. Intra-class correlation coefficients (ICC) were used to determine test-retest reliability of the scores on three subscales of FFI and total FFI. Cronbach alpha coefficients were used to determine internal consistency of the entire questionnaire and of each domain [23]. As recommended, internal consistency of a magnitude of 0.70 or greater was sought. Cronbach alpha was determined as high correlation if values in range of 0.80-0.95 were obtained, where a value >0.95 indicated excessive internal consistency. The correlation coefficient values of <0.4 show weak correlation, 0.4–0.74 illustrate moderate correlation, 0.75–0.9 indicate strong correlation, and >0.9 very strong correlation [24].

Validity

Construct validity was tested by Pearson correlation coefficient approach comparing the correlation of the similar scales of the FFI. Pearson correlation coefficient was used to evaluate the relationship between FFI and foot and ankle outcome score (FAOS), SF-36 questionnaire and Visual Analogue Pain Scale (VAS-pain). It was expected that conceptually related scales would correlate better with the FFI. The correlation coefficients are interpreted as follows: <0.4 was weak, 0.4-0.74 was moderate, 0.75 to 0.9 was strong, and >0.9 was very strong [24]. The level of significance was set at $p<0.05$.

Results

A hundred and ninety patients with foot pain were evaluated and 146 patients (125 women, 21 men) with heel spur were recruited for the study. The flow chart of the study is shown in figure 1. The mean age and BMI of the patients were 46.4±10.3 years and 30.7±5.4 kg/m2 respectively. They had professions as follows; 67.8%, 11.6%, 15.8%, 2.1% and 2.7% of patients were housewife, officer, workman, student and retired respectively. The mean duration of the disease was 15.8±27.2 months. During the translation stage of questionnaire we have changed “four blocks” to distance of 200 meters in Turkish form.

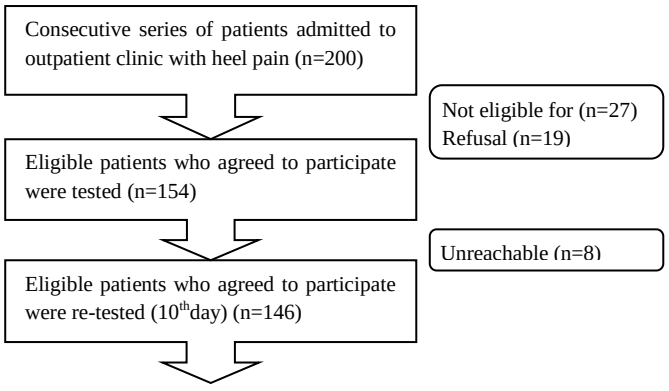

Figure 1: The flow chart of the study

Reliability

Evaluation of test-retest measurement within 10 day showed that there was no difference between two measurements as all p values were greater than 0.05. The random ICC for the total FFI and three subscales ranged from 0.74 to 0.99. The test-retest reliability of the disability with 0.97, activity with 0.99 and total FFI with 0.93 were strong, that of pain with 0.74 was moderate. The Cronbach’s alpha coefficient ranged from 0.78 to 0.83 (Table 1).

Table 1: Descriptive statistics and reliability of FFI (n=146)

	Mean Score±SD			ICC (95% CI)	Cronbach’s alpha
	First assessment	Second assessment	p		
Pain	71.1±9.7	73.7±12.3	0.057	0.74 (0.68-0.80)	0.81
Disability	74.5±11.4	76.4±11.6	0.158	0.97 (0.94-0.99)	0.83
Activity	26.4±14.1	26.7±14.3	0.856	0.99 (0.97-1.00)	0.81
TFFI	57.3±8.6	58.9±8.8	0.758	0.93 (0.88-0.97)	0.78

SD: Standard deviation, ICC: Intra class correlation coefficient, CI: Confidence interval

Validity

In terms of validity, there was a significant correlation between the Turkish version of FFI, VAS, some of the sub-scales of FAOS and SF-36 scores ($p<0.05$). Table 2 gives an overview of correlation coefficients between total and subscales of FFI and the VAS, FAOS and SF-36.

Table 2: Correlation between VAS, the FFI subscales, FAOS and SF-36 subscales (construct validity)

	Pain	Disability	Activity	TFFI
VAS	0.553**	0.441**	0.284**	0.557**
p-Value	0.000	0.000	0.001	0.000
FAOS- Pain	-0.151	-0.212*	-0.098	-0.204*
p-Value	0.069	0.010	0.238	0.014
FAOS-Symptoms	-0.044	-0.028	0.090	-0.078
p-Value	0.597	0.737	0.280	0.307
FAOS-ADL	-0.227**	-0.198*	-0.055	-0.143
p-Value	0.006	0.017	0.511	0.737
FAOS-Sport/rec	-0.095	-0.243**	0.115	-0.205*
p-Value	0.256	0.003	0.169	0.028
FAOS-QoL	-0.160	-0.139	-0.041	-0.144
p-Value	0.054	0.094	0.622	0.066
SF36-Physical functioning	-0.191*	-0.161	-0.149	-0.224**
p-Value	0.021	0.052	0.07	0.002
SF36-Role physical	-0.085	-0.174*	0.044	-0.085
p-Value	0.309	0.035	0.597	0.309
SF36-Bodily pain	-0.356**	-0.232**	0.039	-0.257**
p-Value	0.000	0.005	0.642	0.000
SF36-General health	-0.100	-,016	-0.018	-0.055
p-Value	0.230	0.849	0.825	0.523
SF36-Vitality	-0.204*	-0.119	-0.028	-0.145
p-Value	0.013	0.152	0.737	0.149
SF36-Social functioning	-0.145	-0.110	-0.100	-0.157
p-Value	0.082	0.187	0.581	0.747
SF36-Role emotional	-0.131	-0.171*	0.046	-0.100
p-Value	0.116	0.039	0.581	0.747
SF36-Mental health	-0.179*	-0.152	0.006	-0.131
p-Value	0.030	0.067	0.939	0.339

TFFI: total function test,*p<0.05, **p<0.01

Discussion

One in every five middle-aged person presents foot and ankle pain, and this may compromise locomotion, impairment of balance and a limitation in functional activities of daily living Pathological conditions of the ankle and foot are under evaluation by healthcare professionals and researchers, using self-reported outcome instruments. These instruments make it possible to use of reliable measurements for patients’ perceptions, and specific instruments have been standardized in order to follow up and evaluate the effects of a given intervention [7,9].

The FFI has been widely used in studies of foot and ankle problems, related with various pathologies like acute and chronic diseases, congenital problems, injuries and surgical corrections [11]. FFI is a self- questionnaire with a short administration time making it easy to use in daily practice. It is easy to fill out. The reliability and validity of FFI was evaluated by many studies in different cultural populations [17,25,26]. Beside this it was classified as the fourth most used questionnaire for ankle and foot evaluations between 2002-2011 years [9]. Calcaneal heel spur is a common disorder of the foot that occurs in 15–20 % of the population and it can be seen in every age.

The symptoms of calcaneal spur is more frequently seen in overweight, elderly, and female patients [27,28]. Although calcaneal heel spur can be associated with plantar fasciitis the differential diagnosis can be made by simple clinical tests and physical examination findings.

Herein we aimed to evaluate the validation and reliability the FFI questionnaire in Turkish patients with foot pain due to calcaneal heel spurs. Reliability and validity study of foot function index was first performed by Budiman-Mak et al. [10] in patients with rheumatoid arthritis. For the analysis of our study, the total FFI score was used as well as subscales because we suggest that it is more practical in clinical application similar to a previous study and unlike previous studies that used the scores of each subscale [16,17,25,26,29].

In our study, there was a high correlation between all items of the Turkish FFI questionnaire, which demonstrates good internal consistency. We found that all subscales of the Turkish FFI had good internally consistency and test-re-test reliability similar to Budiman-Mak et al [10]. The Turkish version was reliable for the total questionnaire and subscales domains (Cronbach alpha: 0.78). Furthermore, the reliability studies of the subscales "pain", "disability" and "activity limitation" showed moderate to strong reproducibility with ICC of 0.74, 0.97, 0.99 respectively similar to Martinez et al who tested the validity of Brazilian-Portuguese FFI [9]. These results were higher than the recommended level of 0.70.

The Turkish version of FFI was reliable and internally consistent for the total FFI score, pain, disability, activity limitation subscales of FFI (Cronbach alpha: 0.78, 0.81, 0.83, 0.81 respectively) and it was comparable to those observed in the original version and in other validation studies [10,17,30]. It is known that, a too high Cronbach's alpha coefficient value might indicate a high level of item redundancy. For this reason, it is suggested that Cronbach's alpha should be above 0.70 but not higher than 0.90 similar to the results of our study [21]. Besides, these findings show that the items of the Turkish version are homogenous, as the original version [9,10].

We have used VAS-pain, FAOS and SF-36 for validity analysis. We found positive correlations between VAS-pain and total and subscores of FFI but inverse correlation was observed between subscale of FAOS and SF-36. The scoring system in FFI indicates that the lower are the scores, the healthier are the patients, while in the latter two questionnaires the inverse is the case.

The total score and subscores of Turkish FFI correlated moderately with VAS (weakly with the activity subscales of FFI) similar to Spanish adaptation of FFI [29], while German and Italian adaptation of FFI found a strong correlation with VAS [16,17]. We found weak correlation with FAOS-pain, FAOS-ADL, FAOS-sport and physical function, physical role, bodily pain, vitality emotional role and mental health of SF-36. The values of FAOS-symptoms and FAOS-Qol did not correlate with the total and the subscales of Turkish FFI while it was reported that all subscores of FAOS except FAOS-symptoms were correlated strongly with FFI scores in a previous study [9].

As far as we can see, we have found a correlation with all subscales of SF-36 except two subscales (general health and social functioning) unlike to other studies [9-10,16]. Social and general health status is unrelated to orthopedic problems and could be inconsistent with findings [9]. Spanish adaptation of FFI had a weak correlation with physical and mental health of SF-36 [29]. German adaptation of FFI found a moderate with the physical SF-36, and weak with the mental SF-36 scores [17], while Chinese adaptation to had a strong correlation with the physical SF-36, but weak with the mental SF-36 scores [26]. In our study total FFI scores were correlated moderately with VAS, weakly with FAOS-pain, FAOS-sport, SF-36 physical function and bodily pain subscores. The main problem we encountered in the analysis of parameters consisted with the items of activity limitation. This may be due to the fact that most of our patients with pain and disability did not use assistive devices and had almost no activity limitations. Landorf et al. [13] suggested that FFI has limitations in people without marked disability, particularly in the activity limitation subscale and this subscale was prone to inconsistent scoring. However we considered it would be more appropriate to apply the original form and included the activity limitation subscale Most of the previous studies excluded the activity limitation subscale of FFI in their validity studies [16,17,30].

One of the limitations of our study is to evaluate patients with only calcaneal heel spur; however, it may be necessary to assess the treatment effects indicating the responsiveness of Turkish version of FFI, which may be a subject of future studies. Also further testing in different conditions related with foot pain may be needed to ensure the validity and reliability of this scale in other Turkish patients groups with foot pain.

Conclusion

Our study has demonstrated that the FFI was easy to use, valid and reliable to assess the foot disease in Turkish patients with calcaneal heel spur. It can be used for both in clinic and research studies in the assessment of pain, disability and limitation of the function of the foot. Future studies should be encouraged to investigate the responsiveness of this questionnaire pre and after treatments of specific foot diseases. But we have observed that activity limitation correlated with VAS-pain only. Therefore the use of 'activity limitation' subscale may not be necessary in clinical assessments.

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After obstructive sleep apnea syndrome surgery, preoperative, postoperative early and late change of neutrophil / lymphocyte ratio, platelet / lymphocyte ratio and mean platelet volume

Obstruktif uyku apne sendromu cerrahisinden sonra nötrofil/lenfosit oranı, ortalama tombosit hacmi ve trombosit/ lenfosit oranlarının preoperatif ve postoperatif erken ve geç dönemdeki değişimi

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Abstract

Aim: The aim of this study was to investigate the relationship between the severity of obstructive sleep apnea syndrome (OSAS), neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and mean platelet volume (MPV), preoperative and postoperative early and late levels of these patients surgery related changes were investigated.

Methods: A total of 148 patients (22 women, 14.9% and 126 men, 85.1%) who underwent OSA diagnosis and surgical treatment were included in the study: patients with mild to moderate OSAS [86 (58.1%)], and severe OSAS [62 (41.9%)] patients with apnea hypoapnea index. (AHI: 5-15 mild OSAS, AHI: 15-30 moderate OSAS and AHI >30 severe OSAS). Patients were divided into two groups. Retrospectively, the blood results of these patients were investigated and preoperative, postoperative early and late full blood results were examined.

Results: Weight and BMI values were found to be high in the heavy OSAS group. There was no significant difference between mild-moderate OSAS and severe OSAS groups, preoperative, early and late postoperative periods, and between NLR, PLR and MPV values. Intra-group comparison showed an increase in NLR and PLR in the early postoperative period in both groups. There was no difference between the other values. In late postoperative period, NLR levels decreased to preoperative values while PLR levels were higher than preoperative values.

Conclusion: The similarity of NLR, PLR, and MPV values between the mild-moderate and severe OSAS groups as a marker of systemic inflammation and the fact that airway obstruction was remained unchanged suggests that oxidative stress and systemic inflammation in this disease are due to a variety of factors besides airway obstruction.

Keywords: Obstructive sleep apnea syndrome, Neutrophil lymphocyte ratio, Platelet lymphocyte ratio, Mean platelet volume

Öz

Amaç: Bu çalışmada Obstrüktif uyku apne sendromu (OUAS) şiddeti ile Nötrofil Lenfosit oranı (NLO), Trombosit Lenfosit oranı (TLO) ve Ortalama Trombosit Hacmi (OTH) arasındaki ilişki ve bu hastaların preoperatif ve postoperatif erken ve geç dönemdeki düzeyleri, cerrahiye bağlı değişimleri araştırıldı.

Yöntemler: OUAS tanısı konmuş ve tedavi amacıyla cerrahi operasyon yapılmış toplam 148 hasta (22 kadın %14.9 ve 126 erkek %85.1) çalışmaya alındı. Hastalar apne hipoapne indeksine (AHİ) göre hafif-orta OUAS'lı hastalar (86 (%58.1)), (AHİ:5-15 Hafif OUAS, AHİ:15-30 Orta OUAS) ve Ağır OUAS'lı (62 (%41.9)) hastalar olarak iki gruba ayrıldı. Retrospektif olarak hastaların kan sonuçları tarandı ve preoperatif, postopertif erken ve geç dönem tam kan sonuçları incelendi.

Bulgular: Kilo ve BMI değerleri Ağır OUAS grubunda yüksek saptandı. Hafif-Orta OUAS ile Ağır OUAS grupları, NLO, TLO ve OTH değerleri preoperatif, erken ve geç postoperatif dönemler, gruplar arası karşılaştırıldığında anlamlı fark bulunmadı. Grup içi karşılaştırmada ise her iki grupta da NLO'da ve TLO'da postoperatif erken dönemde artış saptandı. OTH değerler arasında fark bulunmadı. Postoperatif geç dönemde NLO düzeyleri preoperatif değerlere düşerken, TLO düzeyleri preoperatif değerlere göre yükseklik devam etmekte idi.

Sonuç: Sistemik inflamasyonun belirteci olarak kullanılan NLO, TLO ve OTH değerlerinin Hafif-Orta ve Ağır OUAS grupları arasında benzer olması ve hava yolu tıkanıklığının giderilmesine rağmen değişmeyişi bu hastalıktaki oksidatif stres ve sistemik inflamasyonun hava yolu tıkanıklığının yanı sıra çok çeşitli faktörlere bağlı olduğunu düşündürmektedir.

Anahtar kelimeler: Obstruktif uyku apne sendromu, Nötrofil lenfosit oranı, Trombosit lenfosit oranı, Ortalama trombosit hacmi

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Introduction

Obstructive sleep apnea syndrome (OSAS) is a disease with recurrent obstructions of the upper airway during sleep. OSAS is seen in approximately 4% of adult males and 2% of females [1]. Oxidative stress and airway inflammation play an important role in the pathophysiology of OSAS [2]. Neutrophils and leukocytes play an important role in the development of inflammatory response. Numerous cytokine secretions and immune response and inflammatory reactions are initiated. In recent years, neutrophil lymphocyte ratio (NLR), thrombocyte lymphocyte ratio (PLR) and mean platelet volume (MPV) from hemogram data have been used as indicators of systemic inflammation.

The aim of this study is to demonstrate the association between OSAS severity and NLR, PLR, and MPV in patients undergoing surgery due to OSAS, and to reveal early and late changes in these parameters before and after operation.

Materials and methods

After approval of the ethics committee, a total of 222 patients with OSAS due to radio frequency application, uvulopalatopharyngoplasty, tongue root suspension surgery between January 2014 and March 2016 were investigated using the hospital data system. A total of 148 patients (22 women, 14.9% and 126 men, 85.1%) were included in the study. Seventy-four patients who could not have postoperative early and late hemogram studies were excluded due to lack of data. Patients' age, weight, height, BMI and sex were taken from file records. Patients' polysomnography, preoperative, early and late postoperative hemogram results, neutrophil, lymphocyte, platelet and MPV values were obtained from file records. Patients were divided into two groups according to their apnea hypoapnea index (AHI) values: mild to moderate OSAS group (AHI 5-30) and severe OSAS (AHI 30>) group

Statistical analysis

Descriptive statistics are presented with frequency, percent, mean, standard deviation (SD) and median (median), minimum (min), max (max) values. Fisher's Exact Test or Pearson Chi-square test was used to analyze the relationships between categorical variables.

In the normality test, the Shapiro Wilks test was used when the number of samples in the group was less than 50, and the Kolmogorov-Smirnov test was used when it was large. The Mann-Whitney U test was used when the difference between the two groups was not in normal distribution, and the Student t test was used when there was difference between the 2 groups. For each group, the Wilcoxon test was used when the measurements did not fit the normal distribution, and the Paired Samples t test was used for the normal distribution. Repeated Measure ANOVA was used when the parametric assumptions were provided for the comparison between the measurement change differences of the groups. In the other case, the difference between the measurements was compared with the Mann-Whitney U test between the two groups. Friedman test and Wilcoxon signed ranks test were used for preoperative, postoperatively early and late full blood results

Analyzes were done with SPSS 23.0 package program. P values less than 0.05 were considered statistically significant.

Results

When the two groups were compared, the weight and BMI values were significantly higher in the severe OSAS group (Table 1, $p<0.05$). There was no difference between age and height ($p>0.05$). Male gender was higher than female sex in intra-group comparison (Table 1, $p<0.05$). When the AHI score was compared between the groups, it was found as 53±2.3 in the 14±0.7 severe group in the mild-to-moderate group and statistically higher in the severe OSAS group (Table 1, $p<0.05$).

Table 1: Demographic and AHI values of OSAS Groups

	Mild - Moderate OSAS	Severe OSAS
Age	48.4±1	47.4±1.2
Height (cm)	169.8±1.6	172±1.0
Weight	84.7±1.3*	92.8±1.7*
BMI	28.9±0.4	31.1±0.4
Number of women	18 (% 81.8)	4 (%18.2)
Number of males	68 (%54.0)*	58 (%46.0)*
Total patient	86 (%58.1)	62 (%41.9)
AHI	14±0.7*	53±2.3*

OSAS: Obstructive sleep apnea syndrome, BMI: Body mass index, AHI: Apnea hypoapnea index, Mean ± Standard deviation in comparison between groups, *p<0.05

Robotic surgery In 20 patients (23.3%) in the mild-moderate OSAS group, 35 patients (56.5%) in the severe OSAS group were treated. The rate of tongue root suspension and robotic surgery was higher in the severe OSAS group ($p<0.05$). There was no significant difference between the groups in other surgical procedures (pulse radio frequency application, uvulopalatopharyngoplasty, tongue root suspension, robotic surgery) ($p>0.05$) (Table 2).

Table 2: Surgical Procedures of OSAS Groups

Groups	Radio frequency application	Uvulopalato-pharyngoplasty	Tongue root suspension	Robotic surgery
Mild - Moderate OSAS	37 (%43.0)	74 (%86.0)	26 (% 30.2)*	20 (%23.3)*
Severe OSAS	20 (%32.3)	49 (79.0)	39 (% 62.9)*	35 (%56.5)*
Total	57 (%100)	123 (% 100)	65 (% 100)	55 (% 100)

There was no significant difference between mild-moderate OSAS and severe OSAS groups, NLR, PLR, and MPV values preoperatively, early and late postoperatively, and between groups (Table 3, $p<0.05$). Intra-group comparison showed an increase in early postoperative period in NLR in both groups ($p<0.05$). In the late postoperative period, NLR values were found to decrease preoperatively (Table 3, $p>0.05$).

Table 3: Comparison of preoperative (NLR1), postoperative early (NLR2), and late (NLR3) values of Neutrophil Lymphocyte Ratios of OSAS groups

Groups	NLR1	NLR2	NLR3
Mild - Moderate OSAS	1.92±0.83	6.86±4.44*	1.89±0.56
Severe OSAS	1.90±0.85	8.64±4.87*	2.18±1.63

NLR: Neutrophil lymphocyte ratio, Mean scores ± standard deviation, *p<0.05

When the mild-moderate OSAS and severe OSAS PLR values were compared within the group, an increase in preoperative values was detected in the early postoperative period (Table 4, $p<0.05$). There was no significant difference between groups in preoperative and postoperative early and late periods (Table 5, $p>0.05$).

Table 4: Comparison of preoperative (PLR1), postoperative early (PLR2), and late (PLR3) values of platelet lymphocyte ratios of OSAS groups

Groups	PLR1	PLR2	PLR3
Mild - Moderate OSAS	101.3±29	161.4±72*	128.8±42
Severe OSAS	96.4±59	179±66*	135.5±52

PLR: Platelet lymphocyte ratio, Mean scores ± standard deviation,*p<0.05

Table 5: Comparison of preoperative (MPV1), postoperative early (MPV 2), and late (MPV3) values of mean platelet volume ratios of OSAS groups

Groups	MPV1	MPV2	MPV3
Mild - Moderate OSAS	7.62±0.93	7.73±0.89	7.59±1.16
Severe OSAS	7.39±0.99	7.30±0.90	7.34±1.02

MPV: Mean platelet volume, Mean scores ± standard deviation. *p<0.05

Discussion

The aim of this study was to investigate the role of oxidative stress and systemic inflammation in the pathogenesis of OSAS. We found that 1) there was no difference between the severity of the disease and the markers of inflammation, and 2) no evidence of systemic inflammation markers by elimination of airway obstruction.

OSAS is associated with pro-inflammatory and prothrombotic agents [3-5]. Components of leukocytes, such as neutrophils and lymphocytes, play an important role in inflammatory processes. NLR has been proposed as a new marker for systemic inflammatory response in various diseases [6-9]. Various peripheral artery diseases, coronary artery disease, and some gynecologic and hepatobiliary malignancies have high PLR values and are associated with poor prognosis. NLR increases in systemic inflammation, in some gynecologic and gastrointestinal cancers, and in some cardiovascular diseases [10-12]. The platelet size measured as mean platelet volume (MPV) is a good indication of platelet-specific activities such as platelet aggregation, thromboxane A2, platelet factor 4 and thromboglobulin release [10,13]. Mean platelet volume increases in diabetes mellitus [14,15], myocardial infarction [16-18], smoking [19] and renal artery stenosis [20]. Platelet activation plays a role in inflammatory process upregulation by interacting with leukocytes as well as endothelial adhesion and aggregation [21]

Inflammatory markers related to the severity of the disease

In our study, NLR PLR and MPV were found to be comparable between the mild and moderate OSAS patients' group and the severe patients' group. It has been reported that NLR can give an idea about the presence and severity of OSAS [22]. In a study conducted by Sünbül et al. [22] 130 OSAS patients and 65 healthy subjects were compared and NLR was found significantly higher than healthy subjects. In addition, it was stated that AHI score and NLR values showed a significant correlation. In another study, NLR was found to be higher in the OSAS group compared to 171 OSAS patients and 118 control groups [23]. Song et al. [24] 290 patients were divided into four groups according to their AHI value, and compared PLR with OSAS severity (as reflected by AHI) was significantly associated with the study. In our study, there was no relationship between the severity of the disease and PLR. Platelet sizes are given as MPV and are indirectly related to their activity. It has been reported that MPV decreases during particularly active periods during the disease course [10]. Varol et al. [25] reported that OSAS levels were also higher in the MPV. Another study reported a correlation between MPV and AHI in OSAS patients [26]. In a study conducted by Kurt et al. [27] 98 OSAS patients were grouped according to their AHI values, and there was no difference between the AHI groups and the MPV values. We also found no difference between the mild-moderate OSAS group and the severe OSAS group between the groups and intra-group statistical evaluation. In our study, NLR, PLR and MPV did not change with the severity of the disease. This suggests that systemic inflammation and oxidative stress as well as other factors are more important in the pathogenesis of the disease.

Postoperative change of inflammatory markers

In our study, NLR and PLR values were significantly increased in the early postoperative period in both groups, but there was no difference in preoperative and late postoperative period. MPV was found to be similar in all three periods. In literature, no study comparing preoperative and postoperative NLR and PLR values was found in OSAS patients. In a study of 37 patients who received uvulupalatal flap surgery after having diagnosed OSAS, blood and polysomnographic analyzes of pre- and post-operative blood samples were found to have no correlation with polysomnographic parameters [28]. The increase in NLR and PLR in our postoperative, early postoperative period was thought to be associated with secondary inflammation of the operation. Findings of our study suggest that the inflammatory process involved in the pathogenesis of this disease does not affect the operation in the long term.

In conclusion, the fact that NLR, PLR and MPVvalues used as indicators of systemic inflammation are similar between the mild-moderate and severe OSAS groups and that airway obstruction is remained unchanged, suggests that oxidative stress and systemic inflammation in this disease are due to a variety of factors besides airway obstruction. There is a need for further studies to evaluate these.

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Incidental gallbladder cancer: Review of 3856 cholecystectomies

İnsidental safra kesesi kanseri: 3856 kolesistektominin incelemesi

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Abstract

Aim: Gallbladder cancer (GBC) is a rare but fatal disease that causes more than 5000 new cases per year in the United States. In the pre-operative period, it is diagnosed in less than 20% of the cases of GBC. The remaining cases are diagnosed after laparoscopic cholecystectomy or intraoperative. Following the 0.25-3% of laparoscopic cholecystectomy, GBC is incidentally detected during histopathology. However, the incidental GBC constitutes 74-92% of all GBCs. The most important step in this disease is the correct staging. Staging determines disease management and treatment options and predicts survival. Curative surgeries in the treatment of GBC are limited to local resectable disease. In this study, it was aimed to present cases of GBC which was diagnosed incidentally after cholecystectomy and premalignant gallbladder lesions (BillIn: Biliary intraepithelial neoplasia).

Methods: 3856 patients who underwent cholecystectomy between 2009 and 2017 constituted the study universe. Patients who were diagnosed as incidental GBC (eight patients (0.21%)) and BillIn (five patients (0.12%)) were examined as a result of histopathological examination. The patients were recorded in terms of demographic data, histopathology, surgical reports and follow-up.

Results: A total of 13 (0.33%) patients were detected in the study group, including GBC and BillIn. The mean age of patients was 54.8±14.3 (age range 33-83), seven male and six women. Although cholecystectomy was performed more frequently in women (72.7%) as determined in the study universe, GBC was seen more frequently in male gender ($p<0.05$). Distribution of tumor stage in malignant patients was identified; four patients were observed in T2, three patients T1a and T3 GBC in one patient, BillIn in five patients.

Conclusion: GBC and BillIn are rare histopathological findings which are detected after cholecystectomy performed due to gallstone disease. Mean survival time of GBC is lower than other gastrointestinal cancers. The recent pre-operative examinations and a frozen-section examination in case of malignancy suspicion has been suggested in the literature, therefore surgeons should be prepared for advanced therapies.

Keywords: Gallbladder, Incidental cancer, Cholecystectomy

Öz

Amaç: Safra kesesi kanseri (SKK), ABD'de yılda 5000'den fazla yeni vakaya neden olan ender görülen ancak ölümcül bir hastalıktır. Ameliyat öncesi dönemde SKK olgularının %20'sinden azında teşhis konulur. Kalan olgular laparoskopik kolesistektomi sonrası ya da intraoperatif olarak teşhis edilir. SKK, laparoskopik kolesistektomilerin %0,25-3'ünü takiben tesadüfen histopatoloji sırasında saptanır. Bununla birlikte insidental SKK, tüm SKK'ların %74-92'sini oluşturmaktadır. Bu hastalıkta en önemli adım doğru evrelendirilmedir. Evreleme, hastalık yönetimi ve tedavi seçeneklerini belirler ve sürviyi öngörür. SKK tedavisinde küratif ameliyatlar, lokal rezektabl hastalık ile sınırlıdır. Bu çalışmada kolesistektomi sonrası insidental tespit edilen SKK ve premalign safra kesesi lezyonu olan biliyer intraepitelial neoplazi (BillIn) (safra kesesi displazisi) olgularını sunmak amaçlanmıştır.

Yöntemler: Çalışma evrenini 2009-2017 yılları arasında kolesistektomi gerçekleştirilen 3856 hasta oluşturdu. Histopatolojik inceleme sonucunda insidental olarak saptanan SKK (sekiz hasta (%0,21)) ve BillIn (beş hasta (%0,12)) tanısı alan hastalar irdelendi. Hastalar demografik veriler, histopatoloji, ameliyat raporları ve takipler açısından kayıt edildi.

Bulgular: Çalışma grubunda SKK ve BillIn olmak üzere toplam 13 (%0,33) hasta tespit edildi. Hastaların ortalama yaşı 54,8±14,3 (yaş aralığı 33-83), yedisi erkek ve altısı kadın idi. Çalışma evreninde tespit edildiği kadarıyla kolesistektomi kadınlarda (%72,7) daha sık yapılmasına rağmen, SKK erkek cinsiyette daha sık görüldü ($p<0,05$).

Sonuç: SKK ve BillIn safra taşı hastalığına yönelik kolesistektomi sonrası tesadüfen rastlanan histopatolojik bulgulardır. Diğer gastrointestinal kanserlere göre, SKK sağkalımı düşük olan kanserlerdendir. Literatürde önerilen ameliyat öncesi yakın zamanda gerçekleştirilecek görüntüleme tetkikleri, gereğinde frozen inceleme yapılması ve gerekebilecek ileri tedavilere hazırlıklı olmaktır.

Anahtar kelimeler: Safra kesesi, İnsidental kanser, Kolesistektomi

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Introduction

Laparoscopic cholecystectomy is the gold standard for the treatment of benign gallbladder diseases in all over the world, with decreased postoperative pain, premature oral intake, premature discharge and better cosmetic results, with low morbidity rates for the last 20 years. Although developments in imaging techniques are promising, especially with the widespread use of techniques such as abdominal tomography (CT) and ultrasound (USG), early detection of gallbladder cancer (GBC) that does not cause specific symptoms in the early period may not be possible. In general, only 30% of the patients have doubts in the preoperative period and the remaining 70% are revealed in postoperative pathological examination [1-3]. In other words, in the literature, approximately 1 of each 100 laparoscopic cholecystectomy could be diagnosed with cancer [4].

For the first time, Maximillian Stoll mentioned GBC in Vienna in 1777 [5]. After many years, Nevin et al. [6] revealed the first GBC staging and the survival rates following the open cholecystectomy. Drouard et al. [7] showed the port location metastases in 1991. The GBC is a very aggressive disease and 5-year survival rates 3-13%, the mean survival time is 3-11 months. The underlying cause of these ratios is the very late occurrence of the symptoms such as pain, jaundice and the disease is in very advanced stages when diagnosed (T3, T4) [1,8]. The incidental GBC is a cancer diagnosed with postoperative pathological examination that is not diagnosed in the preoperatively period. There is no effective treatment method except for the surgical resection of the GBC, and the complete resection appears as a single curative method [9-11].

The aim of our study is to determine the incidence of incidental GBC in patients who underwent laparoscopic cholecystectomy due to symptomatic gallbladder stone in our clinic, compare with the rates in our country and the world in light of literature information, clinical and to investigate their pathological characteristics, to determine the prognostic factors affecting survival, and to detect recurrence rates.

Materials and methods

We designed a retrospective cohort study. The records of 3856 patients who underwent laparoscopic cholecystectomy due to symptomatic gallbladder stone between 2009 and 2017 at our general surgery clinic were retrospectively examined. In the postoperative period, the demographic characteristics of patients who were diagnosed as GBC and biliary intraepithelial dysplasia (BillIn) with histopathological examination and survival rates were determined, and compared with literature information. In the preoperative period, physical examination, anamnesis, laboratory or radiological examinations were not suspicious for malignancies in any of the patients. All surgeries were performed by specialist general surgeons, with 14 mm-Hg CO2 with standard 4 ports and pneumoperitonium. Tumor staging were recorded according to the criteria in American Joint Committee on Cancer (AJCC) [12]. The postoperative follow-up and treatment of the patients were performed according to international guidelines.

Statistical analysis

Categorical variables are expressed as the frequency and percentage, parametric data with normal distribution are expressed as mean ± standard deviation, parametric data that does not conform to the normal distribution are expressed as median, inter quartile range and value range. In comparison, Fisher's exact test was used for categorical data; the T-Test is used for parametric data. If the value of p is 0.05 or lower than 0.05 in the confidence range of 95%, the differences were considered statistically significant.

Results

A total of 13 (0.33%) patients were detected in the study group including GBC (n=8, 0.20%) and BillIn (n=5). Flow diagram of the study is shown in figure 1. The mean age of patients was 54.8±14.3 (age range 33-83), seven male and six women. Although cholecystectomy was performed more frequently in women (72.7%) as determined in the study universe, GBC was seen more frequently in male gender ($p<0.05$). Distribution of tumor stage in malignant patients was identified; Four patients were observed in T2, three patients T1a and T3 GBC in one patient, BillIn in five patients. Patients with T3 were diagnosed during surgery. Advanced surgical resection was not possible due to poor patient's overall condition. The patient deceased at the postoperative first month. Both extended hepatectomy and lymphatic dissection were performed in patients with T2 GBC; while these patients were alive and followed (the average follow-up period was 18 months). Surgery was not performed due to the detection of metastasis in one patient, the patient deceased at six months after the first surgery. In one patient, no additional surgery could be performed because a patient did not approve the surgery. No additional treatment was applied to patients who were diagnosed with T1a GBC and BillIn.

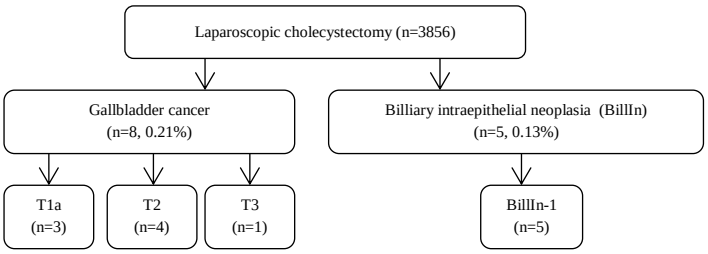

Figure 1: Flow diagram of the study

Discussion

GBC is a rare cancer and is seen at 3 percent in 100,000 worldwide. The incidence is a geographical distribution and is most commonly seen in Chile, Japan and Northern India. The most frequent cancer of the bile pathways is the gastrointestinal tract's most frequent cancer [1,13]. Gallbladder stones, advanced age, sclerosing cholangitis, porcelain pouch factors such as GBC's best known risk factors. In general, the prognosis of GBC is relatively weak and the presence of the tumor's penetration depth and lymph node metastasis was determined as the most important prognostic factors. After cholecystectomy, the unexpected GBC was first reported in 1961. Nowadays only one third of the GBC can be diagnosed in preoperative period [3,14,15]. It is diagnosed with histopathological examination

following laparoscopic cholecystectomy which is performed due to benign pathologies. In the normal population, the risk of women getting to the GBC is 2-6 times higher and the incidence increases with age. However, the male gender is a distinct bad prognostic factor in the GBC and is associated with shorter survival rates [16]. In our study, the prevalence of male patients was significantly higher, but the limited follow-up makes lower the significance of this outcome.

The most important risk factor for gallbladder cancer has been reported to be chronic inflammation. The presence of inflammation is also associated with peroperative perforation and the spread of saffron to the body, which affects the prognosis negatively. In 70-98% of patients, calcium is found in the pouch [16,17]. In our study, no perforation has been reported during the peroperative period, with the determination of the calcium detection rate in the gallbladder. Curative surgical resection improves the survival rate of GBC. Simple cholecystectomy is adequate for T1a GBC and 5-year survival rates for these tumors have been reported as 90-100% [18]. The incidental GBCs are usually found in the early stage (T1) tumors.

Following the laparoscopic cholecystectomy, the port location metastases were determined as 10-30% in the literature for a period of 10 months. In cases without peroperatively perforation, the rate of the port location metastasis is significantly lower [19]. In our study, we did not detect any port metastasis in the study patients.

The detection of a relatively different proportion of the random detected GBC is linked to various reasons. The characteristic of these reasons is that in the prospective studies, especially in situ carcinoma ratio is higher compared to the retrospective studies. Because of the standard pathological examination, there is not enough sampling of the fundus and corpus sections of the cancer [20]. In some countries, gallbladder cancer is endemic, so rates in these regions increase the overall average [3]. In other words, in our country, it is expected to detect the incidence GBC at lower rates than in some parts of the world, but still multi-centered and prospective studies with high volume of patients should be conducted. In our study the ratio of incidental GBC was 0.20%, and that was lower compared to the previously published studies in the literature [15,18]. However, in other studies conducted in the Turkish population, we have determined that these ratios are lower than the literature in accordance with ours [19,20].

We think that one of the limited aspects of our study is the retrospective design of the study and length of the follow-up. The impossibility of additional surgical resection and early adjuvant treatment were also other restrictive problems. The most important reason for these adverse consequences is that laparoscopic cholecystectomy has been performed with low complication rates. To be seen as a trivial initiative, so we think that the pathology results in the postoperative period should not be given the need for follow-up and evaluation.

In our study, the adverse effects of advanced stage of tumors have been detected and positive effects of additional surgical resection in the early period have been observed in the survival. Our incidence GBC rates were determined to be lower than other studies in the literature. Following the cholecystectomy, the pathology results should be followed carefully, without loss of communication with the patients.

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Evaluations of factors affecting the outcome of redo coronary bypass surgery and long term results: A retrospective observational study

Redo koroner arter bypass ameliyatlarının sonuçlara etki eden faktörler ve uzun dönem sonuçların değerlendirilmesi: Retrospektif gözlemsel çalışma

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Abstract

Aim: Advanced atherosclerosis of coronary arteries, existence of patent arterial grafts, redo sternotomy, shortage of available vascular conduits, difficulty of exploration of the coronary vessels are the factors that render the coronary reoperations challenging and they may be responsible of higher mortality and morbidity rates of reoperations. The aim of this study is to evaluate the factors that affect the progression of atherosclerotic coronary artery disease in the post-operative period of coronary artery bypass surgery which results in a redo operation.

Methods: A number of 115 patients who underwent coronary bypass re-operations between January 1997 and August 2007 were included. Patients were divided into two groups as follows: Group 1 was the risk factor positive group, Group 2 was the risk factor negative group. The time interval between the initial operative procedure and the redo operation was calculated and the effect of risk factors upon this time interval and the mortality rates were evaluated.

Results: The time interval between the first operative procedure and the reoperation was 77.31 months in Group 1 and 93.88 months in Group 2. Smoking had a more negative effect on the reoperation rate compared to the other risk factors (p=0.025). Mortality rate was higher in the risk factor positive group (p=0.027). Preoperative EF had a significant effect on the mortality rates (p=0.018).

Conclusion: The presence of any risk factor for CAD increases the chance of having a reoperation. Off-pump surgery technique should be chosen in appropriate cases to lower the mortality risk of redo CABG operations and choosing the combined cardioplegia administration in on-pump redo coronary bypass operations would lower the mortality rate as well.

Keywords: Coronary artery bypass surgery, Vascular graft occlusion, Redo surgery

Öz

Amaç: Koroner arterlerin ilerlemiş aterosiklerozu, patent arteryal greftlerin varlığı, redo sternotomi, muhtemel vasküler kondüitlerin kısalığı, koroner damarların eksplorasyonundaki zorluklar gibi faktörler koroner reoperasyonları zorlu hale getiren etkenler olup reoperasyonlarda gözlenen daha yüksek mortalite ve morbidite oranlarından sorumludurlar. Bu çalışmanın amacı redo koroner arter baypas greftleme (KABG) ameliyatlarında postoperatif dönemde aterosklerotik koroner arter hastalığının progresyonuna etki eden faktörleri değerlendirmektir.

Yöntemler: Ocak 1997 ve Ağustos 2007 tarihleri arasında redo KABG ameliyatı yapılan 115 hasta çalışmaya dahil edildi. Hastalar şu şekilde iki gruba ayrıldı: Grup 1 risk faktörü pozitif olan grup, Grup 2 risk faktörü negatif olan grup. İlk ameliyat ile redo ameliyat arasındaki süre ve bu süre üzerine etki eden risk faktörleri ile mortalite oranları değerlendirildi.

Bulgular: İlk ameliyat ile tekrarlanan ameliyat arasında geçen süre Grup 1'de ortalama 77,31 ay iken Grup 2'de 93,88 ay idi. Diğer risk faktörleri ile karşılaştırıldığında sigara kullanımı tekrarlayan ameliyat üzerinde daha güçlü bir negatif etkiye sahipti (p=0,025). Risk pozitif olan grupta mortalite oranı daha yüksekti (p=0,027). Preoperatif ejeksiyon fraksiyonu mortalite oranları üzerinde önemli bir etkiye sahipti (p=0,018).

Sonuç: Koroner arter hastalığı ile ilgili herhangi bir risk faktörü varlığı redo KABG olasılığını artırmaktadır. Klinik tecrübelerimize dayanarak, redo KABG'nin mortalite oranlarını azaltmak için uygun olan vakalarda off-pump cerrahi tekniği tercih edilmelidir. Aynı zamanda on-pump redo KABG olgularında kombine kardiyopleji uygulaması mortalitenin azaltılmasına yardımcı olacaktır.

Anahtar kelimeler: Koroner arter baypas greftleme, Vasküler greft tıkanması, Redo ameliyat

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Introduction

Redo coronary artery bypass operations are technically more challenging than the initial bypass operations because of more serious conditions of the patients [1-3]. Advanced atherosclerosis is usually present in the existing vein grafts of these patients. Besides that, the native vessel coronary artery atherosclerotic disease (CAD) may be advanced too. Existence of patent arterial grafts, redo sternotomy, shortage of available vascular conduits, difficulty of exploration of the coronary vessels are the other factors that render the coronary reoperations challenging and they may be responsible of higher mortality and morbidity rates of reoperations [2,3].

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The necessity of redo coronary bypass operations depends on multiple factors such as patient related factors, initial operation related factors, compliance of patients with preventive medical therapy after initial bypass surgery against progression of the CAD and the opinion of the surgeon about the benefits of the redo operation. Generally, the reoperation rates in the literature are 3% in the first postoperative 5 years, 10% in 10 years and 20% in 20 years [4]. This study was designed to evaluate the mortality rates and the risk factors that affect the progression of the CAD in the postoperative period of the coronary artery bypass graft (CABG) surgery.

Materials and methods

This retrospective observational study included 115 patients who underwent coronary artery bypass surgery and had coronary angiographic imaging between January 1997 and August 2007 in the Cardiovascular Surgery Clinic of Türkiye Yüksek İhtisas Hospital. The positivity of risk factors for CAD such as family history, smoking, diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL) and obesity was the criteria for including the patients into Group 1. The patients with no risk factors made up the Group 2.

Group 1 consisted of 88 patients in which 16 patients were female and 72 patients were male. The average age of the group was 58±8 years. Group 2 consisted of 27 patients in which four patients were female and 23 patients were male. The average age of the group was 60±11 years.

The time interval between the first operation and re-operation was calculated for each group and the effect of risk factors for CAD on this time interval and the mortality rate was evaluated. Mortality rates amongst the groups according to gender, preoperative ejection fraction (EF), intraoperative inotropic agent and intraaortic balloon pump (IABP) need were also compared.

The operation technique:

Twenty-two patients in Group 1 and 75 patients in Group 2 were operated using on-pump technique. Thirteen patients in Group 1 and 5 patients in Group 2 were operated using off-pump technique.

For the on pump technique, sternotomy was followed by aortocaval cannulation. The site of the aortic cannulation was decided by palpation. The plaque free sites were used for aortic cannulation. Cardiopulmonary bypass (CPB) was initiated by cooling the patient down to 32°C. After application of cross-clamp onto the aorta, the heart was arrested using antegrade and retrograde cardioplegia, and then the distal anastomoses were performed. The proximal anastomoses were performed using a side-biting clamp following defibrillation of the heart.

The off-pump procedures were performed without CPB and cross clamping the aorta. Stabilizers placed on the epicardium were used during the operations.

Patients with high levels of urea and creatine were hydrated and dopamine was administered (2.5 mg/kg per minute). The perfusion pressure was kept around 70 mmHg and hemofiltration was applied during the surgery when required. The patients regaining muscular power following surgery without severe left ventricular dysfunction and postoperative hemorrhage were extubated generally within the first eight hours. Early mobilization was enhanced the next day following surgery.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) for Windows Release 13.0 program was used for statistical analysis. The normality of the data was tested with Kolmogorov Smirnov test. Mann Whitney U test was used for the evaluation of non-parametric data. Pearson chi square test was used for intergroup comparison of the qualitative data. Arithmetic mean and standard deviation was calculated for descriptive statistics and measurable data. The p value of 0.05 and lower than 0.05 was accepted as statistically significant.

Results

The mean time interval between the initial operation and the reoperation was 77.31±6.07 months in the risk factors positive group (Group 1) and 93.88±13.9 months in the risk factors negative group (Group 2) (p=0.280). Thirteen out of 88 patients died (14.8%) in Group 1 and 10 out of 27 patients (37%) died in Group 2 (p=0.012). Age, gender and preoperative EF were found to have no effect on the time interval. Preoperative EF had a significant effect on the mortality rates (p=0.018). Twenty-three patients died in total and mean EF of these patients was 35±10% (Table 1).

Table 1: Factors affecting the mortality rates

	Mortality		*p*
	No (n=92)	Yes (n=23)	
Mean Age (years)	57±8	59±11	0.815
Gender			
Female	16	4	0.634
Male	76	19	
Mean EF (%)	50±8	35±10	0.018
Operation types			
On-pump	16	2	0.021
Of-pump	76	21	
Risk Factor			
Yes	75	13	0.012
No	17	10	

The types and numbers of grafts used for LAD bypass in reoperations were as follows: LIMA in 33 patients, RIMA in 29 patients, SVG in 52 patients and radial artery in 1 patient.

Smoking was found to be significantly affecting the reoperation time interval (p=0.025) (Table 2). Mean reoperation time interval for tobacco product consumers (36 patients, 31.3%) was 62.26±54.4 months. Mean reoperation time interval for non-smokers (79 patients, 68.7%) was 89.84±62.16 months.

Table 2: Reoperation time interval (months) according to risk factor positivity

Risk Factor	Group 1	Group 2	p
Family history of CAD	67 ± 51	86 ± 63	0.205
Smoking	63 ± 54	89 ± 62	0.025
Diabetes mellitus	76 ± 57	82 ± 61	0.779
Hypertension	85 ± 54	78 ± 65	0.298
Obesity	68 ± 54	82 ± 61	0.469
Hyperlipidemia	95 ± 55	77 ± 62	0.102

Table 3: Distribution of the number of the patients who need intraoperative inotropic support

		Group 1 (n=88)			Group 2 (n=27)		
		Deceased		p	Deceased		p
		Yes	No		Yes	No	
Inotropic	Yes	7	13	0.008	3	2	0.249
agent	No	6	62		7	3	
IABP	Yes	5	3	0.001	2	0	0.128
	No	8	72		8	17	

In Group 1, 20 (22%) out of 88 patients needed intraoperative inotropic agent support and 13 (14.7%) of them died (p=0.008). In Group 2, 5 (18.5%) out of 27 patients needed this support and three (11%) of them died (p=0.249). Eight (9%) out of 88 patients needed intraoperative IABP support and three

(3%) of them died in Group 1 (p=0.001). Two (7%) out of 27 patients needed this support in Group 2 and 2 (7%) of them died (p=0.128) (Table 3).

Discussion

The patients may have repeating angina episodes or symptoms of acute coronary syndrome after coronary bypass grafting operations and may need an intervention for revascularization [5]. In a study, it was reported that 31% of the CABG patients needed a revascularization procedure in the postoperative period in a 12 years follow-up [6]. These symptoms of angina in the post-CABG period usually occur due to progressive atherosclerosis in the native vessels or bypass conduits [7].

The angina in the postoperative period may be stable or unstable. Burton et al. reported that unstable angina pectoris may be more common before the reoperation and 20% of the patients may even be asymptomatic [8]. In another study, this asymptomatic patient percentage was reported as 16% [9]. However, there is no significant difference among the mortality rates of symptomatic and asymptomatic patients [10]. In another study of Burton et al they stated that, as an angiographic indication for reoperation, 80% of the patients had coronary bypass graft disorder, 12% had native vessel atherosclerosis besides coronary bypass graft disorder, 8% had solitary native vessel atherosclerosis [8]. Although vein graft occlusions are usually due to atherosclerosis [11,12]; intimal hyperplasia, thrombosis because of thrombocyte dysfunction in the intimal injury site, calcifications in the fatty plaques in the long term period may also back up the graft occlusion process [13]. In support of autopsy findings and bypass graft biopsy findings Qureshi et al reported that 71% of the patients had graft atherosclerosis in postoperative 6-12 years period [14]. The pathology of native vessel and bypass graft atherosclerosis may be the same but atherosclerosis in grafts progresses more rapidly [11] and these atherosclerotic lesions are more fragile and instable in nature [8].

The patency rates of bypass grafts may positively be affected by older age, low serum cholesterol levels, low thrombocyte count (although it slightly affects) and acetylsalicylic acid administration after CABG surgery. Smoking, hyperlipidemic, low EF, family history of CAD and diabetes mellitus were reported to affect negatively the graft patency rates in some studies [15] but in contrast of this, Goldman et al reported that insulin dependent DM and smoking have no effect on the graft patency rates [16]. In some other studies, it is reported that continuous smoking in male patients after first CABG operation increases the graft atherosclerosis and occlusion rates [8]. Life style changes and anti-hyperlipidemic medications may suppress the progression of the atherosclerotic lesions as well as decrease their extensity and size [17,18]. Also in 4S (Scandinavian Simvastatin Survival Study) it is reported that anti-hyperlipidemic therapy reduces the mortality of the coronary disease by 42% and general mortality by 30% [19]. In this study, we found that smoking increases the risk for the need of a reoperation and ventricular dysfunction and positivity of a risk factor for CAD increases the mortality rates.

The survival rates after reoperations are worse than primary operations. Weintraub et al reported that survival rates 5 years and 10 years after the reoperation were 76% and 55% respectively [20]. Loop et al [21] reported that 10 years survival rate was 69% in their study. The factors worsen the survival rates after reoperations could be listed as follows: left ventricle (LV) dysfunction, age, continuous smoking, hypertension, left main coronary artery (LMCA) lesion >50%, three-vessel disease, New York Heart Association (NYHA) class III/IV symptoms, peripheral vascular disease, absence of IMA graft in the primary operation and preoperative kidney failure [21,22]. In the literature it is reported that IMA graft has a positive effect on the late survival rates of reoperations but not as dramatic as the in the primary operation [23].

The state of the patients having more than one reoperation is nearly the same as the patients having first reoperation but in-hospital mortality rates of these patients are moderately higher [24,25]. In a 13 years follow-up of 4518 patients who have more than one reoperations, it is reported that in-hospital mortality rate in the first reoperation was 4.3%, in the second reoperation 5.1% and in the third reoperation was 6.4%. In the same study, the mortality rates after 5 and 10 years were reported as 84% and 66% respectively. The age of the patient is accepted to be the most important factor affecting the late mortality rate of the reoperation. In-hospital mortality of the patients younger than 70 years is reported as 1-2% but it is about 10% in the patients older than 70 years [26].

In a study published by Usta et al [27], which they compared the surgical results of on-pump and off-pump redo coronary bypass surgery, it was reported that mortality rates, postoperative drainage, operation time, intensive care unit time, perioperative myocardial infarction rates were significantly lower in off-pump group compared to on-pump group. In our study, we found that mortality rates were significantly lower in off-pump group similar to that study. But we think that lower case number in off-pump group would have an effect in that result. In another study, the mortality rate was found to be higher when cardioplegia was administered antegrade compared to combined cardioplegia administration [28].

Sabik et al [26] reported that the impaired left ventricle function and presence of diffuse coronary vascular disease increased the mortality rate. In our study, we found that diffuse coronary artery disease and low left ventricle ejection fraction, increased the mortality rate similar to the literature.

It is important to decide when to refer the patients to reoperation as advancements in the percutaneous revascularization techniques can provide an easier and less risky revascularization process. Thus if there is late stenosis in the grafts (≥5 years), multiple stenotic vein grafts, diffuse atherosclerosis in vein grafts, a stenotic vein graft on the LAD, stenotic IMA grafts and LV dysfunction, it is suggested that these patients should be referred to surgical treatment [any reference?].

The intraoperative need for inotropic agent or IABP support may be an indicator of impaired LV functions, incomplete revascularization in the primary operation or impaired graft patency [15]. In a study conducted on 289 reoperation patients, 6% of these patients needed postoperative

IABP support, 52% of them needed postoperative inotropic agent support and the postoperative mortality rates in the first 30 days was reported as 6.6% [29]. We found higher mortality rates in patients who needed IABP or inotropic agent support in favor of these findings.

Conclusion

The presence of any risk factor for CAD increases the chance of having a reoperation. The correlation between low left ventricle ejection fraction, operation technique, administration way of cardioplegia, presence of diffuse coronary vascular disease and postoperative mortality rate in redo coronary bypass surgery was presented in many studies. In conclusion, we think that off-pump surgery technique should be chosen in appropriate cases to lower the mortality risk of redo coronary bypass operations. In addition, we think that choosing the combined cardioplegia administration in on-pump redo coronary bypass operations would lower the mortality rate.

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Carcinoid tumor of appendix: Review of consecutive 5131 appendectomy

Apendiksin karsinoid tümörü: Ardışık 5131 apendektominin incelemesi

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Abstract

Aim: Appendiceal carcinoid tumor (neuroendocrine tumor) is rarely seen, and it is frequently found incidentally after evaluation of appendectomy specimen. Histopathologically, the appendiceal carcinoid tumor is usually the type of enterochromafine cell and stems from a sub-epithelial cell population that differs from the neuroendocrine tumor in other regions. Although it is often detected in appendectomy, appendiceal one is the most common type of primary malignant lesion and is detected in 0.3-0.9% of patients with appendectomy. In this study, it is intended to present an appendix carcinoid tumor series that is diagnosed incidentally after appendectomy.

Methods: 5131 appendectomy that was performed between years of 2009 and 2017 constituted the study universe. 35 (0.68%) patients diagnosed with carcinoid tumors were evaluated in the histopathological examination. The patients were recorded in terms of demographic data, clinical status, histopathology and surgical reports. Additional operations and follow-up data were noted.

Results: 21 of the 35 patients with appendiceal carcinoid tumors were males, and 14 were women. Male/Female ratio was 1.5. The mean age of the patients was 27.3±11.0. There was no difference in terms of gender and age with other appendectomy patients who diagnosed non-tumor (p=0.476 and p=0.413, respectively). The clinical presentation of the patients with all carcinoid tumors was in favor of acute appendicitis. Histopathological examination revealed simultaneous acute appendicitis in 25 (71.4%) patients.

Conclusion: The treatment of the appendiceal carcinoid tumor is controversial, but tumor size, tumor localization, surgical margin and lympho-vascular invasion are the main determining factors. The evaluation of pathological examination and the necessary additional therapies should be planned due to the fact that it is often diagnosed with incidental and is unlikely to be noticeable during surgery.

Keywords: Appendectomy, Carcinoid tumor, Right hemicolectomy

Öz

Amaç: Apendikste karsinoid tümör (nöroendokrin tümör) nadir olarak görülmekle birlikte, apendiks karsinoid tümörün sık olarak bulunduğu bir alandır. Histopatolojik olarak apendiks karsinoid tümör çoğunlukla enterokromaffin hücre tipindedir ve diğer bölgelerdeki nöroendokrin tümörden farklı olan bir subepitelyal hücre popülasyonundan kaynaklanmaktadır. Genellikle tesadüfen apendektomide tespit edilse de, apendiks primer malign lezyonunun en sık rastlanan türüdür ve apendektomi yapılan hastaların %0,3-0,9'unda saptanmaktadır. Bu çalışmada apendektomi sonrası insidental tespit edilen apendiks karsinoid tümör serisini sunmak amaçlanmıştır.

Yöntemler: Çalışma evrenini 2009-2017 yılları arasında gerçekleştirilen 5131 apendektomi olgusu oluşturdu. İncelemede karsinoid tümör saptanan 35 (%0,68) hasta değerlendirildi. Hastalar demografik veriler, klinik durum, histopatoloji, ameliyat raporları ve takipler açısından kayıt edildi.

Bulgular: Apendiks karsinoid tümör saptanan 35 hastanın 21'i erkek, 14'ü kadın olmak üzere Erkek/Kadın oranı 1,5 olarak bulundu. Hastaların yaş ortalamasının 27,3±11,0 olduğu görüldü. Tümör dışı tanı alan diğer apendektomi yapılan hastalar ile cinsiyet ve yaş açısından fark saptanmadı (sırasıyla p=0,476 ve p=0,413). Tüm karsinoid tümör saptanan hastalar için klinik tablo akut apandisit lehinde idi.

Sonuç: Apendiks karsinoid tümörün tedavisi tartışmalı olmakla birlikte tümör boyutu, tümör lokalizayonu, cerrahi sınır ve lenfovasküler invazyon ana belirleyici faktörlerdir. Sıklıkla insidental saptanan ve ameliyat esnasında fark edilme ihtimali düşük olması nedeniyle patolojik inceleme ile değerlendirme ve gerekli ek tedaviler planlanmalıdır.

Anahtar kelimeler: Apendektomi, Karsinoid tümör, Sağ hemikolektomi

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Introduction

It is considered carcinoid tumors is derived from the enterocromaffin cells (EC), which can be seen everywhere in the body, but formed as a primer in the gastrointestinal tract and the main bronchus submucosa. According to the origin of carcinoid tumors; it can be called as carcinoids of foregut, midgut and hindgut. Appendicular carcinoids are found in the group of carcinoids of the midgut. Differences of carcinoids of midgut compared to carcinoids of other origins; they are histologically different staining features, have higher serotonin content, more often cause metastases to carcinoid syndrome and less bone metastases than others [1]. Carcinoid tumors are the most common tumor of the appendix, accounting for 0.5% of the appendectomy materials. In this study, we aimed to present our experience of appendiceal carcinoid tumors under review of literature.

Materials and methods

We designed an observational study to evaluate the patients with carcinoid tumors. Records of patients who underwent appendectomy between January 1, 2009 and December 31, 2017 were retrospectively investigated. Patients with histopathological records of carcinoid tumors constituted the study group. Detailed surgery and pathological reports were recorded. Further surgery and treatment if any was also recorded. Follow-up data is investigated.

Statistical analysis

The frequency and percentage is used to present the data with categorical variables, mean ± standard deviation is used for parametric data that match the normal distribution, median and interquartile range is used for parametric data that does not conform to the normal distribution. In comparison, the t-test for parametric data, Fisher's exact test was used for categorical data. If the value of p is lower than 0.05 in the confidence range of 95%, the differences were considered statistically significant.

Results

During the study period, 5131 appendectomy was performed. 35 (0.68%) of them was diagnosed with carcinoid tumors in histopathological examination. 21 of the 35 patients with appendiceal carcinoid tumors were males, and 14 were women. Male/Female ratio was 1.5. The mean age of the patients was 27.3±11.0. There was no difference in terms of gender and age with other appendectomy patients who diagnosed non-tumor (p=0.476 and p=0.413, respectively). The clinical presentation of the patients with all carcinoid tumors was in favor of acute appendicitis. Histopathological examination revealed simultaneous acute appendicitis in 25 (71.4%) patients.

The histologically distribution of tumors is examined; Grade 1 carcinoid in 32 patients, grade 2 carcinoid in 1 patient, multifocal carcinoid in 1 patient, grade 2 carcinoid and adenocarcinoma in 1 patient. The tumor placement in the appendix is examined; Tip of the appendix in 26 (74%) patients, body in 7 (20%) patients and tip and body in 1 patient who had multifocal tumor. Median tumor diameter was found as 6 mm (4-10, 5mm) (range: 1-24 mm). Tumor size was 15 mm and more in 6 (17%) patients, 20mm in 3 (9%) patients. In all patients, the surgical margin was negative, and lympho-vascular invasion was positively identified in 3 (9%) patients. After pathological examination, 3 patients underwent to right hemicolectomy and 1 patient to total colectomy.

Discussion

Appendiceal carcinoid tumor (neuroendocrine tumor) is rarely seen, but it is an area where carcinoid tumor is frequently found. They form 80% of all appendicitis masses [2]. Appendix is most common localization of carcinoid tumors in the gastrointestinal tract with a rate of 40-50% [3,4]. Modlin and Sandar, however, present the largest epidemiological series with 8305 cases on carcinoid tumors; reported that carcinoid tumors were located in the bronchopulmonary system with a rate of 73.1% in the gastrointestinal tract and 25.9% in the gastrointestinal tract and 18.9% in the gastrointestinal tract with a maximum of 28.7% in the gastrointestinal tract [5-8]. The main reason for changing these rates is the clinical examination of carcinoid tumors in jejunoileum are found at a much higher rate than the tumors in the surgical series and it is suggested that many small intestinal carcinoid tumors cannot be clinically detected [9]. 80% of the carcinoid tumors localized to the appendix are smaller than 1 cm, 15% and 5% are tumors larger than 2 cm. While ¾ of these tumors are located proximal to the appendix, only about 10% of them are localized [10].

Carcinoid tumors can be seen in all ages, but in adults and women they are more frequently detected [2]. Diagnose is usually revealed in appendectomies with acute appendicitis. However, clinical findings of carcinoid syndrome, especially in the presence of metastases, are of importance in terms of preoperative diagnosis. It is known that these tumors secrete many gastrointestinal peptides and hormones, especially 5-hydroxytryptamine (serotonin). Depending on their release, especially carcinomatous syndrome leading to clinical findings such as flushing, diarrhea, asthma or wheezing, valvuler heart diseases and fascial telangiectasia may occur in the skin localized on the head and neck and upper body [1]. In the diagnosis of carcinoid tumors leading to carcinoid syndrome, serotonin and 5-HIAA 5-hydroxy indole acetic acid) levels are important. Ultrasonography and computed tomography can determine the localization and size of the tumor. In addition, I-131 iodobenzylguanidine scintigraphy is particularly useful in the detection of metastatic carcinoid tumors [1,11]. Appendices have a close association with tumor size and metastases, as in other localizations of localized carcinoid tumors. About 90% of carcinoid tumors are benign, and the vast majority of cases are less than 1 cm. The prognosis deteriorates if the size of the tumor is greater than 2 cm. The risk of metastasis in tumors smaller than 1 cm is 2%, while in lesions greater than 2 cm this rate reaches 80%. A 5-year surveillance of appendiceal carcinoid tumors is accepted above 90% [2,10,12,13].

In the treatment of appendicitis carcinoid tumors; Appendectomy is indicated as adequate treatment. The recurrence rate in all cases is 2%. Appendectomy is adequate in the treatment of cases with a diameter less than 1 cm and appendicitis limited, but the treatment of tumors between 1 and 2 cm in diameter is controversial. Right hemicolectomy is

performed in the treatment of tumors larger than 2 cm. In terms of right hemicolectomy treatment, not only tumor size but also many other factors play a role. Lesions larger than 2 cm, localized tumors at the base of the appendix, invasion of lymphatic ducts, serosa and mesoapendix, presence of regional lymph node metastasis, mucin production (mucinous carcinoid tumors), high mitotic fast cellular pleomorphism and childhood carcinoid tumors are defined as the indications for right hemicolectomy in the treatment of carcinoid tumors of appendix [13-16]. In our study, we performed additional right hemicolectomy in patients requiring further treatment according to these guidelines. Total colectomy was performed in one patient because of synchronous involvement of other colon segments.

Hepatic resection in patients with carcinoid syndrome and metastatic liver involvement may be performed if possible; both in terms of loss of symptoms and cure if necessary. Hepatic artery embolization and interferon treatment have been reported to be highly successful in cases where resection is not possible. For patients with disseminated carcinoid tumors, a multidisciplinary approach including chemotherapy regimen is recommended [15,16].

This study has some limitations. First retrospective design of the study lowers the quality of assumptions. Second limitation is that follow-up data couldn't be reported with detail. The study patients represent one hospital in Turkey. These findings suggest that instruction to attend to specific features can enhance the accuracy, but feature selection is crucial and generalization across the world may be limited.

In conclusion, carcinoid tumors of appendix are rarely seen, and mostly incidental after appendectomy. Routine pathological examination of appendectomy specimen is offered to reveal the condition, and to choose necessity of additional therapies.

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Review
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Molecular mechanisms affecting estrogen receptor levels in breast cancer

Meme kanserinde östrojen reseptör seviyelerini etkileyen moleküler mekanizmalar

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Abstract

The initiation of breast cancer, estrogen and its receptor (ER) perform significant functions. ER has two dissimilar forms, and they are commonly called as ER-alpha (-α) and ER-beta (-β). ERs are transcription factors. Expressions of ER-alpha (-α) protein are mainly arranged by the pathway of ubiquitin-proteasome. The hormone-responsive gene expression modulated by ER-α in addition to other nuclear receptors is a complicated process, which involves various cellular responses. And also, ER-α levels are related with the pathology and etiology of breast cancer. In this review which is about the transcription and expression of the ER-α gene may provide the find out biochemical mechanisms behind the breast carcinogenesis. The regulation of ER expression, histone-modifying enzymes, Progesterone receptor (PR), peroxisome proliferator-activated receptors (PPAR), hydrocarbon receptor (AhR), Glucocorticoid receptor (GR), hypoxia and lysine residuals in ER region described in detail in this work. Increasing the number of these studies, are very significant for developing new methods of estrogen-dependent cancers.

Keywords: Breast cancer, Estrogen receptors, Progesterone receptor, Peroxisome proliferator-activated receptor, Aryl hydrocarbon receptor, Glucocorticoid receptor

Öz

Meme kanserinin tetiklenmesinde, östrojen ve reseptörünün (ER) önemli işlevleri bulunmaktadır. ER'nin iki farklı şekli yer almakta ve bunlar ER-alfa (-α) ve ER-beta (-β) olarak adlandırılmaktadır. ER'ler birer transkripsiyon faktörüdür. ER-alfa (-α) proteininin ifadeleri esas olarak ubikuitin-proteazom yolağı ile düzenlenmektedir. Diğer nükleer reseptörlere ek olarak ER-alfa tarafından modüle edilen hormona duyarlı gen ekspresyonu, çeşitli hücresel tepkimeleri içeren karmaşık bir moleküler süreçtir. Ayrıca ER-α düzeyleri, meme kanseri patolojisi ve etyolojisi ile de ilişkilendirilmektedir. ER-α geninin transkripsiyonu ve ekspresyonu ile ilgili olan bu derleme yoluyla meme karsinojenezinin alt yapısında yer alan biyokimyasal mekanizmaların daha net anlaşılabileceği düşünülmektedir. ER ekspresyonu, histon değiştirici enzimler, Progesteron reseptörü (PR), peroksizom proliferatörü ile aktive edilmiş reseptörler (PPAR), aril-hidrokarbon reseptörü (AhR), Glukokortikoid reseptörü (GR), hipoksi ve ER bölgesinde yer alan lizinin kalıntılarının regülasyonu bu derlemede detaylı bir biçimde anlatılmaktadır. Buna benzer çalışmaların sayısının artırılması, östrojen bağımlı kanserler için yeni yöntemlerin geliştirilmesi açısından oldukça önemlidir.

Anahtar kelimeler: Meme kanseri, Östrojen reseptörleri, Progesteron reseptörü, Peroksizom proliferatör aktive reseptör, Aril hidrokarbon reseptörü, Glukokortikoid reseptörü

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Introduction

In current works show that, estrogen associated with the function and differentiation of the gland of mammary. Estrogen hormone performs its molecular affect by binding to its receptors, ER-α and ER-β [1]. Besides these knowledge, the expression of ER-α is related with breast cancer etiology, especially the growth of tumor. Beside of these explanations, it was shown that the expression levels of ER-α is more suitable as a marker for the treatment of breast cancer [2]. For this reasons; in this present study, we have been investigating the regulation of ER expression, histone-modifying enzymes, Glucocorticoid receptor (GR), peroxisome proliferator-activated receptors (PPAR), hydrocarbon receptor (AhR), Progesterone receptor (PR), hypoxia and lysine residuals in ER region [1,2].

Histone deacetylase inhibitors and ER alpha

Histone acetylation remains among the widely studied topics and plays different roles especially in the formation of nucleosome. For instance, lysine acetylation causes changes in the structure of chromatin and by reducing histone-DNA interaction; it induces DNA to provide transcriptional activation [3].

Abnormal activation or deactivation of the transcription depends on the condition of histone acetylation and correlates with tumorigenesis [4]. Via different analyses, histone deacetylases (HDAC) are widely characterized, and they cause the development of most of the specific malignancy forms associated with cellular oncogenes and tumor suppressor genes [5]. Histone deacetylases (HDAC) regulate the expressions of the tumor suppressor genes and affect the triggering or progression of cancer by manipulating the activities of transcriptional factors over the changes in DNA and the structure of chromatin components [6]. Recently, with the acetylations detected in cancer patients via clinical applications using HDAC inhibitors, gene suppressions have been realized by certain regulation mechanisms. Since HDAC inhibitors involve anti-cancer functions, they are among the new therapeutic drug classes in different types of cancer [7].

Estrogen shows the proliferative response in breast epithelium cells by activating ER mediative CCND1 (codes Cyclin D1) gene transcription [8]. CCND1 promoter does not include estrogen response element (ERE). CCND1 realizes the ER alpha up regulation via cyclic-AMP response element (CRE) in the promotor [9]. Decreasing of cyclin D1 mRNA and protein expression is the most important indicator of early antiestrogenic effect [10]. The induction of the increase in the cyclin D1 expression causes resistance against antiestrogens [11]. Cyclin D1 induces the ER-α transcription over ERE sequences in genes regulated with estrogen by binding to ER-α with and without ligand bonds. As a result, Cyclin D shows the increase in ER-α by boosting the transcriptions of the genes with ERE with or without estrogen presence [12].

Cyclin D1 bypasses the estrogen requirements of ER-α positive breast cancer cells, realizes the advanced expression increase free of estrogen, and is not inhibited via antiestrogens [12]. Trichostatin A (TSA) which includes in HDAC inhibitors class, prevents the proliferation of tumor cells in breast cancer cell lines. In studies which is performed by in vivo, this effect is realized by increasing the shift to the resting period in cell cycle, the differentiation or apoptosis [13].

Cellular control of the D type-cyclins is realized via cell cycle and CDK4 and CDK6 activations of cyclin dependent kinase partners mediates this control. Retinoblastoma proteins are phosphorylated with CDK4 and CDK6 activations and E2F oscillation from the transcription factor family is realized [14].

Normally, cyclin D1 accumulation is strictly regulated. However, in almost 50% of the certain type of breast cancer, several expressions of cyclins have been reported. Cyclin D1 expression in overs can be observed in all breast cancers histopathologic types and it is especially correlated with metastasis [12].

In the studies demonstrated that the deficiency of the protein cyclin D1 which localized in breast tissues of transgenic mice with neu and ras oncogenes induced breast cancer causes resistance against breast cancer [15]. Cyclin D1 can be severely expressed via CCND1 gene amplification, chromosomal translocation and Cyclin D1-mRNA stabilization. Cyclin E, p21, p27, E2F-1 of D type cyclins are induced with ubiquitin and degraded in 26 S proteasomes. Cyclin D1 is made a target for ubiquitination by being phosphorylated from 286th threonine residual via glycogen synthesis kinase 3B [16]. In the current analyses, tamoxifen is also detected to inhibit cyclin D1 transcription via ER alpha.

PPAR and ER alpha

PPAR is a transcription factor and activation of PPAR is a multi-phased process and it includes ligand binding, heterodimerization with Retionic X Receptors (RXR) showing DR1 or DR2 motif structure repeating with one or two nucleotide gaps, its interaction with line specific gene promotor elements, enabling of various co-activators and inclusion into the structure of other nuclear co-regulator proteins, and thus activation of various target genes in this way [8,9].

There are three sub-types with the high incidence of sequence protection. Firstly, PPAR alpha 3 has been reported in 1990, and PPARδ (or PPARβ), and PPARγ isomers have been revealed in various laboratory trials. These isomers are formed as a result of using alternative splicing and different promotors [17].

In current studies demonstrate that PPARα acts a pivotal function in the metabolism of lipoproteins and fatty acids. Studies which is conducted on rodents about peroxisome proliferators, although carcinogenic results are obtained in the rodent livers, this affective mechanism has been reported to be different from the epidemiological studies on humans [18].

In terms of the studies on the relation between PPARδ and oncogenes, there are controversial roles especially on the molecular bases of colon cancer ethiology. Current studies dedicated that PPARδ induces tumorigenesis and cell proliferation [19]. Beside these, Prostaglandin J2 (PGJ2) is the most important activator of PPAR gamma [20].

Another study has been shown that Cyclin D1 and ER alpha down regulation by PPAR gamma agonists is banned via cell proteasome inhibitors MG 132 and PS II applications, but the treatments of calpain II and calpeptin of the protease inhibitors do not cause the same inhibition condition [21]. New anticancer drugs have been tried to be developed dependent on PPAR gamma because of its wide expression in various tumor

types and cell lines and its antiproliferative effect. For instance, in one of the new studies, PPAR gamma expression has been determined in 339 clinic tumor samples (in the studies with patient profiles of colon, breast, lung, prostate, glioblastoma and leukemia cancers) [22].

Aryl hydrocarbon receptors (AhR) and ER alpha

Aryl hydrocarbon receptors (AhR) are transcription factors activated with ligand [23]. AhR proteins play an adaptor and sensor role in the environmental xenobiotic exposure [24]. In cytosol, they contribute to the toxicity induced via xenobiotics and carcinogenesis especially in the absence of ligands [25]. In the recent studies, it has been shown that signal inhibition of ERs is associated with AhR activated via ligand. In the studies on rodent models, selective AhR modulators are observed to highly inhibit the estrogen induced gene expression and estrogen dependent breast tumor growth [26]. TCDD is an environmental toxin and causes damage on various endocrine signal systems by activating AhRs. When human breast cancer cell lines (MCF-7, ZR-75, T47D) are treated with TCDD, it is observed that ER alpha induces proteasomal degradation [27]. T47D, expresses both ER alpha and beta. When the cells belonging to this cancer line are treated with 17-beta estradiol and TCDD, a rapid decrease is observed in the ER levels depending on the proteasomal degradation. E2 application does not affect AhR, but TCDD degrades both ER and AhR in T47D and MCF-7 cell lines depending on the proteasome [28]. Studies showed that this response is blocked with proteasome inhibitors [27]. In the previous studies, it has been observed that TCDD down regulates ER alpha in rat uterus and breast cancer cells, and there is a mutual relation between AhR-ER alpha inhibitor links [29]. In another study, TCDD applied with 17-beta estradiol (E_2) is observed to cause ER alpha and AhR degradation in a proteasomal way and especially TCDD down regulates AhR in in vivo and in vitro media [30].

Glucocorticoid receptors (GR) - ER crosstalk

Glucocorticoid receptors (GR) are included in nuclear hormone family and they provide the repression of gene expression [31]. In a ligand bound position, GR gene expression is triggered or repressed depending on the cell type [32]. For example, while GR activation induces apoptosis in lymphocytes, it causes inhibition of apoptosis in breast epithelial cells [33]. Both GR and ER are nuclear receptors included in the steroid hormone receptor family [20]. Both GR and ER have significant functions in various different tissues. Both receptors are expressed in tissues and have opposite roles in estrogen activities of glucocorticoids. For instance, while glucocorticoids show antiproliferative effect in mammary gland, estrogens demonstrate an increasing effect in cell growth and proliferation. Glucocorticoids induce bone resorption in bones but estrogens impede this function. Even if estrogens and glucocorticoids are included in different biological processes in the same cell content, mutual interaction mechanisms have not been clarified between GR and ER signal pathways [34].

In a model developed in a study, MCF-7's potential mechanism in the regulation of ligand dependent ER's glucocorticoid receptor mediative transcription has been analyzed. This study has reported that GR down regulated via ER and realizes this over the pathway of proteasome degradation. The decrease in the GR levels is related with the augment of Mdm2 protein expression (E3 ubiquitin ligase) and thus GR is targeted for proteasome [34].

Hypoxia and ER alpha

Hypoxia and low oxygen ranks take place for the period of neovascularization in various tissues. When tumors subjected to these conditions, it has been shown that the tumor's growth, proliferations, metastases processes change in the metabolism [35]. Cellular adaptation to hypoxic medium affects glucose transportation and metabolism, angiogenesis, gene activations responsible in erythropoiesis and down regulates the beta oxidation pathway of the fatty acids [36]. Regulation ways of the genes induced with hypoxia are realized via the expressions of several transcriptional factors at different levels. For example, factor 1 alpha (HIF1-alpha) induced with hypoxia, several hypoxia tissues and tumors increase and promotors of the genes regulated via low oxygen levels especially include hypoxic response elements - (HREs) specific to this factor [37]. HIF1-alpha with protein levels too low to determine in normal tissues can be identified because of the increase in the expression in many tumor types [37]. Another study has determined a linear correlation between HIF1-alpha expression and neovascularization in brain tumors. In many histopathologically classified breast cancer types, depending on the increase in the pathologic level of tumor, an increase has also been identified in HIF1-alpha level and these kinds of tumors are associated with more aggressive and lower lifespans. The increase of HIF-1 alpha levels in breast tumors is in a linear relationship with VEGF and ER alpha increases. ER alpha positive tumors better responds to endocrine treatment than ER alpha negative aggressive tumors, and an increase can be detected in these kinds of patients [38]. Paradoxically, ER alpha levels are caused by its being a negative prognostic factor just like VEGF and HIF1-alpha [39]. A study has researched E_2's induction of VEGF gene expression in ER positive ZR75 cell line, the change in the HIF1-alpha and ER alpha protein levels in two cell lines under 1% low oxygen conditions, and its effect on transactivation depending on the hormone [40]. When ZR-75 cell line cells are released into growth media at normal oxygen levels (21% O_2) or under hypoxic conditions (1% O_2 or cobalt chloride), it is determined that factor 1 alpha (HIF-1 alpha) protein induced with hypoxia under hypoxic condition is induced after a 3-hour application, and ER alpha protein levels show an important decrease within 6-12 hours [41]. This response is determined to be blocked via proteasome inhibitor MG-132. In addition, under hypoxic condition, while a minimal decrease occurs in cellular Sp1 protein, ER alpha mRNA level is preserved. On the other hand, hypoxic conditions have been determined to decrease the Sp2 gene expressions (mRNA) levels induced with 17-beta estradiol in ZR-75 cells [41].

The connection of Progesterone receptors (PR) to ER

Advanced breast cancer often occurs through lack of steroid hormone receptor or because of resistance to endocrine therapies. More than 95% of the breast cancers are degraded within 6 hours after progestin application. However, the root causes under this down regulation is still unknown [42]. PR are prognostic determiners of breast cancer. In the lack of PR

receptors, sensitivity to growth factors increases concerning the formation of aggressive tumor phenotype [43].

PR are also included in this receptor class. After an 6-8 hour treatment with progestins, one of the ligands, PR are largely down regulated, but the root causes of this regulation is not completely clear yet [44].

The expression of PR regulated and modulated by means of ligands happens both at protein and mRNA levels. The decrease in the PR mRNA level occurs after a 4-20 hours progestin application, and PR mRNA level returns to the previous level within 24-48 hours. On the other hand, the relationship between two PR isoform levels in the PR mRNA fluctuation has not been clarified yet [44]. One or two receptor isoforms can be coded in order to the variation of PR transcripts. Alongside the diversity in the PR mRNA and protein levels are intensely down regulated by binding the specific ligand. After the biosynthetic application of endogenous PRs with H^2, N^{15} and C^{13}, densely found control cells of amino acids have been reported to incur turnover within 21 hours compared to control cells. Besides, half-life is 6 hours in progestin applied cells.

In a current study, the effects of mitogen activated kinases (MAPKs) on PR phosphorylation have been investigated [44,45]. In this research, changing S294A mutation of PR serine residual with alanine is shown and it is determined that this mutation completely hinders the ligand dependent down regulation. These results show that PR breakdown is realized in two alternative ways via 26S proteasome. Especially mature PR down regulation is realized with the activation by ligand binding of PR phosphorylation of serine residuals by MAPKs, and followed by the degradation of the targets in receptor [44,45].

Lysine residuals in ER region

Cellular levels of ER alpha are regulated with ubiquitin dependent proteasome pathway. Thanks to the dynamic relation between ER alpha and protein degradation machine, polyubiquitination of the receptor's lysine residuals easily via down regulation process. Today, lysines controlling the receptor degradation have not been fully clarified. In different studies, two lysines of receptor, K302 and K303, are localized in the hinge region of ER alpha and accompany several regulator functions [34]. While the influence of monoubiquitination of K302 on the ER alpha stability is not clear, the special effects of lysines in the hinge region on post-translational modification have been revealed and these regions have been determined to be suitable places for polyubiquitination [46].

Maturation of ER alpha involves a transactivation process realized via the interaction of receptor with co-chaperones after the binding of ligates to the receptor [47]. In the analyses, several chaperones have been identified. Hsp 70 and Hsp 90 are among them. Chaperones mediate ER alpha progression, and realize this by easing the interaction of ER alpha with co-chaperones via some folding models. CHIP (an E3 ubiquitin ligase), Bag 1 and p23 are among these co-chaperones [48]. At the same time, geldanamycin (GA) increases ER alpha's CHIP relation with Hsp 90 and also increases receptor degradation in the lack of ligand [49]. Co-chaperone Bag 1 and p23 are reported to be included in the Hsp 90-ER alpha complex. However, the roles of co-chaperone Bag 1 and p23 in the receptor turnover have not been clarified yet. Bag 1 is mostly included in the receptor-chaperone complex, and enables the interaction of Hsp related proteins with proteasome via N terminal ubiquitin domain of Bag 1 [50]. By this way, Bag 1 increases the receptor degradation. By being included in the mature receptor-Hsp complex, p23 increases both ligand and basal prompted receptor transactivation [51]. Besides, p23 contend for the link between CHIP and receptor, but p23 has no stabilizing effect on ER alpha. The results of the previous studies show that Bag 1 and P23 may have functional roles in receptor turnovers [52]. In another analysis, ER alpha negative breast cancer cell line C4-1 is used. This line expresses the ER alpha types including the lysine-alanine change in both wild type and K302-303 regions. The polyubiquitination of ER alpha, turnover and receptor co-chaperone interactions of these lysines have been analyzed over C4-12 line. Under the condition without ligand binding, it has been revealed that ER alpha AA rapidly incurs polyubiquitination compared to wild-type (wt) ER alpha cells. The reason for this is the increasing relation of ER alpha-AA with Hsc70 interacting protein (CHIP) Ubiquitin ligase carboxyl terminal and its link with proteasome related co-chaperone Bag 1 [46].

Under the condition with ligand binding, it has been determined that a rapid degradation occurs in wt ER alpha with ubiquitin proteasome pathway after the application of C4-12 cells with both 17-beta estradiol and pure antiestrogen ICI 182,780. On the other hand, in the existance of these ligands, ER alpha AA degrades at a lower level. Moreover, ER alpha AA has been reported to be more resistant to ICI induced polyubiquitination. These two lysine mechanism have a different role in the polyubiquitinated and ICI induced receptor down regulation as a response to antiestrogens. Under the conditions without ligand binding, ER alpha AA's stability decreases and degrades, and under the condition without ligand binding, its stability increases [46].

As a result, K302-303 lysines protects ER alpha without ligand binding from basal turnover by inhibiting CHIP-Bag 1 interaction and inducing the receptors' p23 relation. Therefore, new roles have been revealed for these lysines in the receptor turnover regulation [46].

Conclusion

Increasing the number of related revisions of the function, levels and degradation of ERs, particularly from the side of cancer-specific occurrences, are actually significant for enlightening new approaches of avoidance, diagnosis, and therapy of estrogen-dependent cancers. In conclusion, revelation of the molecular mechanism of the arrangement of ERα protein expression level may assist a new plan to impede the progression of breast cancer, and ER alpha expression position may provide in the correctness of therapeutic processes.

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Case report
Olgu sunumu

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Spontaneous vaginal delivery after a pregnancy complicated with Guillain-Barré syndrome

Guillain-Barré sendromu ile komplike bir gebelikte normal doğum

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Abstract

Guillain-Barré syndrome (GBS) is a rarely encountered, acute autoimmune polyradiculoneuropathy which is usually severe and fulminant. Although it is considered not to have an impact on the prognosis of pregnancy, there is no consensus on its management particularly in pregnant women with advanced motor dysfunctions. Different obstetrical approaches have been suggested. Herein, we discussed a case, which has been diagnosed with GBS in the 3rd trimester in our clinic and gave birth to a healthy infant via spontaneous vaginal delivery without any intrapartum or postpartum maternal complication. Patient presentation, diagnosis, treatment and outcome as well of review of the literature will be discussed.

Keywords: Guillain-Barré syndrome, Pregnancy, Spontaneous vaginal delivery, Immunoglobulin

Öz

Gebeliğin akut idiopatik polinöropatilerin (Guillain-Barré Sendromu) etyopatogenezi ve prognozuna belirgin bir etkisinin olmadığı düşünülmesine rağmen, özellikle ileri motor disfonksiyonlarla giden gebelerde değişik obstetrik yaklaşımlar önerilmektedir. Kliniğimizde 3. trimesterda başlayan akut idiopatik polinöropati tanısı alan intrapartum ve postpartum hiç bir maternal komplikasyon gelişmeden spontan vajinal yolla sağlıklı bir bebeğin doğması bu hastalarda konservatif bir obstetrik yaklaşımın yararlı olabileceğini düşündürmektedir. Hastanın sunumu, tanı, tedavi ve sonuçları ile birlikte literatür gözden geçirilecektir.

Anahtar kelimeler: Guillain-Barré sendromu, Gebelik, Spontan vajinal doğum, İmmunoglobulin

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Introduction

Guillain-Barré Syndrome (GBS) is an acute inflammatory and demyelinating polyneuropathy with a prevalence rate of 1.2-1.9/100.000 in general population [1]. GBS is a severe and progressive syndrome characterized by ascending motor weakness with sudden onset that starts symmetrically [2]. Complaint of sensory loss such as hyporeflexia and paresthesia may accompany motor weakness [3]. Etiopathogenesis remains unclear. Immunopathological events triggered by any infection, immunization, or surgical procedure are considered responsible [4,5]. It has been stated that the disease has no remarkable impact on the etiopathogenesis or the prognosis of pregnancy. The prevalence rate is 13% in the first trimester, 47% in the second trimester and 40% in the third trimester [4]. There is no standard obstetric approach for pregnant women yet [1,2]. Herein, spontaneous vaginal delivery of a pregnant woman with GBS, which started in the third trimester, is going to be discussed with the patient's consent.

Case presentation

A 30-year-old and multiparous and 36-week pregnant woman according to the last menstrual period presented with pins and needles and numbness starting a month ago in her arms and legs. The patient had no history of infectious disease in the last four weeks and her medical history and examination of her systems were unremarkable. Her routine biochemistry tests, complete blood count and vitamin B12 values were within the normal limits. Her CMV IgM results were negative.

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Her neurological examination revealed complete muscle strength in the upper extremities, whereas proximal 4 (according to the 0-5 Medical Research Council [MRC] scale) and distal 5 (according to the 0-5 Medical Research Council [MRC] scale) muscle strength was determined in the lower extremities.

The deep tendon reflexes of her upper extremities were normoactive, whereas the deep tendon reflexes of her lower extremities were hypoactive. On her obstetric evaluation, no sign of fetal distress was obtained from the non-stress test, biophysical profile and umbilical arterial blood flow index. The patient was examined in the neurology department and diagnosed with GBS based on the clinical, imaging and EMG findings, and IVIG therapy was given at a dose of 0.4gr/kg/day for 5 days. The patient had no history of an infection. Therefore she didn't receive any antibiotherapy. On the other hand, she benefited from the IVIG therapy. In her follow ups, there were no indications for her to be admitted to the intensive care unit.

During follow-up, the labor started with spontaneous rupture of membranes (water breaking) when she was 38 weeks and 2 days pregnant. Following an active labor of 5 hours and 20 minutes (5 hours for Period I and 20 minutes for Period II), she gave birth to a 3480 gr baby boy with vertex presentation and 9-10 Apgar via spontaneous vaginal delivery. The patient, who had no intrapartum or postpartum fetal or maternal obstetric complication, received help only with 1% oxytocin for secondary hypotonic uterus dysfunction in the last 2 hours of labor. The baby was discharged from the hospital alive and healthy on the postpartum Day 1. She was mobilized without any problems and she didn't need to be given low molecular weight heparin.

At the last physical examination, the muscle strength of the proximal and distal muscles of her lower and upper extremities was scored as 5 (according to the 0-5 Medical Research Council [MRC] scale). Her deep tendon reflexes were normal and she didn't have any loss sensation on the skin. There were no pathological changes at the electromyography.

Discussion

GBS is a rarely encountered disease characterized by acute, symmetric and progressive degeneration of multiple peripheral and cranial nerves. Although its etiopathogenesis remains unclear, immunopathological events triggered by respiratory or gastrointestinal viral infections, immunization, or surgical procedure before the onset of neurological symptoms are considered responsible [6,7]. History of respiratory tract infection is present in 40% and gastroenteritis is present in 20% of the patients four weeks before the signs of syndrome appear [8,9]. The most common infectious agents include Campylobacter jejuni (26%) and Cytomegalovirus (13%) [4]. The presented patient had no history of infection.

Early diagnosis and treatment is critical. Specific methods used in the treatment of GBS consist of plasmapheresis and IVIG. IVIG and plasmapheresis have comparable efficacy in the prevention of progression of neurological symptoms [4]. Any maternal or fetal complication due to the immunotherapy given for GBS has not been reported in pregnant women [10]. In a review including 30 pregnant women with GBS between 1986 and 2002, it was emphasized that mechanical ventilation was required in 33.3% of the cases, plasmapheresis or IVIG was used in 22 cases, maternal or fetal complication was not encountered in any of the cases, and IVIG might be a better option in GBS of pregnant women as it does not cause significant change in blood pressure.

It is rarely encountered during pregnancy. It is believed that pregnancy neither plays a role in the etiopathogenesis of GBS nor significantly influences the prognosis [3,4]. However, establishing a standard protocol in obstetric approach has failed due to inadequate number of cases. There are authors defending that cesarean section would be appropriate particularly in pregnant women that develop quadriplegia and are not able to use abdominal muscles as the labor would be prolonged and maternal and fetal prognosis would be influenced [5,8]. However, the authors recommending conservative monitoring and vaginal delivery as long as fetal wellbeing continue account for the majority [2,4,6]. The present case as well was followed conservatively until the development of preterm labor in the 38th week of gestation. Spontaneous vaginal delivery was allowed because of early rupture of membranes (water breaking). Any intrapartum or postpartum obstetric complication did not develop or the labor was not prolonged.

Based on this case, we concluded that a pregnant woman with GBS can be followed conservatively with appropriate supportive treatment (IVIG) and the delivery can be done via induction or spontaneous vaginal route after the completion of fetal maturation, and this approach does not have negative impact on maternal or fetal prognosis.

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Successful treatment of a patient with Takayasu's arteritis presenting as subclavian steal syndrome secondary to bilateral occlusion of subclavian arteries: A case report

Bilateral subklavian arter tıkanıklığına subklavian çalma sendromunun eşlik ettiği Takayasu arteritli hastanın başarılı tedavisi: Olgu sunumu

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Abstract

Takayasu's arteritis (TA) is a chronic vasculitis of unknown etiology, characterized by granulomatous inflammation of large-sized arteries. It usually involves aortic arch and its branches. It is controversial but percutaneous transluminal angioplasty (PTA) is preferred for non-active stenosis and occlusion of artery and aorta. We presented a patient who was in remission period with subclavian steal syndrome treated with bilateral endovascular intervention.

Keywords: Takayasu's arteritis, Subclavian steal syndrome, Percutaneous transluminal angioplasty

Öz

Takayasu arteriti (TA), büyük boyutlu arterlerde granülomatöz inflamasyon ile karakterize etiyolojisi bilinmeyen kronik bir vaskülittir. Genellikle arkus aorta ve dallarını tutar. Tartışmalı olmasına rağmen hastalığın aktif olmayan evresinde aort ve dallarının tıkanıklığı için perkütan translüminal anjiyoplasti (PTA) tercih edilmektedir. Bizde bu yazımızda remisyon periyodundaki bilateral endovasküler girişimle tedavi edilen subklavian çalma sendromlu bir olguyu sunduk.

Anahtar kelimeler: Takayasu's arteriti, Subklavian steal sendromu, Perkütan transluminal anjioplasti

Introduction

Takayasu's arteritis (TA) is a vasculitis of unknown etiology, characterized by inflammation of middle- and large-sized arteries, especially the aorta and its branches [1]. Ascending aorta, thoracic descending aorta, pulmonary arteries, abdominal aorta and its branches, and large arteries of the extremities can be affected, in addition to the involvement of aortic arch and its branches. The segmental stenosis, occlusion, dilatation and/or aneurysm of the vessels can be developed due to the inflammation of the vessel wall. As the disease progress, symptoms vary depending on the localization of the involvement. It can be hard to reach a diagnosis and delays in diagnosis can be seen in the early course of disease due to the non-specific symptoms such as fatigue, fever, weight loss. The claudication and neurological symptoms can be seen due to the extremity arterial and cranial arterial system involvement, respectively [1]. If the occlusion is proximal to the subclavian artery, the distal part of the subclavian artery is supplied by the vertebral artery and the perfusion of the brain may be compromised which is also called as subclavian steal syndrome. Subclavian steal syndrome is characterized by dizziness, headache and neck pain during exercise. Corticosteroids and immunosuppressive agents play a key role in the treatment of disease. Endovascular stenting, angioplasty, and by-pass surgery may be performed in case of severe stenosis or total occlusion of the artery [2]. We present a patient with TA who had a history of cerebrovascular disease, weakness of arms with exertion, headache and neck pain. We performed peripheral angiography in the diagnosis of suspected bilateral subclavian artery stenosis and performed stent placement for the bilateral subclavian artery.

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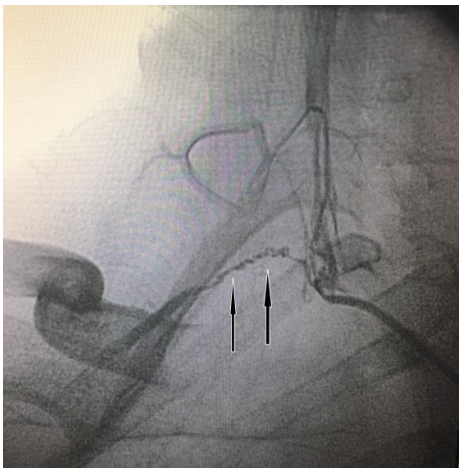

Figure 1: Angiogram revealed a 99% stenosis in the right subclavian artery

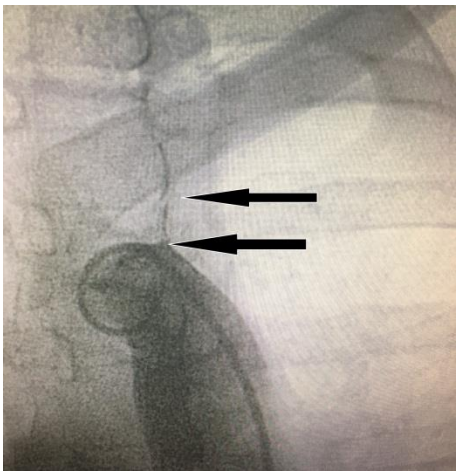

Figure 2: Angiogram revealed total occlusion of the left subclavian artery

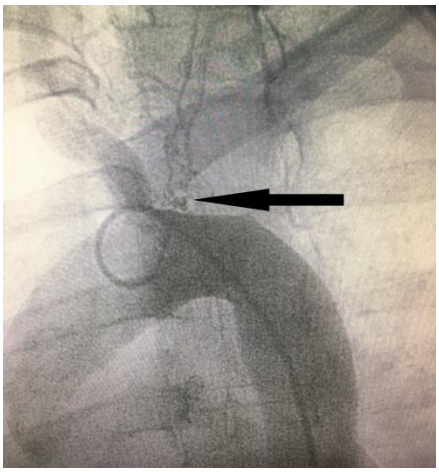

Figure 3: Subtotal occlusion of the left common carotid artery

Case presentation

A 22-year-old patient diagnosed with TA and cerebrovascular disease presented to the rheumatology department with bilateral arm pain which was increased by exertion and relieved by rest within 2-3 minutes. Upon questioning, she stated that a headache and neck pain and dizziness had recently worsened during daily activities such as cooking, sweeping which were relieved by rest. The physical examination revealed weak bilateral radial pulses. The heart rate was 84/min, her blood pressure was 74/42 mmHg in the right arm, and 78/45 mmHg in the left arm. Bilateral pedal pulses were normal, and the blood pressure was 128/82 mmHg in the right leg, and the blood pressure was 132/84 mmHg in the left leg. Her electrocardiogram showed normal sinus rhythm. Her echocardiogram was within normal limits. Along with these findings, we considered the possibility of subclavian steal syndrome and ordered computed tomography angiography (CTA). CTA revealed severe stenosis of bilateral subclavian arteries and diagnostic conventional peripheral angiography was performed. Angiogram revealed a 99% stenosis in the right subclavian artery (Figure 1), total occlusion of the left subclavian artery (Figure 2), and subtotal occlusion of the left common carotid artery (Figure 3).

The percutaneous transluminal angioplasty was decided to revascularize the right and left subclavian arteries. Bare metal stents were deployed into the right and left subclavian arteries (Figure 4, 5). The blood pressure in the left arm increased to 128/75 mmHg after stent implantation and became palpable. Dual antiplatelet (aspirin+clopidogrel) was added to her medications for TA and was discharged. Only clopidogrel treatment was continued at the end of the first month. Control subclavian angiography was performed six months later and it was found that stent implanted to left subclavian artery was patent and there was 30% restenosis in the right subclavian artery (Figure 6, 7). Since the patient was asymptomatic, medical therapy (clopidogrel + corticosteroids and immunosuppressive agents) was continued. The patient gave her informed consent for anonymous use of her personal data for scientific purposes.

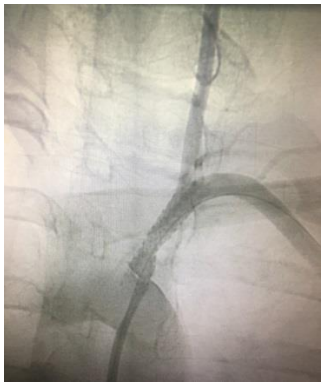

Figure 4: View of stent implanted to left subclavian artery

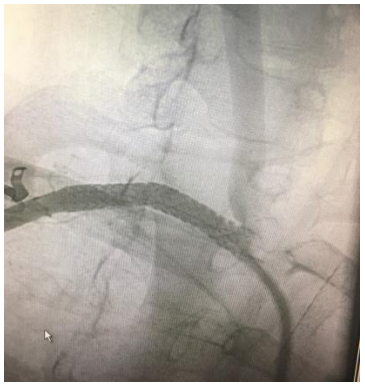

Figure 5: View of stent implanted to right subclavian artery

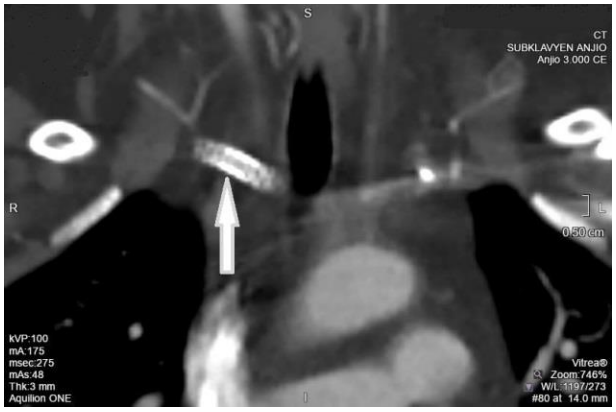

Figure 6: View of control computed tomography angiography for right subclavian artery

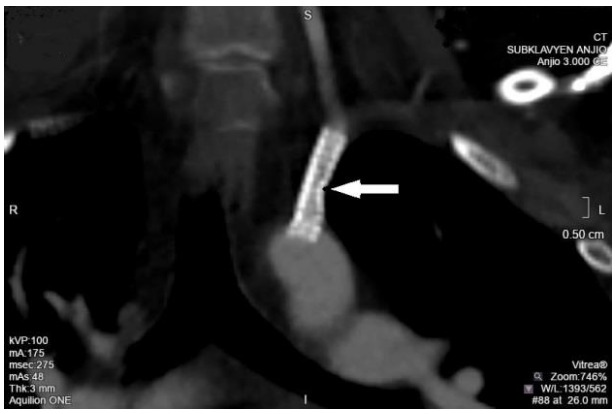

Figure 7: View of control computed tomography angiography for left subclavian artery

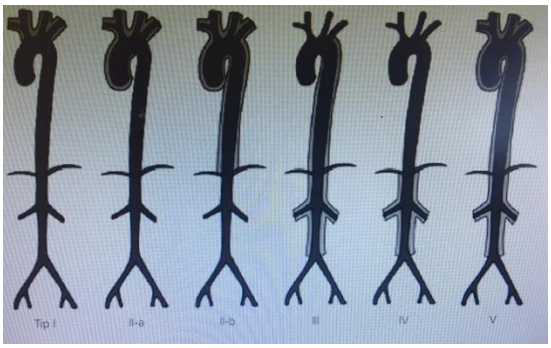

Figure 8: The angiographic classification of Takayasu's arteritis

Discussion

Takayasu's arteritis (TA) is a chronic vasculitis of unknown etiology, characterized by granulomatous inflammation of large-sized arteries. It usually involves aortic arch and its branches. Furthermore, ascending aorta, thoracic descending aorta, pulmonary arteries, abdominal aorta and its branches, and large arteries of the extremities can be affected. The segmental stenosis, occlusion, dilatation and/or aneurysm of the vessels can be developed due to the inflammation of the vessel wall [3]. The conventional angiogram remains an important tool for diagnosis and treatment. TA can be divided into different types based on the extensiveness of the disease. There are several classifications for TA. The classification made by Hata et al. [4] in 1994 is generally used for his purpose. According to this classification, patients are divided into five groups. In type I, aortic arch and its branches are compromised. In type IIa, ascending aorta is compromised in addition to the aortic arch and its branches. In type IIb, thoracic aorta involvement is seen. In type III, thoracic aorta, abdominal aorta, and renal arteries are compromised. In type IV, only abdominal and renal arteries are compromised. Type V is roughly equal to the sum of type IIb and type IV. In other words, aortic arch and its branches, ascending aorta, thoracic aorta, and renal arteries are compromised. The angiographic classification of TA is showed in Figure 8. The most common type is type V followed by type I in our country [5]. Our case met the criteria of type I.

Revascularisation is recommended in patients with upper extremity arterial disease, which is symptomatic in the European guidelines for the diagnosis and treatment of peripheral arterial disease. In symptomatic patients with a stenotic / occluded subclavian artery, both revascularization options (stenting or surgery) should be considered and discussed case by case according to the lesion characteristics and patient's risk [6]. On account of the current development of the endovascular therapy, percutaneous transluminal angioplasty (PTA) is preferred for non-active stenosis and occlusion of artery and aorta [7]. Even though patency of the surgical revascularization is better, endovascular therapy is preferred [8].

In our case, we preferred percutaneous transluminal angioplasty considering the patient and lesion characteristics. We performed stent implantation after balloon angioplasty because of insufficient opening after balloon angioplasty and lack of distal flow. However, considering the inflammatory process in inflammatory diseases, only ballooning may be more appropriate.

In Asian countries, PTA is being performed successfully in treatment of carotid, renal and subclavian artery disease. PTA is indicated in patients with claudication, distal organ ischemia, discrete lesions and significant stenosis. The intervention must be performed in remission period. Min PK et al. [9] showed that endovascular intervention was safe and effective only in remission period at which the disease was under controlled by immunsuppressive agents, in their case series. We presented a patient who was in remission period with subclavian steal syndrome treated with bilateral endovascular intervention. The result was satisfying but we should keep in mind that the long-term outcome of PTA in the setting of TA remains controversial. Maksimowicz-McKinnon et al. [10] showed that 78% of cases developed stenosis although interventions were successful.

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Simultaneously occurred pleural and pericardial effusion related to dasatinib treatment: A case report

Dasatinib tedavisine bağlı eşzamanlı gelişen plevral ve perikardiyal efüzyon: Olgu sunumu

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Abstract

Dasatinib is a proven potent tyrosine kinase inhibitor which is used in the newly diagnosed Philadelphia Chromosome (Ph1) positive chronic myeloid leukemia (CML) treatment when there is no hematological and/or cytogenetic response to imatinib treatment. Pleural and pericardial effusions due to dasatinib therapy may be seen 5 to 30 weeks after the onset of the treatment, but may also develop at any time interval. Pleural effusions are frequently bilateral and exudative, and lymphocyte cell dominance is often observed. It has been observed that when dasatinib treatment is stopped, the side effects which occurred with the treatment are greatly regressed. In this article, we present a case with New York Heart Association (NYHA) functional class III dyspnea under the treatment of dasatinib and developed simultaneous pleural and pericardial effusion, which is rare in the literature. Our aim of presenting this case is to emphasize once again the rarity of simultaneous pleural and pericardial effusion development in dasatinib therapy, and the importance of intermittent cardiopulmonary evaluation before and during the treatment of CML patients.

Keywords: Dasatinib, Pleural effusion, Pericardial effusion, Chronic myeloid leukemia

Öz

Dasatinib, imatinib tedavisine hematolojik ve/veya sitogenetik yanıt alınamayan yeni tanı almış Philadelphia Kromozomu (Ph1) pozitif kronik miyeloid lösemi (KML) tedavisinde kanıtlanmış potent bir tirozin kinaz inhibitörüdür. Dasatinib tedavisine bağlı plevral ve perikardiyal efüzyonlar ilacın başlanmasından genellikle 5-30 hafta sonra görülebilmekle beraber, herhangi bir zaman aralığında da gelişebilir. Plevral efüzyonlar sıklıkla bilateral ve eksüda karakterinde olup lenfosit hücre hakimiyeti çoğunlukla gözlenmektedir. Dasatinib tedavisine devam edilmemesi durumunda ortaya çıkan yan etkilerin büyük oranda gerilediği gözlemlenmiştir. Bu yazıda, dasatinib tedavisi altında New York Heart Association (NYHA) fonksiyonel klas III dispne ile başvuran, eş zamanlı plevral ve perikardiyal efüzyon gelişen, literatürde nadir gözlemlenen bir vaka sunuldu. Bu olguyu sunma amacımız, Dasatinib tedavisinde eşzamanlı plevral ve perikardiyal efüzyon gelişiminin nadir görülmesi, tedavi öncesi ve süresince yapılacak aralıklı kardiyopulmoner değerlendirmenin KML hastalarının takibindeki önemini bir kez daha vurgulamaktır.

Anahtar kelimeler: Dasatinib, Plevral efüzyon, Perikardiyal efüzyon, Kronik miyeloid lösemi

Introduction

Chronic myeloid leukemia (CML) and myeloproliferative diseases are clonal malignancies of the hematopoietic stem cell. The Philadelphia (Ph1) chromosome, an important chromosome in CML which was discovered more than 30 years ago, is the chromosome 9-22 translocation of Abelson proto-oncogene (t9: 22). Recently, tyrosine kinase inhibitors (TKI) are being successfully used as a new treatment option as well as isoallogenic bone marrow transplantation and alpha-interferon treatment in the medical treatment of Ph1 positive CML disease [1].

Dasatinib is a second generation TKI and is used in the treatment of patients who does not respond to imatinib treatment and/or cannot tolerate it [2]. Although dasatinib is known to be a well-tolerated agent, side effects such as pleural, pericardial effusion and dyspnea have been frequently observed as a consequence of fluid retention in a number of clinical trials [3].

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Pulmonary complications, especially pleural effusions, are being encountered as a non-hematologic adverse effect in dasatinib treatment [4]. Recent publications have documented potential and serious cardiac side effects such as pericardial effusion, QT prolongation, arrhythmia, congestive heart failure, myocardial ischemia and myocardial infarction in patients treated with dasatinib [5].

This article is presented due to the sudden and simultaneous development of pleural and pericardial effusion which are serious and important adverse effect that should always be kept in mind in a patient with CML who has been receiving dasatinib therapy for 4 months, also the situation is rarely seen in the literature.

Case presentation

A 50-year-old male patient presented with complaints of significant shortness of breath, dry cough and right sided pain to the emergency department. When the complaints of the patient were questioned, it was learnt that the shortness of breath and its intensity had increased within the last 10 days. The side pain was especially noticeable in the lying position and decreased with sitting and leaning forward. In the history of the patient, he had been diagnosed with CML 3 years ago and received imatinib mesylate treatment for about 2.5 years. Dasatinib 100 mg/day was initiated 18 weeks ago due to the development of resistance and insufficient response to this treatment.

In the physical examination, patient was conscious and general condition was moderate. The patient was agitated and could not lie flat. There was no fever but he was in tachycardia (105/min, rhythmic), hypotension (95/55 mm/Hg) and tachypnea (26/min). In the examination of the cardiovascular system, heart sounds were deep and jugular venous distension was present. In the examination of the lung, respiratory sounds were absent the right middle and right lower zones and they were significantly decreased in the left lower zone. The spleen was 1 cm below the ribs and the traube space was closed in the abdominal examination. Hepatomegaly and peripheral lymphadenomegaly were not detected.

In the laboratory review; leukocyte count was 11500/mm3, hemoglobin was 10.9 g/dL, hematocrit was %33.5, C-reactive protein (CRP) was 23.3 mg/dL (normal range 0-3) and lactate dehydrogenase (LDH) was 291 U/L and troponin I was 0.53 ng/ml. The urine analysis was normal. On the P-A chest X-ray, bilateral pleural effusion, more at the right side compared to th e left side and cardiomegaly were detected (Figure 1).

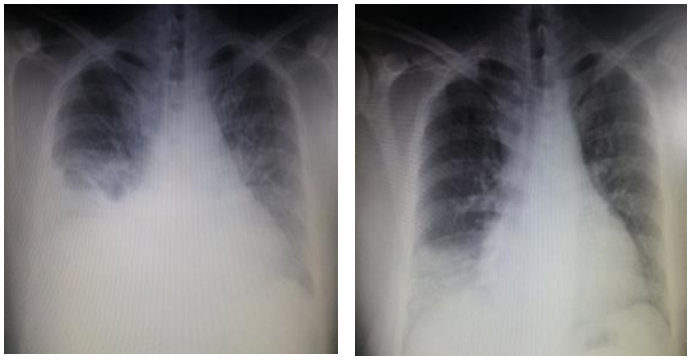

Figure 1: Chest X-ray images of the patient on the 1st day (left image) and after the treatment; on the 12th day (right image)

Bilateral pleural effusion was confirmed by ultrasonography evaluation. Thorax CT revealed a massive pleural effusion extending to the upper quadrant of the right hemithorax and an appearance of effusion reaching a thickness of 3 cm in the intrapericardial space adjacent to the right ventricle. Also, a small amount of pleural effusion was seen in the basal section of the left lung (Figure 2).

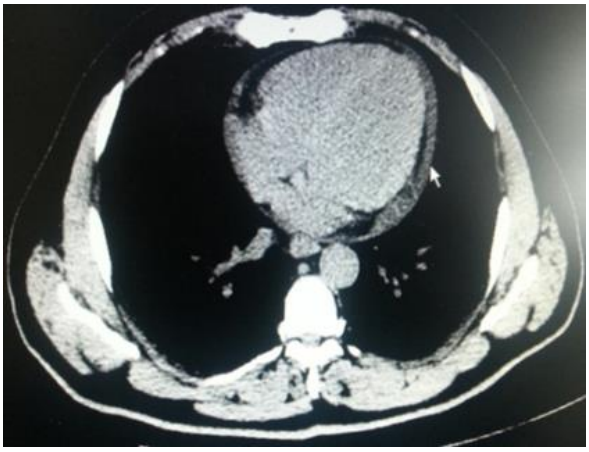

Figure 2**:** Computed tomography of thorax. Appearance of effusion reaching a thickness of 3 cm in the intrapericardial space adjacent to the right ventricle

There was a voltage drop in the electrocardiography of the patient whose troponin I levels were found to be high. There was no evidence of ischemia or arrhythmia. On the 2nd day of the hospitalization, transthoracic echocardiography showed: EF: 55%, pericardial effusion (posterior 14mm, right ventricle 15mm, lateral 11mm) and floating heart appearance without tamponade finding. There was no cardiac valve anomaly. Diagnostic thoracentesis was performed on the right with ultrasound guidance. Pleural effusion fluid obtained via thoracentesis analyzed biochemically. Effusion was found to be exudative according to the Light criteria and lymphocyte dominancy was observed in the microscopic examination (Table 1).

Cytological analysis of the fluid did not reveal malignant cells. ADA level was studied in terms of differential diagnosis of tuberculosis and PCR was performed to reveal Mycobacterium tuberculosis. PCR was negative and ADA level was normal. The levels of ANA, Anti-dsDN, Anti-ssA, Anti-ssB, c-ANCA, p-ANCA, Anti-Cardiolipin IgM and IgG, Anti-RNP, C3 and C4 were also found to be within normal limits for differential diagnosis of collagen connective tissue diseases.

Table 1: Biochemical analysis of the pleural fluid according to light criteria

	Glucose (mg/dl)	LDH (u/l)	Total protein (g/dl)	Albumin (g/dl)
Pleural fluid analysis	177	181	4.1	2.9
Analysis of serum	114	281	7.3	4.1

LDH: Lactate dehydrogenase

The patient's clinical condition was considered to be due to the side effect of dasatinib treatment which is a second-generation tyrosine kinase inhibitor and was administered 18 weeks ago. Dasatinib treatment which was in progress was stopped. Furosemide 80 mg/day and indomethacin capsule 3x25 mg treatments were started. After the treatment started, the patient's symptoms such as shortness of breath and side pain

quickly recovered. On the 12th day of treatment, control chest X-ray showed a significant regression in pleural effusion on the right side (Figure 1). Control echocardiography performed on the 7th day of treatment showed an EF of 48% and hypokinesia with mild mitral and tricuspid insufficiency on apical sections of anteroseptum. The pericardial effusion with a diameter of 0.5 cm in front of the right atrium and ventricle was detected and the effusion decreased severely when compared with the previous ECO findings. The patient who was treated for 14 days and had a rapidly improved clinical condition was discharged with the suggestion of polyclinic control.

Discussion

CML is a disease characterized by Philedelphia chromosome which is a result of translocation on chromosomes 9 and 22. The resulting BCR-ABL fusion gene plays an important role in the pathogenesis of the disease by encoding the tyrosine kinase. Dasatinib is an effective tyrosine kinase inhibitor and has been successfully used at all stages of CML therapy and in the treatment of Ph positive acute lymphoblastic leukemia (ALL) [6].

Dasatinib is a multi-targeted tyrosine kinase inhibitor with effects on many receptors besides BCR-ABL, including platelet-derived growth factor receptor (PDGFR), Src, discoidin domain receptor and c-kit. Studies have shown that ABL inhibition is about 300 times stronger when compared to imatinib [2].

Pleural effusions are detected in about 10-20% of patients under dasatinib therapy, but mostly in 5-28th weeks of the treatment. Particularly at higher doses (140 mg/day) and in patients receiving twice-a-day dosing, significantly higher rates were observed. Several risk factors such as advanced age, acute or blastic phase of the disease, long-term therapy, arterial hypertension, hypercholesterolemia and accompanying autoimmune diseases are also known to be responsible in the development of pleural effusion [7,8].

Dasatinib-related pleural effusions are bilateral in 79% of patients and are usually exudative. Lymphocyte cell dominance is seen in fluid analysis, bronchoalveolar lavage and pleural biopsies. In the majority of these cases, pulmonary symptoms were regressed within 1 week after the drug withdrawal and did not recur after starting on low dose dasatinib therapy in 3 out of 4 cases [9,10].

In a case study involving 13 CML patients who received low dose (50-100 mg / day) dasatinib treatment, 4 patients developed pleural and/or pericardial effusion and fluid accumulation of the two was in the level of life-threatening grade III/IV. In addition, those four patients had no history of any cardiac or pulmonary [11].

In this case we reported, Dasatinib 100 mg/day treatment, started due to inadequate response to high dose imatinib treatment. The patient had no history of heart and/or lung diseases. The patient underwent routine blood tests with short periods while under Dasatinib treatment and monthly evaluated with chest x-rays and ECG's. However, our patient was admitted to our hospital with dyspnea and clinical deterioration on the 18th week after the onset of treatment. Dasatinib treatment was stopped. Tuberculosis, malignancy and collagen connective tissue diseases were considered to be preliminary in terms of differential diagnosis. These diseases were excluded as a result of the performed clinical evaluations. Pleurodesis was not considered as an option because the patient responded to treatment and fluid collection decreased rapidly.

In conclusion, since dasatinib is an effective treatment option that has an increased usage day by day in the treatment of CML, the side effect profile should be well known especially by the clinician following the patient. The cases should be well analyzed in terms of comorbid factors and potential risks before treatment and should be followed closely with periodic cardiac and pulmonary examinations during treatment.

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Gastrointestinal bleeding secondary to use of high-dose methotrexate: A case report

Yüksek doz metotreksat kullanımına ikincil gelişen gastrointestinal kanama: Olgu sunumu

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Abstract

A 69-year-old female patient was admitted to our emergency service with painful oral ulcers and rectal bleeding. She has been used methotrexate (MTX) because of rheumatoid arthritis (RA). The patient has been used methotrexate every day for 10 days instead of a weekly treatment. Pancytopenia was seen in laboratory tests. Rectal bleeding associated with gastrointestinal mucosal erosion was attributed to MTX toxicity and MTX-induced thrombocytopenia. The direct cause of MTX intoxication in this case was accidental daily use instead of a weekly use. This case demonstrates the importance of communicating adequately with health professionals and emphasizes that MTX should be used weekly. It is essential to describe in detail how the medication can be used and what adverse effects may occur as the result of taking MTX.

Keywords: Methotrexate, Rheumatoid arthritis, Thrombocytopenia

Öz

69 yaşında kadın hasta Acil Servis'e ağrılı oral ülserler ve rektal kanama ile başvurdu. Romatoid artrit (RA) sebebiyle metotreksat (MTX) kullanıyordu ve haftalık tedavi yerine 10 gün boyunca her gün olacak şekilde MTX kullanmıştı. Labaratuvar testlerinde pansitopeni görüldü. Gastrointestinal mukozal hasar birlikteliği ile olan rektal kanaması MTX toksisitesine ve MTX bağımlı trombositopeniye bağlandı. Bu olguda MTX intoksikasyonunun direkt sebebi haftalık kullanım yerine yanlışlıkla günlük olarak kullanım idi. Bu vaka sağlık çalışanları ile yeterli iletişim kurmanın önemini göstermektedir ve MTX'ın haftalık olarak kullanılması gerektiğini vurgulamaktadır. MTX tedavisi başlanacağı zaman detaylı bir şekilde ilacın nasıl kullanılacağı ve hangi yan etkileri oluşturabileceğini anlatmak elzemdir.

Anahtar kelimeler: Metotreksat, Romatoid artrit, Trombositopeni

Introduction

Methotrexate (MTX) is a folic acid antagonist with anti-inflammatory and immunosuppressive effects. It is mostly used in neoplastic diseases and in the treatment of inflammatory diseases such as Rheumatoid arthritis (RA). Rarely, it can cause severe side effects such as agranulocytosis on the basis of bone marrow suppression, inflammation in mucosal tissues, hepatic necrosis, cirrhosis of the liver, pulmonary fibrosis and renal dysfunction [1]. We presented a case of newly diagnosed pancytopenia, stomatitis and gastrointestinal hemorrhage in a 69-year-old woman who had been mistakenly used intramuscular MTX every day.

Case presentation

A 69-year old woman with no history of chronic disease except known hypertension was admitted to our clinic with complaints of nausea, vomiting, abdominal pain, bright red stool, oral mucositis and decreased oral intake for the last 3 days. An oral dose of 8 mg/day methylprednisolone and intramuscular MTX 15 mg/week was started 10 days prior with a diagnosis of RA in the rheumatology polyclinic. However, the patient administered methylprednisolone once a week and MTX every day. Vital findings of the case were the following: blood pressure 125/80 mmHg, pulse rate 98/min, temperature 36.8 °C, respiration rate 19/min.

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On the physical examination, there were numerous aphthous lesions in the mouth. The patient had tenderness on deep palpation but had no rebound tenderness, defense or organomegaly. The digital rectal examination was compatible with hematochezia. Significant pathological findings were not found in other system examinations of the patient. The laboratory findings were the following: WBC 1200 /mm^3, neutrophil 300/mm^3 [30%], Hgb 9.5 gr/dl, MCV (Mean Corpuscular Volume) 94 /Fl, thrombocyte 43000 /mm^3, sedimentation 42 mm/hr, CRP (C-Reactive Protein) 8 mg/dL (Table 1).

Table 1: Laboratory findings of the patient

Day/Parameter	Wbc x10^3/uL	Neu x10^3/uL	Hgb gr/dl	Plt x10^3/uL	Ast U/L	Alt U/L	Crt mg/dl
Pre-treatment	1.2	0.3	9.5	43	25	20	0.7
Day 1	1.3	0.4	9,6	59	69	92	0.8
Day 3	1.3	0.4	9.5	54	44	85	0.7
Day 4	1.6	0.7	9.7	155	26	65	0.7
Day 7	2.6	1.5	9.8	160	35	21	0.8
Day 9	29	25	10.4	380	22	19	0.7

Wbc: White blood cell, Neu: Neutrophil, Hgb: Hemoglobin, Plt: Platelet, Ast: Aspartate aminotransferase, Alt: Alanine aminotransferase, Crt: Creatinine

Erythrocytes were normocytic hypochromic, few neutrophils and mature lymphocytes were present, clumping of platelets was observed and no atypical cells were detected upon the examination of peripheral blood smear. Chest X-ray and electrocardiography of the patient were normal. The biochemical values were usual. There was no significant pathologic finding in abdominal CT (Computed Tomography) of the patient who had abdominal pain. No pathology was detected in the direct microscopic examination of stool specimens and in microscopic-macroscopic examinations of the patient with bloody stool. Colonoscopy showed a mucosal-like appearance throughout evident in the descending colon and there were locally ulcerated sites (Figure 1). Pancytopenia secondary to the use of high-dose MTX, mucositis and gastrointestinal bleeding were considered for the patient. MTX was discontinued and intravenous Folinic Acid rescue protocol was administered at 5 mg/day for 4 days. Filgrastim subcutaneous 48 IU 1x1 was initiated for pancytopenia, thrombocytopenia on the 7th day, pancytopenia and gastrointestinal system bleeding stopped on the 9th day of admission. Her pancytopenia improved, she had no bloody stool complaints and lesions in her mouth receded and then, the patient was discharged.

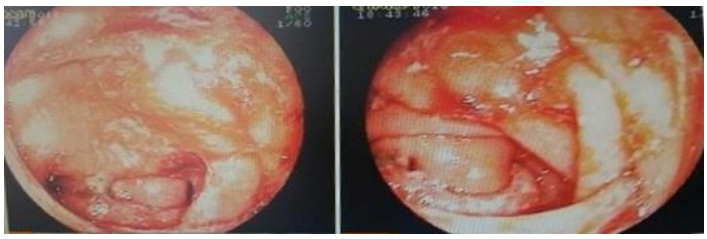

Figure 1: Mucositis and ulcer areas in the descending colon

Discussion

RA characterized by a symmetric, erosive, synovitis and sometimes with multisystem organ involvement is an autoimmune disease with unknown etiology [2]. In RA treatment, disease modifying drugs are used to prevent progression of the disease. The first preferred drug is MTX within this group of drugs [3,4]. MTX is regarded as the leading drug in RA treatment because it has many features such as its long-term use by patients, high clinical reliability, and being able to be combined with biological agents [5]. When MTX therapy is initiated, its effect starts at 3-6 weeks and is usually well-tolerated. Although it is generally well-tolerated, MTX use may cause pancytopenia, hepatotoxicity, pulmonary toxicity, nephrotoxicity, high fever, gastrointestinal adverse effects, and skin eruptions [6,7]. The gastrointestinal tract and bone marrow toxicity of MTX may be dose-dependent, whereas pneumonitis, liver and cardiac toxicity may be dose-independent. In our case, there was a pancytopenia that developed due to a high-dose use of MTX every day. MTX-induced pancytopenia toxicity may be due to high-dose use of MTX or may be due to low-dose [8, 9]. A study conducted by Ohosone et al. [10], found that about 1.4% of patients using a low-dose MTX developed pancytopenia. In the case of MTX-induced pancytopenia, treatment options include the use of the first granulocyte colony-stimulating factor [11,12]. In our case, 48 IU filgrastim therapy improved leukopenia on the 7th day complete blood count. It rarely can have adverse effects on gastrointestinal system mucosa because of the antimitotic and antiproliferative effect of MTX. Intestinal mucositis, bleeding and ulcers are known toxic effects in gastrointestinal tract. In the present case, there were findings compatible with intestinal mucositis in the entire colon, especially in descending colon in the colonoscopy. It is thought that MTX may be associated with increased immune response and gastrointestinal blood flow, although it is not fully elucidated how MTX causes mucositis. In the literature, Tsukada et al. [13] reported a case of gastrointestinal mucosal necrosis developed in a patient using a dose of MTX at 8 mg/week. Unlike our case, there was no high-dose use history and the patient had mucosal necrosis on the gastrointestinal examination.

In conclusion, MTX use in RA therapy may cause unexpected and life-threatening complications as a result of unconscious use although it is effective, safe and tolerable. Patients should be informed how to use the medication and what adverse effects may occur in detail when MTX therapy is initiated. MTX toxicity should be kept in mind when symptoms such as pancytopenia, oral ulcers, and gastrointestinal bleeding occur in patients with RA.

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Anaphylactic shock during splenic hydatid cyst surgery: A case report

Splenik hidatik kist cerrahisinde anafilaktik şok: Olgu sunumu

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Abstract

Hydatid disease is a common parasitic infection caused by Echinococcus granulosus. Isolated splenic involvement is an uncommon condition even in endemic regions. The treatment of a splenic hydatid cyst is mainly surgical. Complications can occur during surgery such as anaphylactic shock. We report here the case of a patient who was admitted in our hospital for splenic hydatid cyst. She was 31 years old. She was admitted for a dull pain in the left hypochondrium. An abdominal examination objectified a patient with normal vital signs, she had a slight tenderness in the left hypochondria and epigastric regions. No hepatomegaly was found. Abdominal computed tomography revealed an isolated splenic cystic lesion measuring about 8, 2 cm in diameters and containing floating membranes. The patient was operated and a left subcostal incision. The Surgical exploration revealed a hydatid cyst occupying the middle region of splenic parenchyma, only a thin layer of splenic tissue was present in superior and inferior surface. At the end of the surgery the patient presented tachycardia, hypotension and extensive skin erythema. Conclusion: hemodynamic instability, should suggest the diagnosis of anaphylaxis in order to begin specific management, all preventive measures can be justified given of severity of anaphylaxis.

Keywords: Anaphylactic shock, Hydatid cyst, Prevention, Surgery

Öz

Hidatik hastalık Echinococcus granulosus'un neden olduğu yaygın bir parazit enfeksiyonudur. İzole splenik tutulum endemik bölgelerde bile nadir bir durumdur. Dalak kist hidatiklerinin tedavisi çoğunlukla cerrahi yöntemdir. Anafilaktik şok gibi cerrahi sırasında komplikasyonlar görülebilir. Burada, splenik kist hidatik için hastanemize yatırılan bir olgu sunulmuştur. Hasta 31 yaşındaydı. Sol hipokondride mütevazı bir ağrı nedeniyle başvurdu. Karın muayenesinde sol hipokondri ve epigastrik bölgelerde hafif hassasiyet vardı. Hepatomegali bulunamadı. Abdominal bilgisayarlı tomografide, çapları 8 cm, çapları 2 cm olan ve yüzer membranlar içeren, izole splenik kistik lezyon izlendi. Hasta ameliyat edildi ve sol subkostal kesi yapıldı. Cerrahi incelemede, splenik parankima orta bölgesini işgal eden hidatik bir kist ortaya çıkmış, üst ve alt yüzeyde sadece ince bir tabaka splenik doku mevcuttu. Ameliyatın sonunda hasta taşikardi, hipotansiyon ve yaygın cilt eritemi oluştu. Sonuçta hemodinamik istikrarsızlık, spesifik tedaviye başlanabilmesi için anafilaksi teşhisi konmalıdır, anafilaksi şiddeti nedeniyle tüm önleyici tedbirler alınmalıdır.

Anahtar kelimeler: Anafilaktik şok, Kist hidatik, Önleme, Cerrahi

Introduction

Hydatid disease (HD), which is caused by Echinococcus granulosus, is a common parasitic infection that often occurs in endemic regions such as the Middle East, Mediterranean, and South America. Although it mainly involves the liver, it has been reported in nearly all parts of the body [1]. Isolated splenic involvement is an uncommon condition even in endemic regions [2]. The incidence of hydatid splenic cysts varies from one series to another. It ranges from 0.5–4% of all cases of HD [1-2]. Splenic hydatid cysts are generally asymptomatic. The symptoms of splenic hydatidosis are usually mild and are generally caused by the pressure on adjacent organs such as the colon, the diaphragm. The patients usually complain of mild discomfort or pain in the left hypochondrium. The diagnosis is established generally during radiological investigation for other reasons. The hydatid fluid is antigenic and highly toxic and can cause a potentially fatal anaphylaxis reaction.

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We herein describe an acute anaphylactic shock during Spleen-preserving surgery of an isolated splenic hydatid cyst in a 31 year old female patient.

Case presentation

A 31 year old female farmer presented with a dull pain in the left hypochondrium which did not shift or radiate. The patient complained of malaise with nausea, vomiting, weight loss and intermittent fever within the last 9 months. She had no history of jaundice, cough or respiratory distress, abdominal trauma, weight loss and her past medical history was unremarkable notably no allergic incidents. Physical examination found a patient with normal vital signs; she had a slight tenderness in the left hypochondria and epigastric regions. No hepatomegaly was found. Abdominal computed tomography (CT) revealed an isolated splenic cystic lesion measuring about 8, 2 cm in diameters and containing floating membranes. There were no cysts in other abdominal viscera (Figure 1). A chest CT scan did not show any cystic lesions.

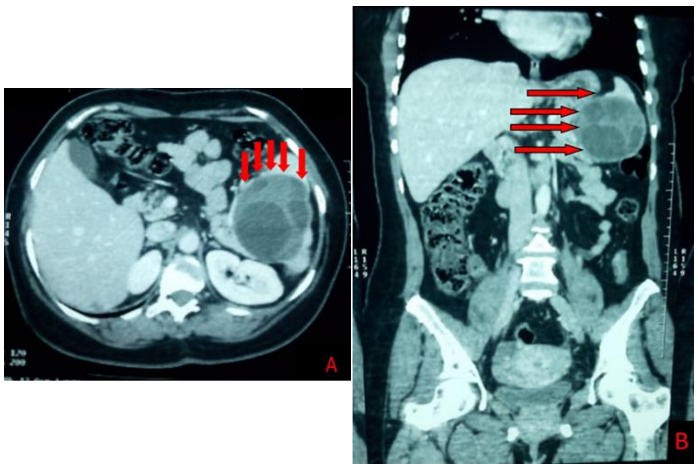

Figure 1: image showing the hydatid cyst. A: axial section and B: coronal section

Surgery was performed via a left subcostal incision. The Surgical exploration revealed a hydatid cyst occupying the middle region of splenic parenchyma, only a thin layer of splenic tissue was present in superior and inferior surface. There were a lot of adhesions between the spleen and the omentum and these adhesions were liberated with difficulty. After protection of the surgical field by compresses imbibed with oxygenated water and then resection of the protruding dome (Figure 2), a clear liquid containing hydatid membranes were aspirated and evacuated. The residual cavity was sterilized with oxygenated water and then drained.

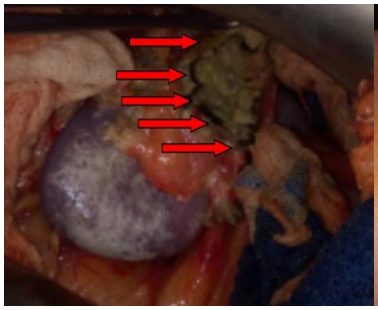

Figure 2: image after de-roofing of the hydatid cyst

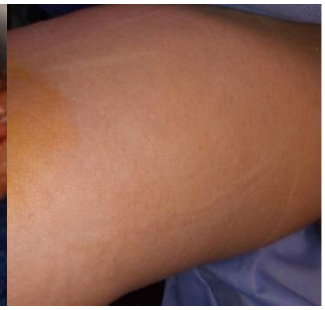

Figure 3: Cutaneous signs in the upper limb

At the end of the surgery the patient presented tachycardia, hypotension and extensive skin erythema (Figure 3). The surgeon was alerted. He performed a rapid wash and drainage of the left hypochondrium. The patient was placed under noradrenaline with bolus of Methylprednisolone. She was extubated a few hours after stabilization of her vital signs.

Discussion

Splenic hydatid cyst (SHC) represents 0.5–4% of all cases of abdominal Hydatid disease across all ages and in both sexes [1,3-8]. SHC usually coexist with liver hydatid cysts (secondary); however, in some cases, the spleen is the primary location [4,9]. Splenic infection usually occurs through an arterial route after the parasite manages to pass through two other filters: hepatic and pulmonary [3,6,10]. SHC may also develop by retrograde spread from the liver into the spleen via the hepatic portal and splenic veins in patients with portal hypertension. The spleen may also be affected by rupture of a hydatid cyst into the peritoneal cavity [4,10].

The clinical signs and symptoms of SHC depend on location, size, and relation to adjacent organs. The most common clinical signs and symptoms are splenomegaly, abdominal lump, dull ache, dyspepsia, constipation due to pressure on the colon, and dyspnea due to pushing up of the left diaphragm. Some patients may present with complications, such as infection of the cyst; rupture of the cyst into the peritoneal or pleural cavity; fistula formation into hollow organs, like the colon or stomach; rupture of SHC into the bronchial tree; splenothoracic fistula; sympathetic pleural effusion; calcification; hypersplenism; or signs of anaphylactic shock [4,10,11].

The diagnosis of SHC is based on medical history and geographical background of the patient, a physical examination, radiological imaging, serology, fine needle aspiration cytology (FNAB), and histopathological examinations of resected cysts. Serological tests are used for diagnosis, screening, and follow-up for recurrence. The differential diagnoses of SHC include non-parasitic cysts and tumors of the diaphragm, stomach, colon, left kidney, or pancreas. Non-parasitic cysts can be divided into primary (true cysts) and secondary (pseudo-cysts).

Surgery remains the main treatment for SHC [3]. The main goals of surgery are to prevent complications; eliminate local disease; and minimize morbidity, mortality, and recurrence rates and intraoperative complication such as hemorrhage or anaphylactic shock.

It remains controversial whether a total splenectomy is more beneficial than a spleen-preserving approach in patients with SHC. A splenectomy is advocated by the majority of surgeons, as it provides minimal risk for recurrence. However, splenectomy is associated with sepsis-related deaths in 1.9% of adults and 4% of children. Thus, conservative surgical procedures have been increasingly proposed, including partial splenectomy, enucleation, deroofing with omentoplasty, internal drainage with cystojejunal anastomosis, or external drainage [3,11]. An alternative to surgery is percutaneous drainage and administration of a sclerosing agent, such as 96% alcohol and 1% polidocanol under ultrasonography guidance [3, 8]. One of the problems likely to be encountered with this method is intraperitoneal spillage of the cystic contents during the procedure responsible for another recurrence of the disease. Moreover, the rates of anaphylactic reactions occurring during percutaneous treatment are similar to that of open surgery [8].

The intraoperative complications may be hemorrhage or anaphylactic shock as described in our case; Secondary to a passage of the hydatid fluid into the peritoneum or into the blood.

Anaphylactic shock occurring spontaneously [12] or caused by cystic ruptures have been described [13,14].Various intraoperative factors can cause hydatid fluid contamination which may trigger anaphylactic reactions. The symptoms vary from mild urticaria to anaphylactic shock [15]. The incidence of intraoperative anaphylaxis varies [16]. The mechanism of these reactions is complex. In some cases, it is typically a type I hypersensitivity reaction associated with immunoglobulin E in response to high plasma concentration of antigens Echinococcus [17]. Anaphylactic or anaphylactoid reactions may also be secondary to complement activation with liberation of anaphylatoxins [18]. The symptomatology is variable depending on the severity. During anesthesia cardiovascular signs, such hypotension, tachycardia, and arrhythmia predominate. Cutaneous symptoms, such as rash, flushing, and urticaria, are common in the neck, face, and especially on the anterior chest but these signs are often hidden by the surgical draping. Occurrence of bronchospasm is less frequent and less sensitive, especially after general anesthesia. In incomplete presentations (only one symptom may be present: hypotension, bronchospasm, etc) diagnosis of anaphylactic shock occurs after elimination of other causes: acute myocardial infarction, carcinoid syndrome, and hypovolemic shock.

Prevention of anaphylaxis of hydatid cyst is surgical; In order to avoid over distension of the cyst a scolicidal agent is slowly injected. The cyst is gently manipulated. Other techniques have been described [19,20]. Laparoscopy appears to be effective and safe in the treatment of hydatid cyst, in the analysis of 5943 percutaneous treatment procedures on hepatic and non-hepatic echinococcal cysts, the risk of anaphylactic reactions was low, with 0.03% of lethal anaphylaxis and 1.7% of reversible allergic reactions [21]. Medical prevention including histamine H1, H2 receptor blockers, and corticosteroids remains controversial. In a prospective study, the preoperative administration of H1 and H2 receptor blockers has mitigated hemodynamic responses secondary to spillage of hydatid cyst [22].

Hydatid cyst surgery is often simple. The occurrence of hemodynamic instability, apart from the bleeding and hypovolemia, should suggest the diagnosis of anaphylaxis in order to begin specific management. All preventive medical and surgical measures can be justified given of severity of anaphylaxis; a retrospective study is desirable to clarify the subject, the incidence of this type of complication and the appropriate measures to avoid it.

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Colonic lymphoma presented as acute abdomen: A case report and review of literature

Akut karına sebep olan kolonik lenfoma; Olgu sunumu ve literatür derlemesi

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Abstract

The primary gastrointestinal tract (GIS) lymphomas constitute approximately 1% of all GIS tumors. Primary GIS involvement in Hodgkin lymphoma is extremely rare. In this study, we aimed to present a case of colonic lymphoma that grows rapidly in young adult patients and causes acute abdomen. A 20-year-old woman presented with complaints of nausea, vomiting and diarrhea. Ultrasonography revealed mass and free fluid in the right lower quadrant. A 9cm diameter solid mass was observed in the cecum with tomography. As a result of these findings and clinical evaluation, emergency laparotomy was decided. A 10 cm diameter mass terminal ileum and cecum was seen and right hemicolectomy was performed. Because the age of the presented patient is young and the complaints are faint, no diagnosis has been made until the 9cm size is reached. It should be kept in mind that such situations may be met and further testing should be avoided if necessary.

Keywords: Hodgkin lymphoma, Acute abdomen, Colon tumor

Öz

Primer gastrointestinal sistem (GİS) lenfomaları tüm GİS tümörlerinin yaklaşık %1'ini oluşturmaktadır. Hodgin lenfomada primer GİS tutulumu son derece nadirdir. Bu çalışmada genç yetişkin hastada hızla büyüyen ve akut karın tablosuna sebep olan kolonik lenfoma olgusunu sunmayı amaçladık. 20 yaşında kadın bulantı, kusma ve ishal şikayetleriyle başvurdu. Ultrasonografi incelemesinde sağ alt kadranda kitle ve serbest sıvı görüldü. Tomografide Çekumu içinde alan periçekal 9cm çaplı solid kitle görüldü. Bu bulgular ve klinik değerlendirme sonucunda acil laparotomiye karar verildi. Laparotomide terminal ileum ve çekumu içine almış 10cm çaplı kitle görüldü ve sağ hemikolektomi yapıldı. Sunulan hastanın yaşının genç olması ve şikayetlerinin silik olması nedeniyle 9cm boyutuna ulaşılana kadar tanısı konulamamıştır. Bu tür durumlar ile karşılabileceği akılda tutulmalı ve gereğinde ileri tetkikten kaçınılmamalıdır.

Anahtar kelimeler: Hodgkin lenfoma, Akut karın, Kolon tümörü

Introduction

Primary gastrointestinal tract (GIS) lymphomas constitute approximately 0.9% of all lymphomas [1]. Primer GIS lymphoma was first described by Billroth in 1871 [2]. Dawson criteria are used most frequently in the definition of primary GIS lymphoma [3]. The most common organ in the gastrointestinal tract is the stomach (50-70%) followed by small intestines (20-35%), esophagus (5% - 10%) and esophagus (<1%). Primary colon lymphomas constitute approximately 0.1-0.5% of malignant tumors originating from the colon [4].

Primary colon involvement in the Hodgkin's lymphoma (HL) is extremely rare and only isolated cases have been reported in the literature. These cases were mostly treated with modalities based on basic surgery [5,6]. Complications can be various in colonic tumors, and first presentation as a complication has not been evaluated earlier [5,7].

In this study, our aim is to emphasize the importance of early diagnosis and surgical treatment of colon lymphoma due to complications caused by diagnostic delays, and is to perform a review of literature.

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Case presentation

A 20-year-old woman applied to her emergency clinic with complaints of nausea, vomiting and diarrhea. On the physical examination, the mass was palpated in the lower right quadrant. Laboratory examination was normal except for leucocyte count (11,000 /mm3) and lactate dehydrogenase level (518 U/L). Ultrasonography revealed mass and free fluid in the right lower quadrant. In the cecum, a mass of 9 cm diameter solid mass was found and free air was seen around the perforation in tomography study (Figure 1). As a result of these findings and clinical evaluation, emergency laparotomy was decided. In laparotomy, a 10 cm diameter mass in terminal ileum and cecum was seen, and right hemicolectomy was performed. The patient also came in earlier postoperative periods and stated that they had temporary abdominal pain and nausea complaints. No acute abdomen was detected, and medical treatment was continued. The patient was discharged on the 6th day without any problems. Pathologic examination revealed diffuse high grade B cell lymphoma of the sigmoid origin. Patients was informed and followed by oncology for oncologic treatment.

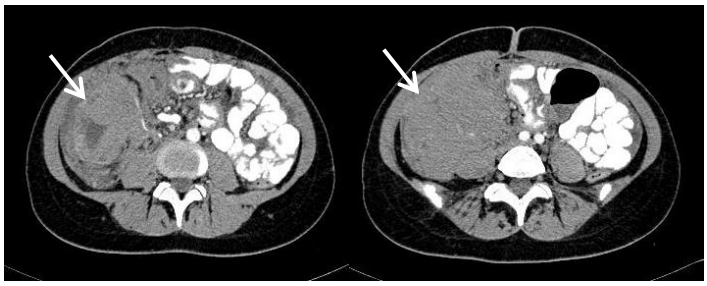

Figure 1: Abdominal computed tomography shows a mass (arrow)

Discussion

Primary colorectal lymphomas account for 6% to 12% of all gastrointestinal tract lymphomas. It is usually seen between the 4th and 7th decades of life and the average age at diagnosis is 55 [8]. Inflammatory bowel diseases (Crohn's disease, ulcerative colitis) and immunosuppression are important risk factors. The most common symptom is abdominal pain followed by loss of appetite and weight loss. In lesser proportions, mass in the abdomen, rectal bleeding, change in bowel habits may be seen. Bowel obstruction and perforation are rare [9].

Since histological diagnosis is very difficult, diagnosis can be achieved by immunophenotypic and genotypic studies of the surgically removed target. Non-Hodgkin's Lymphomas originate from T cells, B cells or histiocytes. The type of cell the tumor originates from is usually determined based on the phenotypic and molecular characteristics of the tumor cells, 80% to 85% of the B cell origin and the remaining 10% to 15% of the T cell tumors. The cell type has been shown to have a worse prognosis than the B cell type [10-13]. The reason for this difference cannot be explained.

Diagnostic colonoscopy, computed tomography and double contrast colonography are frequently used. In double contrast barium studies and computed tomography examinations, polypoid, infiltrative, mesenteric dilated endoexoenteric cavitary masses, thickening of mucosal nodules and cornea may be seen [1,2]. Occasionally, focal lumen narrowing, aneurysmal dilatation, or fistula formation in an ulcerative form may be observed. Colonoscopy is very useful both for macroscopic evaluation of the kitten and for microscopic evaluation by biopsy.

The rare occurrence of this disease complicates clinical trials and the most appropriate treatment method cannot be identified. Most authors suggest surgical treatment methods used in colorectal carcinomas without chemotherapy or with chemotherapy [12,13]. Surgical intervention plays an important role in the treatment of the disease. Curative intentional surgery may be recommended for those with localized disease, palliative surgical procedures may be used to correct obstruction and other symptoms. However, surgical treatment is also important in patients with perforation, bleeding, and fistulae [9,14]. In a multicenter study conducted, only patients with chemotherapy showed that the outcome was worse than with chemotherapy or without chemotherapy [14]. However, this result can be explained by the fact that the majority of patients receiving chemotherapy have a T-cell type that is worse prognostic [14,15]. One of the reported complications of chemotherapy used in gastrointestinal tract lymphomas is tumor necrosis which causes bowel perforation [16,17]. A transmural tumor that invades and weakens the intestinal wall may lead to necrosis and bowel perforation after chemotherapy [18,19]. There is still no consensus on the timing of combined chemotherapy and surgical treatment. In a study conducted by Kim et al. [20], none of the 23 patients with colorectal lymphoma who received only chemotherapy as treatment had perforation during chemotherapy. Therefore, there is no strong correlation between chemotherapy and bowel perforation. Evidence that primary surgery is the treatment of primary colorectal lymphomas is not strong. Chemotherapy can be considered as a primary treatment if surgical treatment is at high risk, if the patient does not want surgical treatment and if it accepts a small risk of perforation during chemotherapy. The limitations of our study are small number of patients and retrospective. The rarity of the disease makes it difficult to perform a prospective study. A meta-analysis study to be done will help in this regard.

In conclusion, primary colon lymphoma is a rare disease. It is still unclear whether the surgeon or chemotherapy will be offered first. Many controversial issues are still uncertain and further work is needed. Early laparotomy may have a positive effect on surgical morbidity, mortality and survival time in colon lymphomas due to rapid clinical course.

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Subarachnoid hemorrhage complicated with cerebral venous thrombosis in pregnancy: A case report

Gebelikte serebral venöz tromboz ile komplike subaraknoid kanama: Olgu sunumu

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Abstract

The conditions most commonly associated with cerebral venous thrombosis are the ones characterized by hormonal changes, which include pregnancy, puerperium, and oral contraceptive use. The classical signs and symptoms of cerebral venous thrombosis include headache, papilledema, convulsions, focal deficits, coma, and death. Cerebral venous thrombosis particularly affects superior sagittal or lateral sinus, but also sinuses to which cortical deep veins open. Cerebral venous thrombosis can cause serious neurological syndromes, but thanks to the introduction and widespread use of cerebral angiography, computerized brain tomography, and cranial magnetic resonance imaging, it can be diagnosed in a timely manner. In this case report we report a 22-year-old woman with unknown pregnancy status who was subsequently diagnosed to have pregnancy and cerebral venous thrombosis and subarachnoid hemorrhage after presenting to emergency room with severe headache followed by altered consciousness.

Keywords: Pregnancy, Cerebral venous thrombosis, Subarachnoid hemorrhage

Öz

Serebral venöz trombozun en sık görüldüğü durumlar; gebelik, puerperium ve oral kontraseptif kullanımını da içine alan hormonal değişikliklerin görüldüğü tablolardır. Serebral venöz trombozun klasik tarifi; baş ağrısı, papilla ödemi, kasılmalar, fokal defisitler, koma ve ölümdür. Serebral venöz tromboz özellikle superior sagittal veya lateral sinüs ve kortikal derin venlerin açıldığı sinüslerde tespit edilmektedir. Ciddi nörolojik sendromlara yol açabilen serebral venöz trombozun erken tanısı serebral anjiyografinin tanınması ve yaygın kullanımıyla, bilgisayarlı beyin tomografisi ve kraniyal manyetik rezonans görüntüleme ile sağlamıştır. Bu olgu sunumunda şiddetli baş ağrısı ve sonrasında gelişen bilinç bulanıklığı ile acil servise başvuran 22 yaşında, gebe olup olmadığı bilinmeyen ama tetkiklerde gebe olduğu anlaşılan serebral venöz tromboz ve subaraknoid kanama tanısı konan hastayı sunmayı amaçladık.

Anahtar kelimeler: Gebelik, Serebral venöz tromboz, Subaraknoid kanama

Introduction

Among cerebrovascular disorders, thrombosis of cerebral veins and sinuses is a rare condition, accounting for 1-2% of all stroke episodes in adults [1]. Although etiological causes include pregnancy, puerperium, oral contraceptive use, coagulopathies, intracranial infections, cranial tumors, penetrating head trauma, lumbar puncture, malignancy, dehydration, inflammatory bowel disease, connective tissue diseases, Behçet Disease, sarcoidosis, nephrotic syndrome, parenteral infusions, and various medications, the exact cause remains unknown in 20–25% of cases [2,3].

The clinical presentation may include mild headache or focal neurological loss, although patients may also be comatose [4]. Unlike arterial stroke, cerebral venous thrombosis (CVT) is common among the young people and children, with 75% of cases being female [5].

In this case report we report a 22-year-old woman with unknown pregnancy status who was subsequently diagnosed to have pregnancy and cerebral venous thrombosis and subarachnoid hemorrhage after presenting to emergency room with severe headache followed by altered consciousness.

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Case presentation

A 22-year-old woman presented to emergency room with severe headache, nausea, and vomiting starting 5 days ago and it was followed by loss of consciousness. Her relatives gave the information that her headache was of throbbing character, spreading from the nuchal region to the top of her head, and lasting for entire day. Her recent medical history was notable for an upper respiratory infection one week ago when her symptoms had begun. Her past and family history were not remarkable. Her vital signs were as follows: Body temperature: 36.5 ºC, pulse rate: 65/min, blood pressure: 106/61 mmHg, and respiratory rate: 20 /min. Her general physical examination was normal. On neurological examination, she was confused and poorly oriented, and she showed weak cooperation with the medical team. No pupil edema was present and her light reflexes were bilaterally positive. Her motor examination was without any abnormality and she showed no pathological reflexes. Laboratory examination revealed a white blood cell of 12800 and a β hcg level greater than 1000. She had a ten week gestation. A lumbar puncture examination revealed cerebrospinal fluid with no leucocyte, glucose level of 50, protein level of 41.8, old erythrocyte count of 310 and xanthochromia being positive. A magnetic resonance venography revealed venous thrombosis of both lateral sinuses but her computed tomography of the brain (CT) was normal. The patient was diagnosed with cerebral venous thrombosis and subarachnoid hemorrhage. She was transferred to the neurology clinic for further care. The medical treatment of the patient was regulated, and surgical intervention was not considered. She did not come to the follow up so there is no information about the baby. Informed consent was obtained from patient.

Discussion

CVT induces a variety of pathological changes in brain. Its classical manifestation involves large bilateral hemorrhagic infarcts affecting cortex and adjacent white matter. Although it's true incidence is unknown due to a lack of specific etiological studies, its incidence is on the rise among women and the elderly [6].

Hereditary thrombophilia syndromes are responsible for 50% of thromboembolic events during pregnancy when the risk of venous thrombosis increases by 5-6 folds. CVT leading to cerebral infarction and hemorrhage is a complication of pregnancy. Cerebral sinus thrombosis typically occurs during puerperium and most commonly involves the superior sagittal sinus [1]. In line with previous reports, our patient was a case of pregnancy-induced CVT during early pregnancy, but she also had a subarachnoid hemorrhage.

In CVT, headache is the most common cause of emergency department admission (80-95%) [1,2]. Apart from headache, patients may have neurological signs such as aphasia, neglect, hemianopsia, nystagmus, diplopia, cranial nerve palsy, visual field defects, sensory loss, and hemiparesis [2,7]. When CVT is considered a diagnostic possibility based on clinical findings, CT with or without contrast should be primarily taken for diagnostic purposes. Direct and indirect (nonspecific) signs of cerebral venous thrombosis on CT have been reported. Unfortunately, CT may be normal in 20-40% of cases [8]. Angiography and magnetic resonance imaging (MRI) should to be taken in cases without pathognomonic CT changes. Particularly superior sagittal sinus thrombosis can be readily diagnosed with MRI [9]. Other diagnostic tools include cerebrospinal fluid examination, Electroencephalography (75% abnormal and changes nonspecific), brain scintigraphy with isotope, and tests directed to underlying causes. Whereas our patient had a normal CT, MR venography made the diagnosis by demonstrating venous thrombosis in both lateral sinuses. Subarachnoid hemorrhage has rarely been reported in association with CVT, and we diagnosed it by xanthochromia positivity of erythrocytes detected in lumbar puncture. Since the clinical presentation of the disease is highly varied, no consensus exists regarding its treatment. Despite being dependent on clinical presentation, treatment of CVT consists of different combinations of anticonvulsants, antibiotics, intracranial pressure reducing methods, and antithrombotic medications. Anticoagulant use is controversial due to a risk of bleeding of a hemorrhagic infarct. Heparin is beneficial for patients with cerebral venous thrombosis although some controversies exist surrounding its intracranial hemorrhage risk and indications. In most cases, high-dose heparin is the treatment of choice when CT shows no hemorrhagic infarction. However, patients with hemorrhagic infarcts may also benefit from anticoagulant therapy and heparin [10].

CVT is a rare albeit fatal disorder. It becomes even more fatal when it is associated with subarachnoid hemorrhage. Pregnancy should be definitely questioned and CVT should be remembered as a diagnostic possibility when a woman presents to emergency department with headache and altered consciousness.

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Congenital short femur: A case report

Konjenital kısa femur: Olgu sunumu

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Abstract

Congenital short femur (CSF) is a very rare condition and after the ultrasonography has been actively used, the placement of the antenatal diagnosis is actually quite facilitated. It is usually not accompanied by chromosomal abnormalities. Our case presentation has shown the importance of both femur lengths and all other extremity images while performing antenatal scanning.

Keywords: Congenital short femur, Proximal focal femoral deficiency, Antenatal diagnosis

Öz

Konjenital kısa femur çok nadir görülen bir durumdur ve ultrasonografinin kullanılması sonrası antenatal olarak teşhis edilmesi oldukça kolaylaşmıştır.Genellikle kromozomal anomaliler eşlik etmez. Bizim vaka takdimimiz ultrasonografik tarama yaparken heriki ekstremite uzunluklarının ölçülmesinin hatta bütün ekstremite uzunluklarının ayrı ayrı ölçülmesinin önemini vurgulamaktadır.

Anahtar kelimeler: Konjenital kısa femur, Proximal fokal femoral deficit, Antenatal tarama

Introduction

Congenital short femur (CSF) is an extremely rare limb anomaly with an incidence of 1.1–2 in 100 000 live births. The diagnosis of this anomaly has been enhanced by widespread use of ultrasonography [1]. CSF is not usually accompanied with chromosomal abnormalities and mental disorders. The results of surgical repair are usually good [2]. Determine whether isolated femoral abnormality is part of the syndrome is the most important issue [3]. However, some congenital short femur cases involving skeletal disorders may be accompanied by global dysplasia syndromes and termination of gestation may be a reasonable option in such cases [4].

The proximal end of the femur is congenital absent. Most cases have been reported in the orthopedic literature and in the radiological literature. Femur defects are highly heterogeneous, and both femur length and proximal shape change significantly. Although a familial event has been reported, the mode of transmission is unknown [5]. CSF is frequently mixed with Unilateral Isolated Proximal Femoral Focal Deficiency (PFFD). But these two anomalies are different. CSF is the isolated shortness of the femur. Unilateral Isolated Proximal Femoral Focal Deficiency is an entity that includes the proximal absence of the femur from the partial absence of the femur. These two situations are actually different. Several classification schemes for PFFD have been proposed. This classification is between the acetabulum and the proximal end femur anatomical relationship accounts and has prognostic significance. The classification of Aitken is based on radiographic view [6]. The disease varies from a benign form (A) to a severe form (D) according to the degree of femoral insufficiency. In our study, we report a case of isolated, unilateral congenital short femur detected in a postpartum patient.

Case presentation

A 27-year-old pregnant woman admitted to give birth. This pregnancy was the first gestation of the patient. We found unilateral short femur during routine baby examination after delivery (Figure 1). The family did not have a story about skeletal anomalies or other illnesses. There was no relationship between mother and father and both parents were healthy.

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No thoracic, cardiac, gastrointestinal, genitourinary and neurological anomalies were observed in fetal findings. There were no other skeletal anomalies. There was no history of the mother about diabetes, drug use, exposure to teratogenic radiation, and viral infection during pregnancy. It was routinely followed during the pregnancy and there was no high-risk condition in the screening tests.

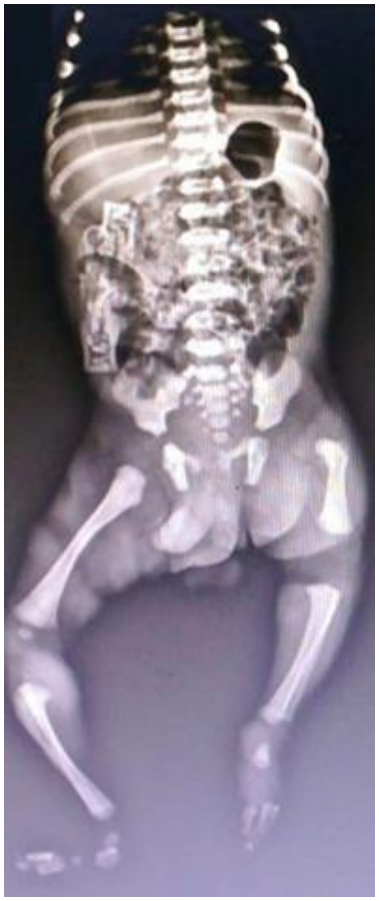

Figure 1: X-ray of the baby

Discussion

CSF is usually sporadic, and about 85-90% of cases are unilateral. Despite the fact that the CSF has several familial reported cases, the genetic pathway is not known [6-7]. Prenatal diagnosis of femoral anomalies is possible. But only 19% of the cases are prenatal diagnosed and 68% are diagnosed postnatally [8].

The critical period for skeletal development is the first 4 and 8 weeks. As a result, exposures during these periods (such as poor diabetic control, thalidomide-like drug use narrative, viral infections, radiation, focal ischemia, chemical toxicity, trauma, familial transitions) may be risky [9,10,11]. Some cases diagnosed at approximately 14 weeks of gestation by transvaginal ultrasonography have been reported in the literature. Some cases diagnosed at approximately 14 weeks of gestation by transvaginal ultrasonography have been reported in the literature.

CSF is actually a femur dysplasia. But it is often mistakenly diagnosed as PFFD although PFFD is completely different in terms of radiological and functional outcomes [12].

Many diseases (kyphomelic dysplasia, campomelic dysplasia, osteogenesis imperfecta, achondroplasia, achondrogenesis, thanatophoric dysplasia, short limb polydactyly and malformations of skeletal dysplasia) are usually considered in differential diagnosis, but these diseases often affect other bones [13].

Prenatal diagnosis is also very important because of the contribution of the developing technology. Ultrasonography scanning is sometimes performed with single extreme measurements for measurement. For this reason, these anomalies and single extremity development disorders can be overlooked.

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Gastric stromal tumor with pregnancy: A case report

Gebelikte gastrik stromal tümör: Olgu sunumu

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Abstract

Gastrointestinal stromal tumors (GISTs) are rare mesenchymal tumors that develop in the wall of the gastrointestinal tract. There is few given information throughout literature concerning gestation associated with GIST. We report here the case of a patient who was admitted in our hospital for GIST discovered during the second trimester of pregnancy. She was 44 years old, in the fifth months of pregnancy. She was admitted for biliary colic pain. An abdominal examination objectified a distended abdomen with uterine height of 15 cm and right hypochondrium mass of 15 cm. Abdominal ultrasound and magnetic resonance imaging showed a large lesion process in the right hypochondrium region. Endoscopy objectified an aspect of extrinsic compression at the front of the stomach. The patient was operated and an umbilical median incision was performed, exploration showed the presence of a hug mass measuring 25 cm occupying almost all of the right hypochondrium, pushing the liver up and the uterus down, adheres to the stomach at the level of the small curvature with an implantation base of about 3 cm. Histological and immune histochemical study of hepatic process showed a GIST of high risk of malignancy. Only some cases have been reported in the literature on GIST during pregnancy showing the rarity of the pathology that requires multidisciplinary care.

Keywords: Pregnancy, Gestation, Imatinib, Gastrointestinal stromal tumor

Öz

Gastrointestinal stromal tümörler (GIST) gastrointestinal sistemi duvarında gelişen nadir mezenkimal tümörlerdir. Gebelikte GIST ile ilgili literatürde az miktarda bilgi bulunmaktadır. Biz burada gebelik ikinci trimesterde tespit edilen bir GIST olgusunu rapor ediyoruz. Olgu 44 yaşında ve hamileliğin beşinci ayındaydı. Biliyer kolik ağrısı ile başvurdu. Abdominal muayenede 15 cm'lik rahim yüksekliği ve sağ hypochondrium 15 cm kitle tespit edildi. Abdominal ultrasonografi ve manyetik rezonans görüntüleme ile sağ hypochondrium bölgesinde büyük bir lezyon gösterildi. Endoskopi ile midenin önünde dışsal bası görüldü. Hasta ameliyata alındı ve orta hat kesi yapıldı. Eksplorasyonda neredeyse tüm sağ hypochondrium işgal eden, karaciğeri yukarı ve rahimi aşağı iten, küçük kurvatür düzeyinde mideye yapışan, yaklaşık 3 cm'lik bir implantasyon tabanı olan 25 cm kitle tespit edildi. Histolojik ve immun histokimyasal çalışmalar, yüksek malignite riskli GIST gösterdi. Literatürde gebelik sırasında sadece olgu sunumu olarak bildirilen GIST, multidisipliner bakım gerektiren nadir bir patolojidir.

Anahtar kelimeler: Hamilelik, Gestasyon, Imatinib, Gastrointestinal stromal tümör

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the digestive tract. They most often occur in the stomach followed by the duodenum. The diagnosis of GIST during pregnancy is very rare. There are less than 21 cases reported in literature about gastrointestinal stromal tumors diagnosed during pregnancy one of them reported in our hospital in 2004 by Cherif and all, here we report the second case of a gastric GIST diagnosed during pregnancy in our hospital [1].

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Case presentation

She is a 44-years-old patient, with an unremarkable medical and family history, mother of 5 children, in the fifth month of pregnancy. She admitted for treatment of moderate hepatic colic pain, dating back to seven months, atypical epigastric pain, epigastric fullness relieved by post prandial vomiting.

Clinical examination found a patient in a good general state, a distended abdomen with uterine height of 15 cm, and mass of the right hypochondrium smooth and painful of 15 cm.

Laboratory tests showed a hypochromic microcytic anemia with a biological inflammatory syndrome.

The morphological assessment including abdominal ultrasound has objectified a hepatic cystic and tissue mass, with thickened and irregular contours.

Hepatic magnetic resonance imaging found a large lesion process in the right hypochondrium region; this lesion is heterogeneous with dual component: a liquefied center (rich in mucin and blood) and very irregular peripheral component with irregular and asymmetric internal contours. This mass is localized in the right hypochondrium region, tacking the liver and coming into contact with the stomach wall (small curvature) (Figure 1).

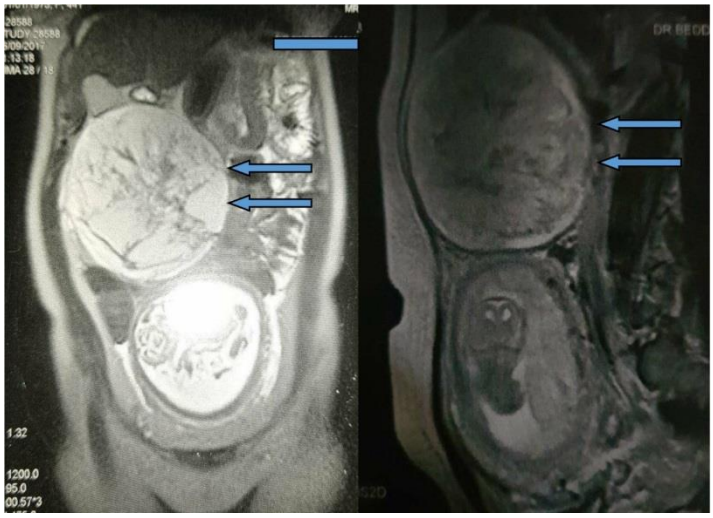

Figure 1: Magnetic resonance images of the stromal tumor and pregnancy.

A pelvic ultrasound has shown an evolutionary single-fetus pregnancy, estimated at 34 weeks of pregnancy. An upper gastrointestinal endoscopy was performed given the gastric compressive aspect of the tumor. It highlighted an aspect of extrinsic compression at the front of the stomach, without mucosa lesions.

After discussing the issue in a multidisciplinary meeting in the presence of Obstetricians, the diagnosis of gastric GIST was suspected. Imatinib is contraindicated in pregnancy so the multidisciplinary decision was to operate the patient during pregnancy and perform an effective tocolysis by the obstetricians during the surgical procedure.

The patient was operated without incident an umbilical median incision was performed, exploration showed the presence of a hug mass measuring 25 cm occupying almost all of the right hypochondrium, pushing the liver up and the uterus down, adheres to the stomach at the level of the small curvature with an implantation base of about 3 cm, after protection of the operative field by fields soaked with serum the mass was externalized from the abdomen and its implantation base was cut on the stomach with a safety margin of 1 cm then the gastric breach was manually closed (Figure 2).

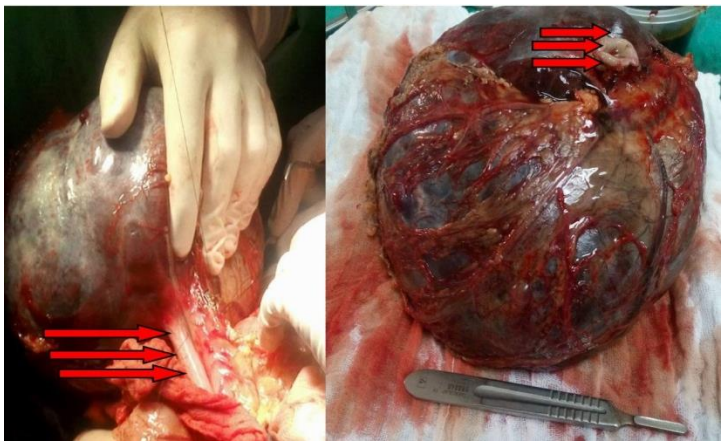

Figure 2: Left image: view of the tumor before the base section, Right image: view of the tumor after extraction (the red arrow show the base of implantation).

The postoperative follow up were uneventful. The histological study confirmed the diagnostic of GIST. Resection's limits of stomach were healthy.and the postoperative decision was to start the imatinib immediately after delivery.

Discussion

The incidence of GIST is approximately 10 to 20 cases per million people and year. The diagnosis must be made early to preserve the prognosis. They are much rarer during pregnancy; few cases have been reported in the literature [2].

The incidence of these tumors in the United States is estimated at 3000 - 4000 cases per year, with a median age of 60 years [3]. The majority of GISTs are localized in the stomach (60%) and small intestine (30%), especially when associated with pregnancy [2]. the remaining 10% are located in the esophagus and rectum [4]. Their occurrence is sporadic in most cases, but there are some familial predispositions, such as neurofibromatosis type I and exceptional familial forms described by Carney and Stratakis or related to a constitutional mutation of KIT or PDGFRA [5].

Association of GIST and pregnancy is rare. Also the challenge is to make the diagnosis early and begin treatments that preserve the pregnancy.

The clinical presentation during pregnancy is not specific: gastrointestinal bleeding, unexplained anemia or abdominal mass. Cases of GIST reported in the literature, show a non-specific symptoms. However, only the histological analysis allows confirming the diagnosis [6].

GISTs are usually well-circumscribed without encapsulation; they grow preferentially on the serosal side of the bowel wall. Macroscopically, the measurement of the maximum diameter of the primary tumor is an important parameter for evaluating the evolutionary potential. It is important to sample the tumor, for the differential diagnosis with other sarcomas (e.g. liposarcoma), and because there may be variations in the proliferation index [7]. Histologically, cell density is generally high and homogeneous, and necrotic alterations, edema and/or bleeding are as most frequent as tumors are large. The cells are fusiform in 70% of cases, most often with a fascicular architecture, suggesting a smooth muscle proliferation [8].

The average diameter of symptomatic tumors is 6 cm against 1.5 cm for asymptomatic tumors. Our patient had a tumor exceeding 25 cm. The cases reported in the literature had tumors diameter ranging between 4 and 23 cm [9].

Useful tests for the diagnosis of GIST depend on the size and location of the tumor. For tumors less than 5 cm and gastric or colorectal localization, the diagnosis is made by endoscopy and confirmed by ultrasonography. For small GIST of the small intestine, the diagnosis is made by enteroscopy. In the case of very large GIST, the gold standard is the abdominal computed tomography or magnetic resonance imaging in pregnancy, which was performed in our case [9].

All GISTs are potentially malignant, and the risk of recurrence after resection can be assessed according to the size and mitotic index. It is likely that other parameters, such as gastric localization, presence of necrosis and the type of mutation, have prognostic value [10].

GIST metastases are localized in the liver in 2/3 of cases and in the peritoneum in one quarter of cases. Lymph node metastases are rare, not justifying their dissection when the diagnosis is suspected. Lung metastasis are also rare, and their occurrence may justify reviewing the diagnosis [6].

Unfortunately, due to the rarity of the disease there are no recommendations for the management of GIST during pregnancy [11]. In review of literature a total of 12 cases were retrieved regarding women who were diagnosed with GIST during the gestational period, eleven out of the twelve pregnant women had laparotomy and/or surgical excision of the tumor, Two patients underwent pregnancy termination at 7 and 15 week of gestation, while on treatment with imatinib, Seven patients started imatinib postpartum such as we describe in our case. Six women remained disease free from 9 to 36 months and two patients with advanced disease showed partial response and stable disease, respectively. There are no reported cases with metastatic involvement of placenta or fetus [12].

The primary treatment of choice for localized or resectable GIST is surgery. The best chance for cure is complete surgical excision of the tumor in clear margins [13-15].

Imatinib mesylate is a tyrosine kinase inhibitor that selectively inhibits BCR-ABL KIT and PDGFR tyrosine kinases and has become the standard of care on adjuvant setting as well as in metastatic disease. The introduction of kinase inhibitors has increased survival of patients with GIST with an approximate median survival of 5 years [16,17].

The safety of imatinib administration during pregnancy is yet to be documented. Current experimental data show teratogenic effects when administered in female rats during the organogenesis period [18,19].

Published data by Pye et al [16], concerning imatinib administration during gestational period in 180 pregnant women revealed that only 50% of them had an uneventful infant delivery, whereas the rest ended either in elective termination or in spontaneous abortion [20,21].

Due to the limited number of cases described throughout the international literature, we cannot reach conclusions concerning the safety of imatinib administration in pregnant women with GIST.

Another significant factor that must be taken into consideration when treating pregnant women with cancer is the time of delivery. During a pregnancy complicated with cancer, the optimal time for delivery is placed between the 35th and the 37th week of gestation.

In conclusion, preterm delivery should be avoided if possible and one must always account for premature neonatal complications. Thus, a multidisciplinary approach involving surgeons, obstetricians and oncologists should take place under the scope of both maternal and fetal health. In addition, the patient's perspective regarding the therapeutic plan should be accounted for.

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Multiple primary cancers: About an observation with 3 different tumors: Case report

Çoklu primer kanserler: 3 farklı tümörle yapılan bir gözlem hakkında: Olgu sunumu

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Abstract

The case described in this article concerned a 55 years old woman who presented three different neoplasia during a period of 6 years. They included adenocarcinoma of the left breast, an endometrial leiomyosarcoma, and a lymphoma. For these pathologies, hormonal factors seem to play a role in the genesis of the first two carcinomas.

Keywords: Metachronous cancers, Breast cancer, Leiomyosarcoma, Lymphoma, Radiotherapy

Öz

Bu makalede açıklanan olgu, 6 yıl boyunca üç farklı neoplazi sunan 55 yaşında bir kadın ile ilgilidir. Sol meme adenokarsinomu, endometriyal leiomyosarkom ve lenfoma vardı. Bu patolojiler için hormonal faktörler ilk iki karsinomun oluşumunda rol oynar gibi görünmektedir.

Anahtar kelimeler: Metakron kanser, Meme kanseri, Leiomyosarkom, Lenfoma, Radyoterapi

Introduction

The observation of multiple, simultaneous or successive primary cancers can reach the same individual without presenting links between them [1].

The coexistence of several primary cancers in the same individual is a phenomenon known in the oncological literature with a frequency estimated between 2.6% and 3.9% [2]. Such a pathological event seems rare in our environment.

The purpose of this study was to discuss etiological and clinical aspects; the therapeutic implications and the possible role of certain carcinogenesis factors.

Case presentation

The first localization was in February 2011 by the accidental discovery of a left breast nodule with skin retraction. The clinical examination coupled with a true-cut biopsy followed by histological examination had made it possible to diagnose Grade III medullary adenocarcinoma of Scarff and Bloom.

The extension assessment did not identify a secondary localization. The patient had a mastectomy and left axillary dissection with multidisciplinary therapeutic management: chemotherapy (6 cycles) and external radiotherapy at the dose of 42 Gy in 15 fractions of 2.8 Gy / Fr.

The second localization was diagnosed 2 years after the first one. The clinical examination and the ultrasound data had suspected an endo- uterine mass whose histological analysis of the hysterectomy showed uterine leiomyosarcoma. The extension assessment had not shown secondary local or regional locations, the patient received pelvic irradiation at a dose of 50 Gy in fractions of 2 Gy / Fr.

The third localization was discovered in June 2017, 4 years after the second cancer during the biannual control consultations, by the appearance of a right axillary nodule, the histological and immunohistochemical result was in favor of lymphocytic lymphoma (Patient under chemotherapy).

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Discussion

Metachronous cancers are defined by the occurrence of two or more multiple neoplasms on different organs, they represent 0.5 to 11% of the cancers, with a tendency to increase related to the effectiveness of the treatments, a better follow-up patients, and an improvement in longevity with the possibility of developing other cancers [1]. Both sexes are affected; the age of the first cancer is on average 60 years, the second cancer occurs between 3 and 6 years later, at shorter intervals, which concords with our results [1].

Throughout the literature, the most frequent sites of multiple cancers are successively the digestive, gynecological and ENT sphere [3].

Two of the 3 cancers of our case sit respectively in the breast and the endometrium.

In our case, the hormonal factor seems the most important factor in carcinogenesis, other factors are also incriminated in the genesis of certain cancers [2,3], we mention the familial cancers, colo-rectal cancers in familial rectocolic polyposes .The risk of developing cancer of the bladder, prostate, skin, colon, lung, and breast is higher in a patient with renal cell carcinoma mainly in its tubulo-papillary subtype [4].

Certain gene mutations are responsible for multiple cancers, for example in Li-Fraumeni syndrome (mutation of the P53 gene). In addition to these familial cases, some authors have shown that patients with breast, skin, colon or non-Hodgkin lymphoma have an increased risk of developing some second primary cancers [4].

Concerning this pathology, certain diagnostic errors can appear. There are cancers that give late metastases whose histological structure is different from that of the primary lesion. Bilateral cancers of even organs such as the mammary gland are not multiple cancers per se because they are united by the same biological phenomena or because one can be the metastasis of the other [5].

In conclusion, despite the rarity of this pathology, the presence of any cancer requires a prolonged follow-up of the patient even in case of apparent cure.

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Case report
Olgu sunumu

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Use of preputial skin as cutaneous graft in post excision of a verrucous hemangioma of the thumb

Başparmağın verrükoz hemanjiom eksizyonu sonrası kutanöz greft olarak Sünnet derisinin kullanılması

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Abstract

Although the use of preputial skin as cutaneous graft is not new, it was seldom been utilized and reported by surgeon all over the world. The preputial skin graft has many advantages when use as a full thickness skin graft to cover a defect over certain importance area. Herein, we reported a case of a rare vascular anomaly of thumb; Verrucous Hemangioma when a surgical excision was indicated, but the skin defect would have been too large to be directly closed, therefore the foreskin was taken as a full-thickness skin graft to cover the cutaneous defect of the thumb. The procedure was taken in a single stage with the ritual circumcision. The graft intake was favourable and provided a good functional repair with satisfactory aesthetic characteristic. Similar cases have not been reported before in the literature or at least in author's origin of country.

Keywords: Preputial, Foreskin, Skin graft, Verrucous Hemangioma, Circumcision

Öz

Sünnet derisinin deri grefti olarak kullanımı yeni olmamasına rağmen, tüm dünyada cerrah tarafından nadiren kullanılmış ve bildirilmiştir. Sünnet derisi grefti belirli bir alandaki bir kusurun üstesinden gelmek için tam kalınlıkta bir deri grefti olarak kullanıldığında birçok avantaja sahiptir. Burada, nadir görülen bir vasküler anomali olgusu bildirildi; Verrükoz hemanjiom, cerrahi eksizyon gerekli görüldü, ancak deri defekti direkt olarak kapanmak için yeterli olmayacaktı, bu nedenle sünnet derisinin kutanöz defektini kaplamak için tam kalınlıkta bir deri grefti olarak alındı. İşlem, ritüel sünnetiyle tek bir aşamada alındı. Greft alımı elverişli ve tatmin edici bir estetik özellik ile iyi bir fonksiyonel onarım sağladı. Benzer vakalar daha önce literatürde veya en azından yazarın ülkesinin orijininde bildirilmemiştir.

Anahtar kelimeler: Preputial, Sünnet derisi, Deri grefti, Verrükoz hemanjiom, Sünnet

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Introduction

Verrucous hemangioma (VH) is an uncommon capillary vascular malformation, frequently clinically mistaken for Angiokeratoma. About 95% of the cases arose from the lower extremity and these are commonly unilateral. It might involve unusual anatomic positions such as the abdomen, arm, and glans penis [1]. VH if left incompletely excised have a great chance of recurrence. The prepuce skin is a good autologous full-thickness skin graft in some conditions and most frequently been used in urethral reconstruction for congenital or acquired penile defects, in burn reconstruction, eyelid resurfacing, and in syndactyly repair [2,3]. However in the last 20 years, use of preputial skin graft (PSG) has been increasingly described for many more conditions such contracture release, eyelid and anal canal reconstruction, intraoral burn reconstruction, defect closure post nevus excision and penile skin defect repair [4].

To the best of our knowledge, there was no literature reported a VH located at the thumb in children. In this report, we demonstrated the excision of VH of the thumb and the use of foreskin following a ritual circumcision as a full thickness skin graft for coverage. We also discussed the comparison between the preputial graft to its counterpart and a brief literature review.

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Case presentation

Two years and six months old boy was brought to Out-patient Clinic with a complaint of swelling of his right thumb since at birth. The lesion gradually increased in size, painless and occasionally bled upon contact. Physical examination revealed a well-defined 2 cm x 2 cm hard dome shape with multiple dark bluish spots located at the skin overlying interphalangeal joint of right thumb on the ulnar aspect (Figure 1). The mass was firm, immobile, non-tender, non-pulsatile, no ulceration and no bleeding. Based on clinical findings a provisional diagnosis of a low flow vascular malformation was made.

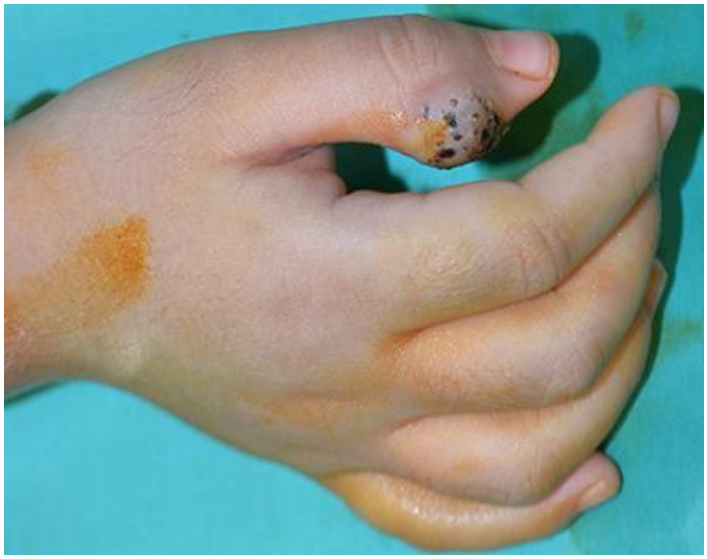

Figure 1: Vascular malformation of the right thumb

The child was scheduled for an excision with a cutaneous graft as coverage for the defect. The parent had decided that the child to undergo the ritual circumcision in the same setting as the excision surgery and had agreed that to use the excised foreskin as the cutaneous coverage of the said defect. The lesion was excised and the circumcision was performed using the dorsal slit technique. The graft was fixed to the defect with an absorbable suture. Histopathology examination revealed a proliferation of anastomosing capillaries with focal cavernous dilatation. The epidermis layer showed hyperkeratosis and acanthosis. There was intact basal granular layer with elongation of the rete ridges. Vascular proliferation was also seen at mid-dermis and these capillaries were lined by flattened endothelial cells without nuclear atypia and no mitosis was seen (Figure 2). Hence the final diagnosis was VH. Six month post operation showed the skin graft has healed well with no functional limitation (Figure 3). There was also no residual or new vascular anomaly.

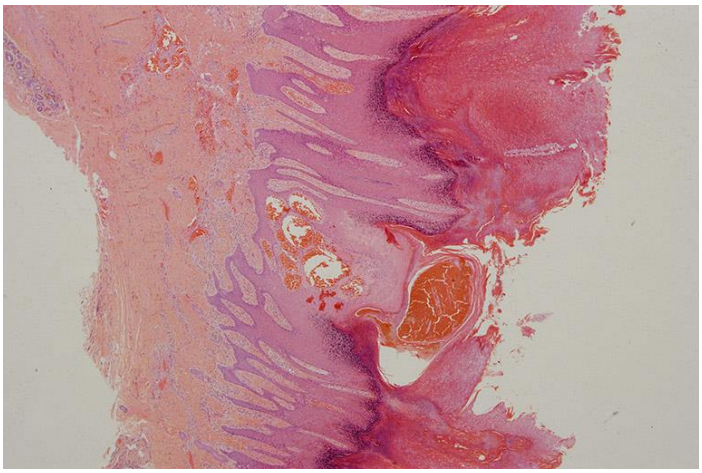

Figure 2: The epidermis layer showed hyperkeratosis and acanthosis with an intact basal granular layer with elongation of the rete ridges. There was proliferation of capillaries within epidermis and dermis without nuclear atypia and no mitosis was seen (H&E: 40x)

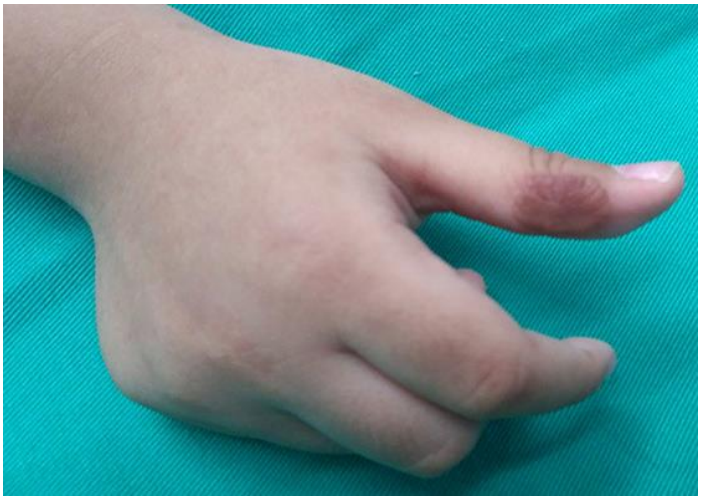

Figure 3: Six months post operation with skin graft healed well and stable. No new or residual vascular anomaly was noted.

Discussion

The clinic-pathologic characteristics of VH were first reported by Imperial and Helwig in 1967 in a study of 21 cases and distinguished it from its imitator, Angiokeratoma. VH signifies a rare congenital vascular anomaly that presents at birth or in early childhood. It is usually unilateral and localized to the lower limbs. VH in upper limb is very unusual and although few had described it on fingers but no literature had ever reported VH at thumb in children population as in our case. It also does not involute spontaneously and can persist after inadequate excision [2]. With time it darkens, thickens to become hyperkeratotic, and occasionally bleeds with ulceration, without regression [5]. Contrarily to other forms of vascular anomalies, in VH categorization as a vascular neoplasm or vascular malformation cannot be established [6]. Regardless of its misrepresentative name, VH is considered by most a malformation rather than a true hemangioma [7] and it was lately been categorized as ‘unclassified’ in the 2014 International Society for the Study of Vascular Anomalies (ISSVA) classification. However, North et al. [5] textbook on vascular anomalies pathology as well as per McCuaig CC proposal (2017), suggested that Verrucous Venulocapillary Malformation is a more appropriate designation for this lesion.

By histopathology examination, it should be distinguished by the presence of epidermal verrucous hyperplasia along with dilated capillaries and venules extending deep into the dermis with a low mitotic rate [1,5]. It also marks proliferative response of the epidermis highlighting hyperkeratosis, irregular epidermal acanthosis and papillomatosis. There is presently no specific immune-histochemical marker for VH and therefore the diagnosis should be considered after vigilant clinic-pathological correlation [7]. Early diagnosis and intervention is vital in selected patients for timely surgical excision and better cosmetic result as they do not involute spontaneously [8,9]. Inadequate excision of VH would lead to potential recurrence of the lesion from the deeper components [6,9]. As in our case, early diagnosis and surgical excision is essential as to prevent further growth and recurrence. However the excision of the lesion to a free margin had left the defect too large to be closed primarily therefore a full thickness skin graft (FTG) from the excise foreskin following a circumcision was utilized to cover the defect, hence avoiding unnecessary donor site scar.

Skin grafting originated 2500 to 3000 years ago, but it was not until the 19th century that it was presented again as a reconstructive option [4]. Baronio described the first skin graft application in 1804 on animal model whereas in humans, Bunger was the first to demonstrated it. A graft is the simplest way to cover skin defect. It comprises of the transfer of a part of skin, of variable thickness and size, which is completely separate from its original site and moved to cover the area to be repaired. Based on the thickness of the explants, skin grafts are categorized as FTG and split thickness Graft (STG) [8]. The pros and cons of FTGs over their STGs counterparts are well documented in various literature [10]. Because of poor acceptance of the resulting scars, STGs are generally reserved for deep and full thickness dermal burns, extensive skin losses in areas other than the face, and where the recipient bed is poorly vascularized. Full thickness skin grafts commonly applied to close small areas, offer solid elastic material, producing satisfactory scarring results not subject to retraction. They are particularly valuable for repair of skin loss on the face and fingers, as an alternative to local flaps [4]. Their composition of full thickness of epidermis and dermis make them able to deliver excellent color, texture and thickness matches for facial defects [8]. Most FTGs are harvest from above the shoulders, whose color, texture and thickness best match to the tissue adjacent to facial defects [11].

In last decade, an extraordinary type of FTG; PSG has been used as an alternative graft source and its application is well described in hypospadias surgery until now [4]. But PSG is still rarely used as a routine FTG among surgeons given to its easy to harvest and utilize [2,4]. Histopathologic study has revealed the prepuce mucosa to be highly vascular and to have epithelial characteristics akin to mouth, vaginal, and esophageal mucosa and very advantageous in intraoral, eyelid, and urethral repairs [10]. A study done by Mcheik et al [4], concluded that keratinocyte resulting from foreskin have a high capacity of division which enabled them to propose with their patients for wound healing especially for burns in children. The unique gains of PSG over other FTG donor sites consist of; expendable, thin and pliable; almost no donor site morbidity and no need for donor site care; very low tendency to contract; good adaptation and natural color matching, especially along the mucosal side; absence of hair follicles; hidden donor site; can be harvested with simple instrument & technique and perhaps the most significant, being an extra graft reserve site [2,4,10].

Contraindications to the use of foreskin are similar for circumcision in general, including prematurity, or a family history of bleeding disorders [12]. The main disadvantages are its only applicability to the male circumcised population and the pigmentation changes seen in the reconstructed area which restricts its usage in face and neck area [2,10]. But it can be used in extremity and scalp defects [2]. Mohammed et al [12] made a research on the use of PSGs for post-burn contractures of digits in children found that all children did not have graft loss, and all the wounds healed within 2 weeks. However hyperpigmentation of the grafts was observed, which was satisfactory well accepted.

As for in our case who happen to be a Muslim boy where ritual circumcision was a common practice had made it easier and justified to conduct the procedure. When Islam was established, the ritual of circumcision became ensconced in it. The practice was widely spread among the Arabs even before their conversion to Islam. Whether or not it was to be an absolute commitment was disputed by numerous schools of thought [13]. Circumcision is the surgical method for harvesting PSG. As with any surgical procedure, bleeding and infection are possibly the most common complications. Urethral injury and penile necrosis are extraordinary complications [14]. In some countries, circumcision is the most common surgical procedure in boys and regularly performed with very low complication rates [4].

Castellsague et al [15] reported that, with circumcision, the incidence of human papilloma infections in men and cervical cancer in their partners has decreased significantly and this procedure has become famous in some non-majority Muslim state in Asia like China and South Korea. Pang et al [16] discovered 60% of the South Korean population to be circumcised while in Turkey, circumcision is conducted generally as a symbolic ritual and a preventive medical procedure. For the similar reasons, it is recognized that 48% of infants in Canada are circumcised [17]. Moreover, there are also some absolute medical indications for circumcision, such as phimosis secondary to balanitis xerotica, obliterans and recurrent balanophosthitis, while the relative indications are paraphimosis, phimosis, redundant foreskin, and hypospadias surgery [18].

With Muslim dominance society, and circumcision being a common ritual procedure, we utilised the foreskin of children to fulfil both aims: the ritual was performed and, at the same time, the foreskin was used for coverage of the excision, obviating the need for a new donor site and second exposure to general anesthesia. The use of foreskin for male children with localized vascular malformation of the thumb has proved to be a successful method for the coverage of the hand defect with no donor site morbidity. In our case the lesion was surgically excised and showed no relapse at 6 months, indicating that surgery remain as a primary modality of treatment for a localized VH.

In conclusion, although PSG is still not in routine use, the acceptance of the prepuce skin as an alternative full-thickness donor site needs some special attention and reported series have shown promising results. Every surgeon must keep PSG in mind

as an option for donor site. VH or Verrucous Venulocapillary Malformation is a rare condition, must be distinguished for an early diagnosis for surgical intervention and to have a good cosmetic outcome. We present this case for its sheer rarity of its presentation, its notoriety for recurrence and the use of PSG as an adequate coverage after an excision.

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Endotracheal adrenaline use a newborn with pulmonary hemorrhage: A case report

Yenidoğanda endotrakeal yolla verilen adrenalin ile tedavi edilen pulmoner kanama: Olgu sunumu

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Abstract

Pulmonary hemorrhage in the newborn is an acute and idiopathic event characterized by discharge of bloody fluid from the respiratory tract or endotracheal tube. In this case report we discussed 5 hours old neonate with pulmonary bleeding. We showed that endotracheal adrenaline use, gastric lavage with cold water and use of vitamin K in the treatment of neonates with pulmonary bleeding might shorten the duration of treatment and lower the mortality rate.

Keywords: Pulmonary hemorrhage, Newborn, Adrenalin, Vitamin K

Öz

Pulmoner kanama bebeklerde görülen ve nedeni tam olarak aydınlatılamamış olan akciğerlerde kanama ile karakterize bir klinik durumdur. Bu olgu sunumunda yaşamının 5.saatinde pulmoner kanaması görülen bir bebek tartışılmıştır. Etyolojisi net olarak saptanamayan pulmoner kanama vakalarında endotrakeal yol ile adrenalin tedavisi, midenin soğuk mayi ile yıkanması ve K vitamini tedavisinin birlikte yapılması durumunda iyileşmeyi hızlandıracağı ve mortaliteyi azaltacağı kanaatinde varıldı.

Anahtar kelimeler: Pulmoner kanama, Yenidoğan, Adrenalin, K vitamini

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Introduction

Pulmonary hemorrhage in the newborn is an acute, idiopathic clinical event characterized by discharge of bloody fluid from the respiratory tract and lungs of especially premature and low birth weight infants. Pulmonary hemorrhage has the highest mortality rate in very low birth weight premature infants. While the incidence of pulmonary hemorrhage varies from 1% to 11% at live births, incidence varies from 3% to 32% in very low birth weight premature infants [1-4]. Pulmonary hemorrhage has 50-82% mortality rate in premature infants [3]. Pulmonary hemorrhage is an uncommon symptom in mature infants. In this study we aimed to report an infant with pulmonary bleeding and respiratory distress who had treatment of endotracheal adrenaline, gastric lavage with cold saline water and vitamin K, and we discussed the pulmonary hemorrhage as an uncommon symptom of mature infant.

Case presentation

Apgar score of male newborn who was born weight 3410 gr, in 39 week of gestational age and son of 24 years old mother was 7. The reason of consultation were intercostal retractions, moaning, pulmonary bleeding (there was no consanguinity status between parents and there was a healthy brother of baby, there was no specific pathology in prenatal history). At the physical examination of the baby, general status was not good. The baby was intubated and connected to mechanic ventilator because of his low capillary oxygen saturation levels. While intubation process was performed, active bleeding was found in gastric lavage. So we administered fresh frozen plasma and vitamin K to the patient. Report of thorax ultrasonography (USG) didn't show any pleural fluid, and echocardiography and transphontanel USG of the patient were also normal.

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Patient‘s blood tests were found as; Hemoglobin: 17.0 g/dL, leukocyte: 16700 /uL, platelets: 207000 /uL, aPTT: 35.9 sec, aspartate transaminase: 95.7 U/L, alanine transaminase: 16.4 U/L, pH: 6.9 (normal range: 7.35-7.45), HCO_3: 7.8 mEql/L (22-26) and pCO_2: 47.0 mmHg (35-45). PT test could not be calculated by laboratory despite three attempts. Serum urea, blood urea nitrogen and creatinine levels were in normal reference ranges.

There was ground glass opacity in patient’s chest x-ray (Figure 1). Patient’s respiratory tract has been washed by could fluid with infusion of adrenaline by his intubation tube, and gastric lavage was performed with cold saline water. Ranitidine, sodium bicarbonate, antibiotherapy and IV fluids were used for the management of the patient. Four hours later, blood tests showed that INR: 1.21, aPTT: 26.2 sec, and chest x-ray was normal (Figure 2).

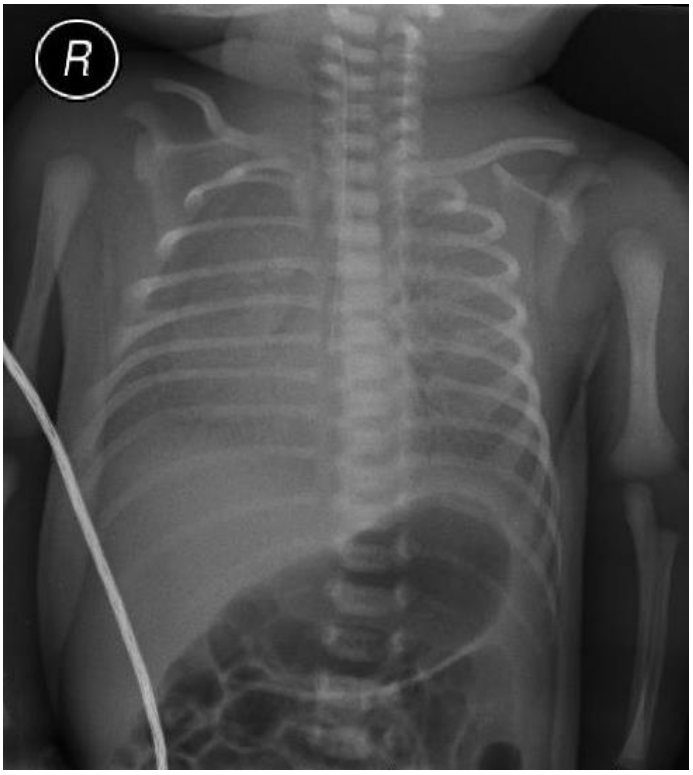

Figure 1: Chest x-ray of the patient at initial examination

We transfused platelet suspension for low (46000 /uL) platelet count on blood analysis during the second day of stay. At his follow-up bleeding was not been observed again and respiratory findings improved. At the day 8 the patient was extubated, afterwards at the day 28 patient needed oxygen therapy, and bronchopulmonary dysplasia (BPD) protocol (prednisolon, salbutamol) was applied. The baby was discharged at 31th day of the treatment.

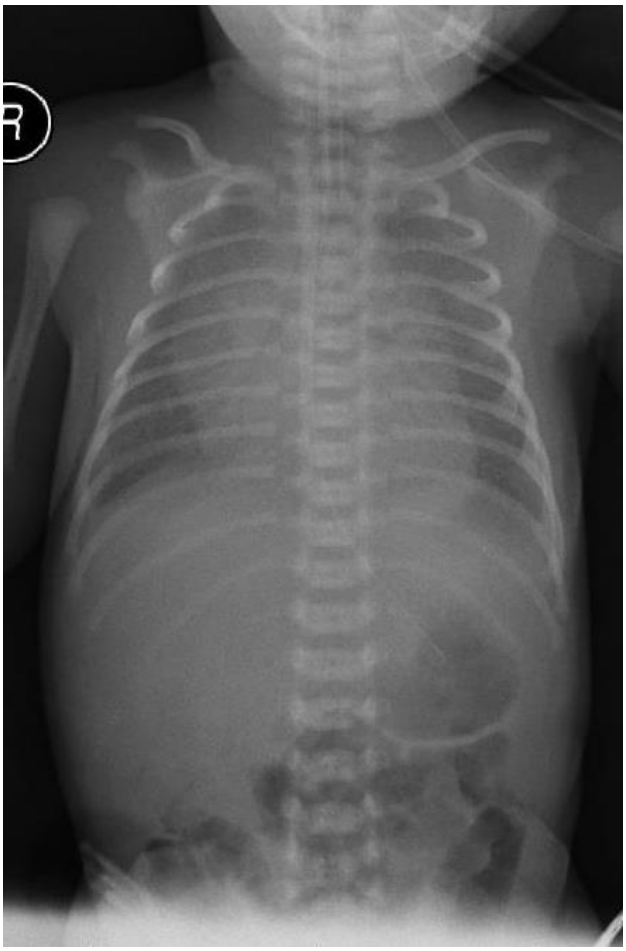

Figure 2: Chest x-ray after the patient's treatment

Discussion

Incidence of Pulmonary hemorrhage in the newborn is %1-12 at live births. On the other hand in very low birth weight premature infant, incidence is higher, and also occurs serious, rapidly progressive and mortal. There were few clinical researches about pulmonary hemorrhage and risk factors in the newborn at the literature [3-5].

Etiology of diseases still unknown but there are some risk factors such as low gestational age, resuscitation at birth room, asphyxia, lacking of antenatal steroid, patent ductus arteriosus (PDA), infection and surfactant treatment [6-7]. Antenatal steroid use is an important protective factor on premature [8].

In a study conducted by Ferreira et al. [8] with 67 cases of pulmonary hemorrhage in Brazil in 2014, when the first and fifth minute Apgar values were analyzed, no correlation was found between pulmonary hemorrhage and increased use of surfactant and increased incidence of pulmonary hemorrhage with increasing dose. Özalkaya et al. [3] in 2015 reported a research that cases with Pulmonary hemorrhage were mainly premature with the respiratory distress syndrome (RDS) and got surfactant treatment at the sometimes of their lives. Our case was a mature neonate and there were no risk factors.

Hemorrhagic disease of the newborn develops because of lacking of vitamin K. Vitamin K deficient bleeding is usually classified by three distinct time periods after birth. Early onset occurs within 24 hours of birth, classic onset occurs within two to seven days, late onset occurs within two weeks to twelve weeks. Bleeding can occur in one or multiple areas, and can be

with high rates of mortality, morbidity including: umbilical, nasal, urogenital, gastrointestinal, intracranial, pulmonary areas of body. Patients with vitamin K deficiency tend to have prolongation of PT, aPTT and normal platelet counts. There are no specific tests to diagnose hemorrhagic disease of the newborn. However, if PT and aPTT levels get normal after the administration of vitamin K, we can confirm diagnose of hemorrhagic disease of the newborn [9]. We confirmed the case as hemorrhagic disease of the newborn because we have seen levels of PT and aPTT normalized after administration of vitamin K.

Quick diagnosis and treatment can lower the mortality, and takes important part of prognosis. Pulmonary hemorrhage can be diagnosed using chest x-ray, lung USG, and arterial blood analysis. Chest x-ray findings are not specific but can be helpful if there were ground glass and raised opacity [4]. İn patient ground glass opacity chest x-ray and blood analysis were confirmed the diagnosis.

Up to date treatments of pulmonary hemorrhage are endotracheal adrenaline, use high frequency ventilation and supportive interventions [10]. We use vitamin K and gastric lavage as supplemental interventions after the patient etiology was confirmed so. Four hours later with our treatments patient's clinical and radiologic findings rapidly improved. At the follow ups we diagnosed BPD on our patient and we thought this could be the secondary to pulmonary bleeding history of the patient.

In conclusion, we decided that gastrointestinal bleeding could not be excluded in neonates with pulmonary bleeding with unknown etiology. Use of endotracheal adrenaline, vitamin K administration and gastric lavage with cold saline water may lower healing time and mortality rates. Regression of symptoms and radiologic findings within four hours can be helpful to identify subgroups of this disease and can contribute new strategies in the treatment of newborns hemorrhagic disease.

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Case report
Olgu sunumu

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Recurrent unilateral gonadoblastoma: A rare histopathological presentation

Tekrarlayan unilateral gonadoblastom: Nadir bir histopatolojik sunum

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Abstract

Gonadoblastoma is a rare benign tumor that has the potential for malignant transformation and affects patients with disorders of sexual development. The exact prevalence of gonadoblastoma is not known. The association of gonadoblastomas with dysgerminoma is seen in 50-60% of cases and with other malignant germ cell tumours like yolk sac tumour, embryonal carcinoma and choriocarcinoma in 10% of cases. We herewith report a rare case of recurrent unilateral gonadoblastoma in a 10 year old Indian male who presented with abnormal passage of urine since birth. Physical examination showed a phenotypic male with undescended right testis and ambiguous external genitalia. Computed tomography scan reported mixed density solid cystic mass in pelvis with peripherally enhancing solid component and a few punctuate foci of calcification. Histo-pathological examination showed a heterogeneous tumor comprising of malignant seminomatous, sertoli and leydig cell tumor along with yolk cell tumor component. Serum alpha fetoprotein was raised to 1210 ng/ml.

Keywords: Gonadoblastoma, Seminoma, Yolk sac tumor, Ambiguous genitalia

Öz

Gonadoblastom, malign transformasyon potansiyeli olan ve cinsel gelişim bozukluğu olan hastaları etkileyen nadir bir benign tümördür. Gonadoblastomun kesin prevalansı bilinmemektedir. Gonadoblastomaların dysgerminoma ile ilişkisi olguların %50-60'ında ve vakaların %10'unda yolk kesesi tümörü, embriyonal karsinom ve koriokarsinom gibi diğer malign germ hücreli tümörlerde görülür. Bu yazıda, doğumdan beri idrarın anormal geçişi ile başvuran 10 yaşındaki bir Hintli erkeğin nadir bir tekrarlayan tek taraflı gonadoblastoma vakasını sunduk. Fizik muayenede inmemiş sağ testis ve belirsiz dış genital bölgede fenotipik bir erkek vardı. Bilgisayarlı tomografi taraması, pelviste periferik olarak gelişen katı bileşen ve birkaç noktalama kalsifikasyon odakları ile karışık yoğunluktaki katı kistik kitleyi bildirdi. Histo-patolojik inceleme, yumurta hücresi tümör bileşeniyle birlikte malign seminomatöz, sertoli ve leydig hücresi tümörünü içeren heterojen bir tümör gösterdi. Serum alfa fetoprotein 1210 ng/ml düzeyine çıktı.

Anahtar kelimeler: Gonadoblastoma, Seminom, Yolk sak tümörü, Belirsiz genitalya

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Introduction

Gonadoblastoma is a rare neoplasm, first described by Scully in 1953, comprising of mixed germ-cell and sex-cord derivatives usually occurring in dysgenetic gonads [1,2]. About 80% of the gonadoblastoma cases are phenotypically females while 20% are males [1,3]. Highest incidence of gonadoblastoma is observed in the second decade followed by third and first decades of life respectively [3]. Patients of gonadoblastoma usually present with primary amenorrhoea, virilization and abnormal genitalia [2,3].

About 50% of the cases of gonadoblastoma are found to be associated with dysgerminoma and about 10% cases of gonadoblastoma present with other malignant germ-cell tumours like teratoma, embryonal carcinoma and choriocarcinoma [3,4]. Only 2 cases of gonadoblastoma have been reported in normal male patients with scrotal testicles [5]. Gonadoblastoma coexistent with yolk sac tumour has been reported in a patient having female phenotype [6]. Esin S et al., have reported only 7 cases of gonadoblastoma in women with normal karyotype in 17 years of their study, with youngest being 10 years and the oldest 27 years [6]. Gorosito et al have also reported gonadoblastomas in pregnant women [3].

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Disorders of sex development occur with an estimated incidence of 1:5000 [1]. Here, we report a rare case of recurrent unilateral gonadoblastoma with yolk sac tumor in a male phenotype child with ambiguous intra-pelvic genitalia.

Case presentation

A 10 year old Indian child with ambiguous external genitalia, reported to the Paediatric Surgery Outpatients Department in September 2014, with complaints of abnormal passage of urine since birth. On examination patient had ambiguous external genitalia with rudimentary phallus and normal appearing left testis. Right testis was not palpable in the scrotum. Face, breast, abdomen and gluteal region had normal male appearance. Per abdominal examination revealed a firm mass of about 5 x 4 x 4 cm in the right iliac fosse. Ultrasound examination showed a heterogeneous mass with cystic and focal calcified areas located between the urinary bladder and upper sacrum. CT scan reported mixed density solid cystic mass in pelvis with peripherally enhancing solid component and a few punctuate foci of calcification (Figure 1). The right ureter was dilated and tortuous with ectopic insertion below the neck of urinary bladder possibly in the prostate. Serum LDH was raised (575U/L), with a gross elevation of beta hCG and testosterone levels. Serum alpha-feto protein was also high (1210 ng/ml). Y chromosome was detected on karyotyping. The tumour was excised and submitted for histo-pathological diagnosis.

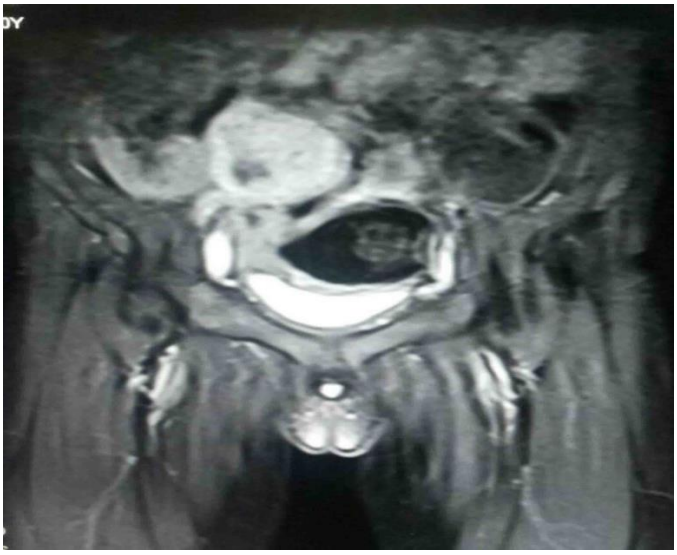

Figure 1: Computed tomography scan reported mixed density solid cystic mass in pelvis with peripherally enhancing solid component and a few punctuate foci of calcification.

On gross examination, tumour had an irregular surface measuring 12 x 9.5 x 8 cm. The cut surface was fleshy grey white with necrotic areas and foci of haemorrhage. Haematoxylin and Eosin (H&E) stained paraffin sections showed tubular seminiferous structures with proliferation of the germinal cells and small cells with round to oval nuclei and inconspicuous cytoplasm resembling immature sertoli cells (Figures 2 & 3). Summation of the above histopathological findings suggested a final diagnosis of gonadoblastoma. The differential diagnosis considered were germ cell tumors like dysgerminoma, teratomas, embryonal carcinoma, yolk sac tumor and choriocarcinoma. Patient's recovery after surgery was uneventful without any complaints in follow up period after 6 months. The level of alpha-fetoprotein analysis done after 1 month of surgery was 13ng/ml.

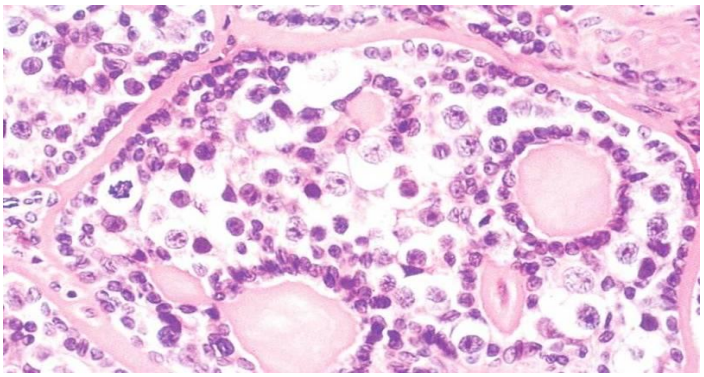

Figure 2: Microphotograph showing blastogenic tissue poorly differentiating into large polygonal germ cells and elongated sex- cord elements. Haematoxylin and Eosin x 40X

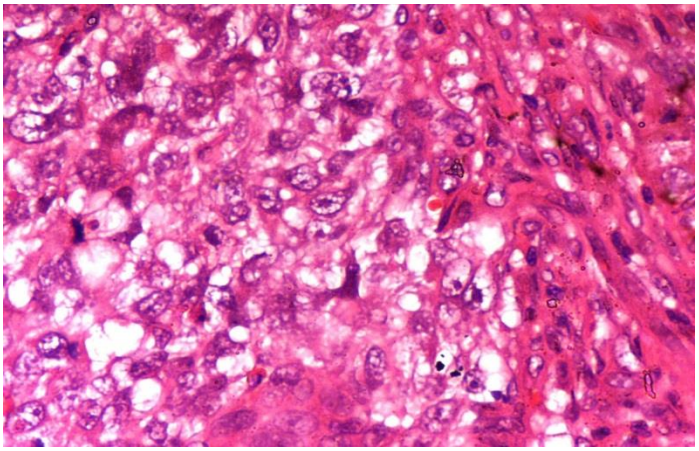

Figure 3: Section showing differentiation of tumor cells into sex-cord and germinal tubular elements. Haematoxylin and Eosin x 40X

Subsequently in January 2015, the patient presented with complaints of discomfort in the abdomen. On per-abdomen examination, a firm non-tender mass of about 4 cm size was palpable in the right lower abdomen. Contrast enhanced MRI showed altered signal intensity mass of about 3.5x3.8x3.8cm in the pelvis in front of S1 to L5 vertebra with intense heterogeneous post contrast enhancement and few centrally placed areas of necrosis (Figure 4). Fine needle aspiration cytology smears showed large tumour cells exhibiting nuclear pleomorphism, hyperchromasia, increased nuclear-cytoplasmic ratio with prominent nucleoli and numerous mitotic figures consistent with gonado-blast cells.

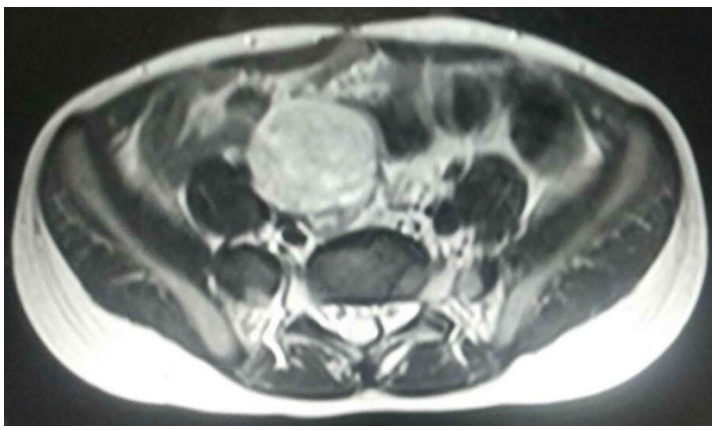

Figure 4: Contrast enhanced MRI showed altered signal intensity mass of about 3.5x3.8x3.8cm in the pelvis in front of S1 to L5 vertebra with intense heterogeneous post contrast enhancement and few centrally placed areas of necrosis.

The mass was excised and submitted for histopathological diagnosis. Macroscopically tumor was 4.5 x 3.5 x 1.5 cm in size with grey white cut surface, with focal areas of hemorrhage and necrosis. H&E stained sections showed seminiferous tubules filled with proliferating large semino-blastic germ cells and proliferating Sertoli and Leydig cells. In some areas Schiller-dual bodies lined by large gynandro-blastic cells were seen with hyaline globules (Figure 5). The germ cells were positive for OCT3/4 (Figure 6). Serum alpha-fetoprotein level was estimated to be 225ng/ml. Our patient was administered six cycles of combination chemotherapy of bleomycin (15 units), etoposide (100µg/m2) and cisplatin (33µg/m2) and is fine after 6 months of follow up period.

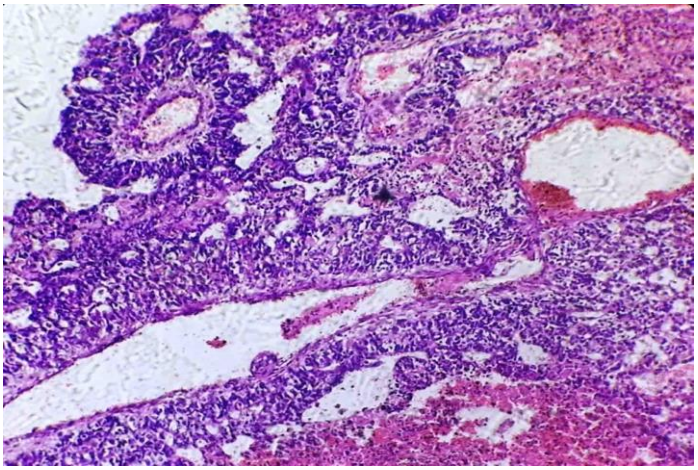

Figure 5: Section from the tumor area shows seminiferous tubules filled with proliferating large semino-blastic germ cells and proliferating Sertoli and Leydig cells with a foci of Schiller-dual body lined by large gynandro-blastic tumor cells. Haematoxylin and Eosin x 40X

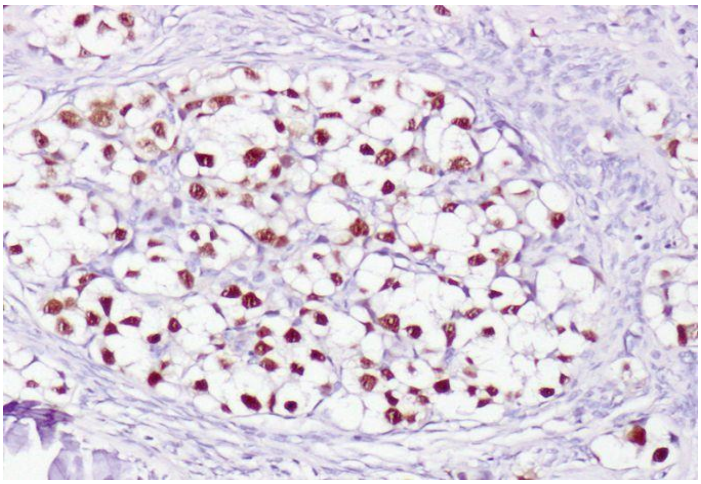

Figure 6: Microphotograph shows positivity for OCT 3/4 in the germ cells. Immunostain OCT 3/4 x 40X

Discussion

Gonadoblastoma is a rare neoplasm of mixed origin from the sex cord and germ cells reported in the earlier literature from sites of dysgenetic streak ovaries or abdominal testes [4]. They are found in 25%-30% cases of XY gonadal dysgenesis and in 15%-20% cases of 45X/46XY anomaly [1,3]. A very small number of gonadoblastomas develop in 46XX females with no evidence of Y chromosome [4]. Majority (60%) of the phenotypically female patients are virilised and the rest 40% appear exhibits poor genital development [7]. The patient in the present case had one descended testis and male phenotype suggestive of XY genotype, although further genetic testing in the form of chromosomal analysis including karyotype and array CGH is warranted. Radiological examination showed tumour in front of the sacrum along the path of descending gonad. Histo-pathological examination showed a heterogeneous tumour comprising of malignant seminomatous and sertoli and leydig cell tumour along with yolk cell tumour component. Serum alpha fetoprotein was raised to 1210 ng/ml, diagnostic of yolk sac tumour. The findings of heterogeneous malignant hybrid andro-gynandro-blastic tumour were found to be consistent with gonadoblastoma. Gonadoblastoma with male seminomatous and gynecomatous yolk sac tumour has not been reported in earlier literatures.

About 50% of the cases of gonadoblastoma reported in the earlier literatures presented with dysgerminoma tumor component [3,5]. The incidence of yolk sac elements with gonadoblastoma is found to be 10% of all the cases of malignant germ cell tumours associated with gonadoblastoma [5]. Gelincik et al [7] described one case of bilateral gonadoblastoma coexistent with dysgerminoma on one side and dysgerminoma and yolk sac tumour on the other side in a 10 year old girl with 46XX karyotype. Only a single report has been found of gonadoblastoma with seminomatous tumour component in a male genotype child with ambiguous genitalia [8]. Sertoli cell tumour proliferation with gonadoblastoma has been reported in a 19 year old phenotypic female with gonadal dysgenesis [9].

The phenotype of the gonad in which the gonadoblastoma originated is usually indetermined due to presence of other germ cell tumor components, most likely a dysgerminoma [10]. Robert Scully [1] described 2 cases of gonadoblastoma located at the site where ovaries are normally situated, but normal ovarian tissue was not detected and the exact phenotype of the gonads in which the tumors originated could not be ascertained. The tumor was termed gonadoblastoma because it developed at ovarian site apparently recapitulating development of gonads in the individuals having abnormal development of the genitalia [1,7]. In another case a gonadoblastoma presented at left inguinal region suggestive of testicular phenotype, and with seminomatous component in a 43 year old patient with other genitalia appearing phenotypically female [9]. Our case had one descended scrotal testis and presented with unilateral gonadoblastoma with both the male germ-cell seminomatous and female yolk sac tumor components at a site common for un-descended testis and ovary. These findings suggested that an un-descended gonad may present ambiguous hermaphrodite or bisexual pheno-type giving rise to gonadoblastoma with both the male and female germ cell components together. These findings have not been reported in the earlier literatures till date.

Germ cell tumors frequently produce serum markers such as hCG, LDH and AFP. Elevated serum hCG levels are present in 3% of dysgerminomas [10]. The peptide hormones inhibin and Antimullerian Hormone (AMH) both produced by the granulosa cells are potential candidates for diagnosis and follow up of granulosa cell tumors [11]. A highly informative marker for the presence of gonadoblastoma and their invasive counterparts (dysgerminoma and seminoma as well as embryonal carcinoma) is the transcription factor OCT3/4, also known as POU5F1 [12,13].

Patients with a pure gonadoblastoma without other germ cell components are known to have an excellent prognosis provided both side gonads were excised [14,15]. The prognosis of patients of gonadoblastoma associated with dysgerminoma is also good.14 Presence of other germ cell tumors like yolk sac tumor makes the prognosis unfavourable and chemotherapy may be needed after surgery [13,14]. For the patients having dysgenetic gonads, bilateral oophorectomy and hysterectomy was recommended as treatment of choice. In the case of a 46 XX karyotype, the necessity of bilateral gonadectomy is less clear and rareness of the situation makes it difficult to decide the appropriate treatment [14]. Chromosomal analysis is useful to diagnose androgen insensitivity/male pseudohermaphroditism (46,XY) and Turner syndrome (45,XO) [14,15]. In the present case, the recurrent tumor after 6 months was apparently more aggressive cyto-morphologically and was given adjuvant chemo-therapy. Our patient had an uneventful recovery and is without any remarkable complaints after 6 months of follow up.

This rare case of gonadoblastoma in a phenotypically male child with abnormal gonads should prompt us to perform a genitourinary exam to assess for phallic size, hypospadias, presence of palpable gonads either in the scrotal fold or inguinal region and for other dysmorphic features/malformations that may indicate an underlying syndrome. Basal hormone and tumor marker levels with imaging like pelvic ultrasound or MRI to look for internal genital anatomy and gonad position should be employed and gonadal biopsy performed with chromosomal analysis and FISH, if possible.

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The technicians of Histopathology Lab.

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Case report
Olgu sunumu

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A catastrophic leptospirosis case with multisystemic involvement

Multisistemik tutulumlu katastrofik leptospirozis vakası

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Abstract

Leptospirosis is a systemic infection with varying degree of clinical manifestations from mild to fatal disease. Clinical suspicion is very important to identify leptospirosis. A field worker patient was admitted to our clinic with emerging acute hepatitis and renal failure accompanying conjunctivitis, autoimmune hemolytic anemia, thrombocytopenia, pneumonia and epididymorchitis. During the follow-up the patient was transmitted to intensive care unit, and hemodialysis with plasma exchange was performed. Usually mild disease is treated in outpatient clinics because severe organ failure is experienced rarely. Alternative treatments such as plasma exchange and corticosteroids may also provide benefits especially in patients who were unresponsive to classical therapies.

Keywords: Leptospirosis, Acute Hepatitis, Plasmapheresis, Hemodialysis

Öz

Leptospirozis, hafif ile ölümcül hastalığa kadar değişen derecede klinik bulgulara sahip sistemik bir enfeksiyondur. Teşhis konusundaki en önemli vizyonun klinik şüpheniz olduğu düşünülmektedir. Kliniğimize, konjontivit, otoimmün hemolitik anemi, trombositopeni, pnömoni ve epididimo-orşitin eşlik ettiği akut hepatit ve böbrek yetmezliği tablosuyla başvuran ; takibinde yoğun bakım ünitesine alınıp plazma değişimi ve hemodiyaliz ile takip edilen tarlada çalışan bir işçiyi sunduk. Leptospiroziste genellikle hafif hastalık ayaktan tedavi edilirken, ciddi organ yetmezliği nadiren görülür. Plazma değişimi ve kortikosteroidler gibi alternatif tedaviler, özellikle klasik tedavilere yanıtsız kabul edilen hastalarda fayda sağlayabilir.

Anahtar kelimeler: Leptospirozis, Akut hepatit, Plazmaferez, Hemodiyaliz

Introduction

Leptospirosis is a well-known systemic infection caused by a zoonotic spirochete with varying degree of clinical manifestations [1,2]. Animals are usually infected by nearly 200 different serovars of leptospira nonetheless humans may also be infected by contaminated water either with urine from infected animals or direct contact [2]. The incidence is mainly modified by ecological conditions. Tropical climates, rural areas and low socioeconomic levels are thought to be associated with transmission. Although outbreaks are reported from different areas, determining incidence of sporadic events can be considered challenging. Clinical manifestations vary from mild to fatal disease [1-5]. The most important vision towards diagnosis should be clinical suspicion [6]. In this report, we want to draw attention to multi-systemic involvement of an overlooked spirochete infection.

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Informed Consent: The author stated that the written consent was obtained from the patient presented in the study.
Hasta Onamı: Yazar çalışmada sunulan hastadan yazılı onam alındığını ifade etmiştir.

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Case presentation

The patient, 65 years old male working as field worker with no known disease had examined and prescribed an antibiotic from a local clinic two days before admission to our service. He was complaining of fever accompanying nausea, vomiting, abdominal pain with occasional diarrhea, burning sense in urine, redness of eyes, cough and yellow sputum. Vital signs were as follow: temperature 39.1° C, blood pressure 125/75 mmHg, pulse 112 beats per minute. Physical examination revealed widespread pulmonary crackles and positive pre-tibial edema. On laboratory examination increased liver function tests, lactate dehydrogenase and creatine kinase; disrupted renal functions were present. Laboratory values on admission were as follows; Creatine kinase: 4086 U/L (26-140), hemoglobin: 16 gr/dl, hematocrit: 50%, platelet: $65x10^3$ / uL (110000-450000), white blood cell: 9660 (4000-11000), blood urea nitrogen: 61 mg/dl (8-25), aspartate transaminase: 3404 U/L (0-40), alanine transaminase: 1240 U/L (0-41), total bilirubin: 4.0 mg/dl (0-1), direct bilirubin: 2.6 mg/dl (0-0,2), lactate dehydrogenase: 2989 U/L (100-190), creatinine: 4.51 mg/dl (0.9-1.3), Aptt: 46.7 sn (22-34), Ptt: 27 sec (11-15), INR: 2.4. Stool analysis for infectious agents was negative. Post renal causes and major renal vascular diseases were excluded by renal ultrasound and color doppler flow imaging. Peripheral blood smear revealed blister cells, anisocytosis, and few spherocytes with single frequent thrombocytes additionally was negative for plasmodium. Hepatitis markers including hepatitis A and E serology showed no abnormality. The picture was involved conjunctivitis, hepatic and renal failure with respiratory problems likewise considering the history, it was compatible with leptospirosis. He was commenced on ceftriaxone 2gr. /day and metronidazole 1.5gr./day but transferred to intensive care unit by virtue of multi-systemic involvement as well as confusion with progressive dyspnea. Chest radiography revealed diffuse patchy infiltrates more on left lung compatible with pulmonary edema accompanying pneumonia (Figure 1).

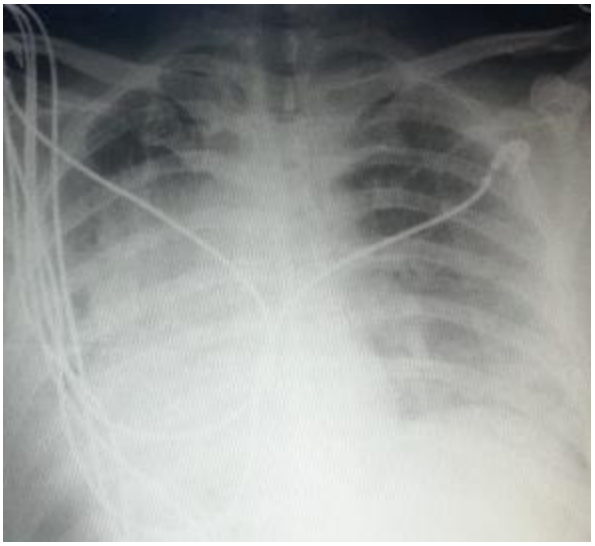

Figure 1: The Chest X-ray on admission

Noninvasive mechanic ventilation with CPAP was required for 10 hours. Blood cultures were sterile however the antibiotherapy was modified as tetracycline 1 gr/day with meropeneme 2 gr. /day due to persistent fever. Due to septic shock on 7th and 9th days of admission plasma exchange sessions with fresh frozen plasma and albumin combination were performed. Moreover inotropic support and hemodialysis for two times were required. Confusion and dyspnea were improved after plasma exchange and hemodialysis sessions. On 10th day clinical and biochemical responses were achieved. Testicular redness accompanied with pain revealed epididymoorchitis, what was confirmed with scrotal ultrasonography. The abnormal levels of bilirubin was thought to be secondary to septic biliary stasis and confirmed with abdominal ultrasonography that excluded biliary tract diseases. Liver enzymes and renal function tests had tendency to return to normal values. The control chest radiography on 20th day revealed significant regression (Figure 2).

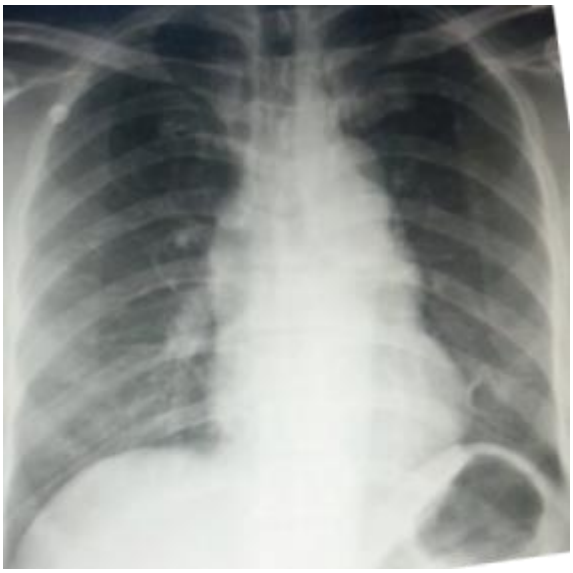

Figure 2: The Chest X-ray at discharge

Serology for leptospira IgM was positive and although micro-agglutination was planned, the test couldn't be studied due to absence of kit. The patient was discharged after a febrile periods with full renal recovery (Table 1). Written informed consent was obtained from patient who participated in this study.

Table 1: The course of laboratory levels from admission to discharge

Date of the test	AST/ALT (U/L)	Tbil/Dbil (Mg/dl)	LDH (U/L)	Htc/Plt (%/µL)	Cr (mg/dl)
October 25	3404/1240	4/2.6	2969	50.2/65	4.51
October 27	4511/3141	7.5/5.1	2989	41/91	8.41
October 30	775/213	9.6/6.6	361	37.8/31	9.4
November 1	203/91	17/10.2	323	35.9/61.5	12.5
November 4	137/100	28.4/18.1	333	36.8/144	6.71
November 12	69/39	11.5/6.2	212	30.1/323	1.94
November 21	58/34	6.7/3.2	166	36.7/538	1,6
November 24	50/29	4.1/1.9	172	35.3/422	0.91

Plasmapeheresis and hemodialysis performed every other day from 27.10.2012

AST: Aspartate transaminase, ALT: Alanine transaminase, Tbil: Total bilirubin, Dbil: Direct bilirubin, LDH: Lactate dehydrogenase, Htc: Hematocrit, Plt: Platelet, Cr: Creatinine

Discussion

Leptospirosis is defined as a disease which can be misdiagnosed at the onset and has a challenging diagnosis process. The agent can be cultured but diagnostic process includes mainly on serology moreover mimicking a lot of febrile

disease generates the challenging part [2,7-9]. Bacteria shed on kidneys and exports via urine thus transmission path is expected spread by infected animals' urine [10,11]. The picture is usually manifested as mild disease more than 90% of patients and can be confused with self-limited viral conditions. Rarely severe involvement of organs such as meningitis, acute renal failure, acute hepatitis, myocarditis and pulmonary hemorrhage can be experienced [11-14]. The mortality rate of severe disease is described within 5% - 40 % [15]. Possible risk factors are considered as traveling to tropical countries, water and soil occupations and low socioeconomic levels moreover tropical climates favors the survival of strains nearly for two months [2,3]. The diagnosis is usually performed based on clinical suspicion and confirmation of laboratory tests which antibodies are expected to be detect within 7 days. The serology has sensitivity of 90% and specificity of 94% moreover all serology tests should be confirmed with micro-agglutination test if positive sample detected. Therapies should include penicillin, cephalosporins, tetracycline or doxycycline according to the severity of disease [14]. Our patient who is a field worker and encountered from rural area was admitted to our clinic with emerging acute hepatitis and renal failure accompanying conjunctivitis, autoimmune hemolytic anemia, thrombocytopenia, pneumonia and epididymorchitis on follow-up. The antibiotherapy began for leptospirosis with clinical suspicion immediately until the serology has resulted. The serology was compatible with Leptospira whereas has resulted in one week. Micro-agglutination test was planned however technical requirements cannot be satisfied. It was the first case for us when we had to hospitalize the patient with leptospirosis. Previously we had treated leptospirosis only as outpatient therapy. We also experienced the effect of plasmapheresis and corticosteroids.

There are just few cases were reported about beneficial effects of plasma exchange, corticosteroids and intravenous immunoglobulin. That was the reason why we wanted to draw attention to early diagnosis and management of Leptospirosis. Such awareness of this disease will prevent probable catastrophic consequences of treatable fatal disease. Furthermore alternative treatments such as plasma exchange and corticosteroids may also provide benefits.

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Schwannoma as a rare cause of syncope: A case report

Nadir bir senkop nedeni olarak schwannoma: Olgu sunumu

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Abstract

Syncope is a loss of consciousness due to transient global cerebral hypoperfusion and characterized by rapid onset, short term and spontaneous complete recovery. The cases with syncope need to be carefully and thoroughly evaluated. Our patient who is 56 year old male was admitted with complaints of syncope and hand numbness. We presented mediastinal schwannoma as a rare cause of syncope in our case.

Keywords: Syncope, Schwannoma, Mediastinal tumor

Öz

Senkop hızlı başlangıç, kısa süre ve spontan tam iyileşme ile karakterize, geçici global serebral hipoperfüzyona bağlı bilinç kaybıdır. Senkoplu olguların dikkatli ve detaylı değerlendirilmesi gerekir. 56 yaşında erkek hastamız senkop ve kolda uyuşma şikayetleri ile başvurdu. Biz de bu vakamızda senkopun nadir bir nedeni olarak mediastinal Schwannomayı sunduk.

Anahtar kelimeler: Senkop, Schwannom, Mediastinal tümör

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Introduction

Syncope is a sudden postural tonus and loss of consciousness that develops in a short time resulting from temporary impairment of cerebral perfusion; and it results in spontaneous recovery. Syncope is classified according to the underlying etiologic cause. Cardiac arrhythmias, structural heart diseases, neurogenic causes and cerebrovascular diseases are the main causes [1]. Treatment and prognosis of the etiologic causes are very different from each other, so it is necessary to evaluate the syncope cases carefully and in detail.

Mediastinal Schwannomas are largely benign and asymptomatic, but may cause thoracic pain, Horner's syndrome, aphonia and weakness in the upper extremity due to pressure of the lesion. In our case, we evaluated mediastinal schwannoma in the differential diagnosis of the syncope which is an atypical application.

Case presentation

A 56-year-old male patient was admitted to our polyclinic with complaints of syncope and hand numbness twice in the last 2 weeks. There was no chronic illness and no drug use history in the background of the patient. There was 20 packet/year cigarette use. The physical examination of the patient was normal. The height was 170 cm, weight was 72 kg, blood pressure was 130/70 mmHg and the pulse was 70 beat/min. Electrocardiogram (ECG) showed normal sinus rhythm and no pathological finding was evaluated in echocardiography. Tilt test was normal. Laboratory findings were; Glucose: 94 mg/dl (70-110), creatinine: 0.9 mg/dl (0.7-1.2), aspartate transaminase: 14 U/L (0-40), alanine transaminase: 9 U/L (0-40), leukocyte: 7.1 10^9/L (4-10), hemoglobin: 16 gr/dl (12-16), sedimentation (1st hour): 13 mm (1-23). In chest X- Ray; an increase in mediastinal density that caused deviation of the trachea slightly to the right side, was observed (Figure 1). In thoracic computed tomography (CT) of the patient, a smooth surface mediastinal mass was observed along the upper left paratracheal area.

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The left main carotid artery, the vertebral artery, the thyroid gland, the left lobe and trachea pressure were observed, but there was no significant invasion (Figure 2). Tumor markers were normal. No metastatic sign was observed in abdominal dynamic magnetic resonance imaging (MRI) and diffusion weighted brain MRI. The tumor was removed by radical surgical resection with thoracotomy. The pathology of the mass removed by surgical resection and which was macroscopically soft, encased in fibrous capsule was evaluated to be Ancient Schwannoma. Diffuse S-100 positivity was observed in tumor cells. No complaints of syncope and numbness in the hands were observed in postoperative 1-month follow-up of the patient.

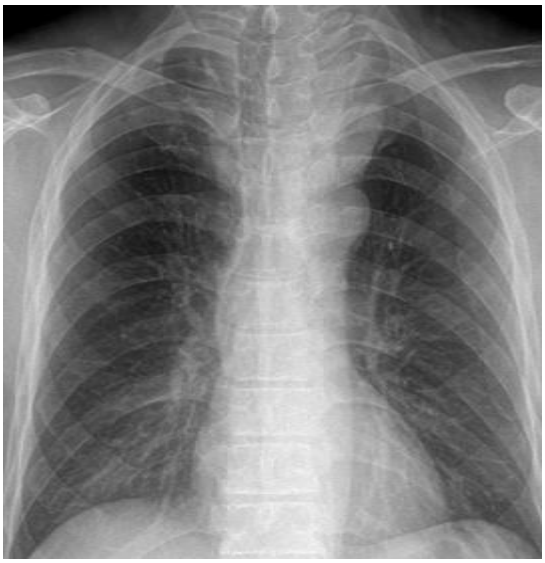

Figure 1: Mediastinal mass in chest X-Ray

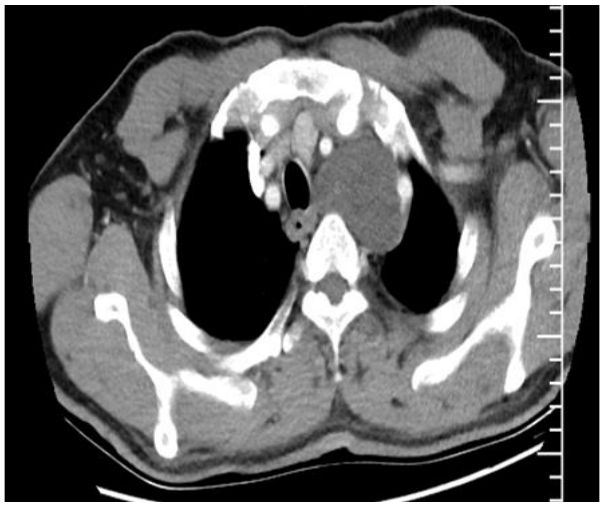

Figure 2: Mediastinal mass in pulmonary computed tomography scan

Discussion

Syncope is a loss of consciousness due to transient global cerebral hypoperfusion and characterized by rapid onset, short term and spontaneous complete recovery [1]. Although it is usually benign, syncope may be a result of a cardiogenic, neurogenic, or metabolic disease. Cardiovascular causes of syncope can be categorized as follows; aortic stenosis, hypertrophic obstructive cardiomyopathy, primary pulmonary hypertension, sick sinus syndrome, long QT syndrome, supraventricular tachycardia and heart blocks [1,2]. Our patient's ECG was in normal sinus rhythm and his echocardiographic examination was also normal. Also, there was not a drug use to prolong QT (antiarrhythmic, vasodilator, psychotropic, antibiotic, non-sedating antihistamine).

The most common cause of noncardiac syncope is neurocardiogenic syncope and it is also called vasovagal syncope. Vasovagal syncope is divided into two groups as cardioinhibitor and vasodepressor. It is thought that it results from an abnormality in neurocardiovascular interactions responsible for systemic and cerebral perfusion. Other causes of noncardiac syncope are orthostatic hypotension, cerebrovascular diseases, neurological disorders such as migraine, vertigo, psychogenic diseases such as conversion, emotional states such as excitement and fear, or metabolic disorders such as hypoglycemia, hypoxia, hyperventilation and dehydration [1,3,4]. In the examination of our patient, tilt test was normal. There was not a psychological disorder, migraine or vertigo. Diffusion brain MR was normal in terms of cerebrovascular disease.

Neurogenic tumors constitute approximately 20% of all adult mediastinal tumors and are the most common cause of posterior mediastinal mass. Schwannomas are the most common (approximately 50%) mediastinal neurogenic tumors and frequently affect patients aged 20-30 years [5]. Schwannoma is a benign tumor originating from the Schwann cells forming the peripheral nerve sheath. In our case, Schwannoma was found in the mediastinal area.

Mediastinal Schwannomas are largely benign and asymptomatic, but may cause thoracic pain, Horner's syndrome, aphonia and weakness in the upper extremity due to pressure of the lesion [6]. Our case applied to the hospital with syncope developing due to the pressure of mediastinal mass on left main carotid and vertebral artery.

They are generally seen as well-defined solitary mass on chest X-Ray and thoracic CT. Calcification and cystic changes can be observed [7]. In rare cases, malignant changes can be observed in schwannomas especially with Von Recklinghausen disease [4]. In patients with malignant features, irregular borders and invasion on surrounding bone tissues are seen frequently. In our case, the mass had no significant invasion and it was smooth surface.

Radical surgical resection with thoracotomy is the treatment of choice for all (benign or malign) peripheral nervous origin tumors [9]. In our case, a mass which was macroscopically soft and encased in fibrous capsule was removed by surgical resection.

In conclusion, although syncope is usually benign, every patient must be evaluated by a good physical examination and a detailed history. It was emphasized that neurogenic causes and mediastinal schwannomas must be taken into account in differential diagnosis, apart from cardiac arrhythmias, structural heart diseases, cerebrovascular diseases.

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Case of testicular epidermoid cyst: Sonographic and histopathologic findings

Testiküler epidermoid kist olgusu: Sonografik ve histopatolojik bulgular

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Abstract

Testicular epidermoid cyst is a benign, non-teratomatous tumor. Patients typically present with a painless and non-tender, testicular mass. Preoperative ultrasound is major diagnostic procedure combining with normal biochemical tumor markers. The certain diagnosis is histopathological. We present the sonographic and histopathological findings of a 27-year-old male patient with epidermoid cyst who underwent inguinal orchiectomy in this case report.

Keywords: Epidermoid cyst, Surgery, Testes, Tumor, Ultrasound, Histopathology

Öz

Testiküler epidermoid kist benign, non-teratomatöz bir tümördür. Hastalar tipik olarak ağrısız ve hassas olmayan testiküler kitle ile başvururlar. Preoperatif ultrasonografi, normal biyokimyasal tümör belirteçleri ile birlikte başlıca tanı prosedürüdür. Kesin tanı histopatolojiktir. Bu olgu sunumunda inguinal orşiektomiye giden 27 yaşındaki bir epidermoid kist hastasının sonografik ve histopatolojik bulgularını sunduk.

Anahtar kelimeler: Epidermoid kist, Cerrahi, Testis, Tümör, Ultrasonografi, Histopatoloji

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Introduction

Intratesticular epidermoid cyst is a benign tumor and corresponds to 1-2% of all testicular neoplasms [1]. The first case report of testicular epidermoid cyst was published by Dockerty and Priestly in 1942. The patients' ages range from 3 years to 77 years, usually between 2 and 4 decades. It is more commonly unilateral. It has a slightly higher prevalence in right testis and white males. Additionally it originates from keratin-producing epithelium [2-6]. Although some radiological features and negative tumor markers have diagnostic value for this lesion, clinical diagnosis is a major problem for the surgeon.

In adult epidermoid cysts, orchiectomy is adequate treatment; whereas in prepubertal cases, enucleation is applied. We aimed to present the sonographic and histopathological findings of a 27-year-old male patient with epidermoid cyst who underwent inguinal orchiectomy in this case report.

Case presentation

A 27-year-old male patient was admitted to the urology clinic with the complaints of swelling and pain in the left testis for one month. There were no important features in the history of the patient who had 2 cm hard palpable mass in the left testicle on the physical examination. The right testis was evaluated as normal. In the scrotal ultrasonography (US) examination made by 7.5 MHz transducer [Aplio 500, Toshiba Medical Systems, Tokyo, Japan]; a 18x18x17 mm in diameter, heterogeneous, hypoechoic, lamellated "onion skin" mass with hyperechoic and hypoechoic rings; without vascularity on color Doppler, was observed in the left testis; and a solid mass with an irregular contour was observed in the anterior segment. Although typical sonographic findings of epidermoid cyst were detected, a germ cell tumor was in consideration of differential diagnosis due to the irregularity of the short segment (Figure 1). Hemogram and routine biochemical assays including βHCG and αFP values were normal in the laboratory tests of the patient. Posterior-anterior chest x-ray showed no evidence of any features and the patient was informed and approved preoperatively.

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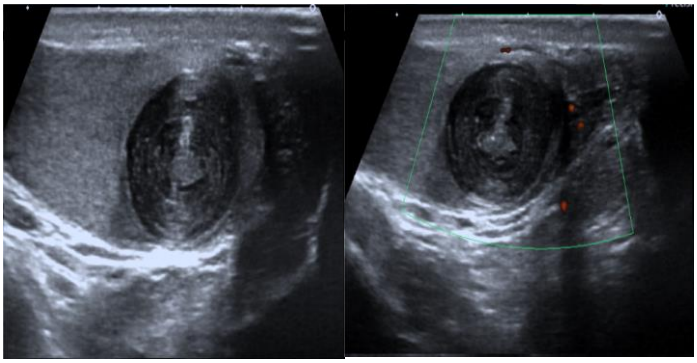

Figure 1: Hypoechogenic mass with 18x18x17 mm in diameter with smoothly confined lobular contour, inner hyperechoic and hypoechoic rings, central hyperechoic fat and absence of vascularity in the left testis

The patient underwent inguinal orchiectomy with clinical diagnosis of a malignant testicular tumor. Histopathologic examination of the orchiectomy material revealed smoothly limited nodular lesion in cream-yellow color with dimensions of 1.7x1.7x1.5 cm with intratesticular placement at 2 mm distance to tunica vaginalis. The histopathological findings of the orchiectomy material of the patient were compatible with the epidermoid cyst (Figure 2, 3). Post-op complication was not observed and the patient was discharged on the 2nd day after the operation.

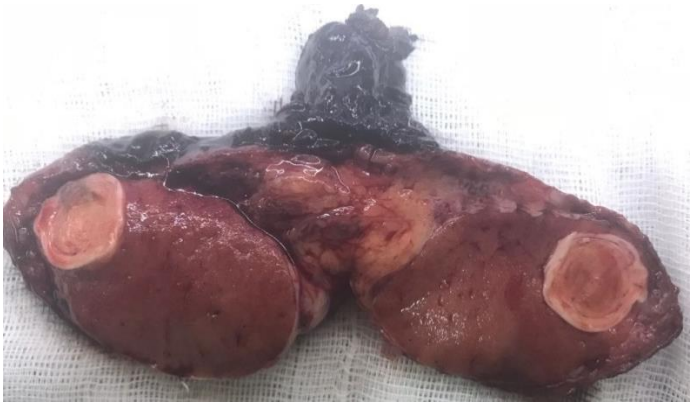

Figure 2: Orchiectomy material with dimensions of 8x5x3 cm with a spermatic cord of 1 cm in diameter and a length of 0.8 cm. In the section view; smoothly limited nodular lesion in cream-yellow color with dimensions of 1.7x1.7x1.5 cm with intratesticular placement at 2 mm distance to tunica vaginalis.

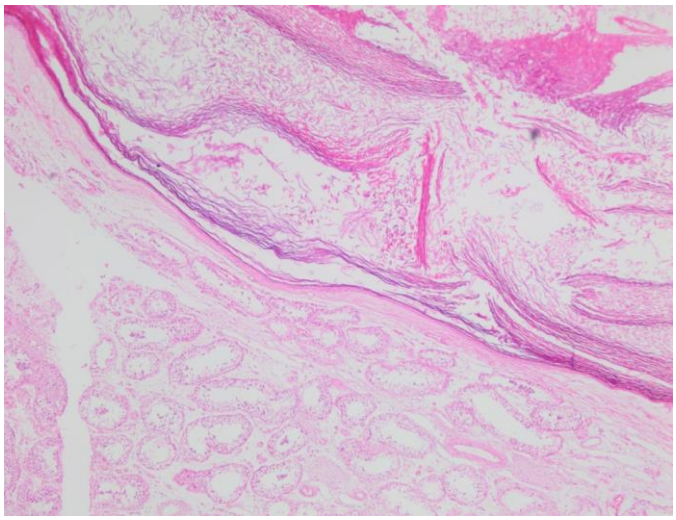

Figure 3: An epidermoid cyst is seen on the upper right and normal testicular parenchyma is seen on the bottom left of this image. The cyst wall contains keratinized squamous epithelium. The lumen of the cyst contains laminated keratin [H&E x40].

Discussion

Testicular epidermoid cyst is detected 1% in adults and accounts for 3% of pediatric testicular tumors. It is seen in patients from early childhood to the elderly, but most patients range in age from 10 to 40 [7]. There is no consensus about histogenesis of epidermoid cysts, which have been suggested as squamous metaplasia of the rete testis or seminiferous epithelium in the past, but today it is thought to be monodermal and / or unilateral development of e a teratoma [8].

The diameter of epidermoid cyst, which typically appears as painless testis enlargement, is usually between 1 and 3 cm [8]. The US findings vary according to the cystic maturity-compactness and the quality of the keratin in the cyst. It is seen as a well-bordered ovoid lesion with variable echogenicity. Several US characteristic views for epidermoid cysts have been described; as a target or echogenic halo, a hyperechogenic or hypoechoic concentric ring with classic onion ring pattern. This appearance corresponds to the natural development of the cyst. In addition, there is usually no blood flow in the cyst in color Doppler US as an important sign [9,10]. In our case, blood flow was not detected in the cyst in the Doppler US, which was layered with internal structure in the form of onion skin.

Intratesticular solid masses should be considered malignant up to the point where it is proved otherwise. Features such as negative tumor markers, onion ring configuration, and lesion avascularity on Doppler US are important for differentiation of epidermoid cysts from other germ cell tumors [8]. Approximately 95% of the malignant testicular masses are of germ cell tumors, of which the most common histologic subtype is seminoma. The prognosis of seminoma is better than other malignant tumors because of the good radiotherapy and chemotherapy response.

Seminomas are hypoechoic and typically homogeneous in appearance [11-13]. Histologically, germ cell tumors without seminomatous cells are called nonseminomatous germ cell tumors. This group includes yolk sac tumor, embryonal cell carcinoma, teratocarcinoma, teratoma and choriocarcinoma. With US these tumors are seen as heterogeneous, irregular bordered masses. Sonographically; nonseminomatous germ cell tumors contain much more necrosis-compatible cystic areas and echogenic foci that may be compatible with calcification, hemorrhage and fibrosis compared to seminomas [11,14].

Until now, the recurrence of an epidermoid cyst or the occurrence of metastasis has not been reported. However, Woo et al. reported a seminoma development in the same testicle 5 years after the conservative treatment of testicular epidermoid cyst [15].

In adult epidermoid cysts, orchiectomy is adequate treatment, whereas enucleation is applied in prepubertal cases. If the epidermoid cyst can be recognized as a result of the the frozen section procedure and there are no teratomatous elements in the cyst wall, enucleation is sufficient for the treatment. Orchiectomy is recommended if there is no enucleation criteria; the mass is large and/or multiple. Considering orchiectomy complications such as psychological, hormonal and fertilization that will occur in the later life of the patient, the importance of enucleation increases in the pediatric patient group and young patients [16].

In our case, radical orchiectomy was preferred because there were findings suggesting a benign tumor in the preoperative ultrasonography examination, and the contralateral testis was normal. Besides, the patient was older. Preoperative serum tumor markers were normal in our patient. Because of this situation, radical orchiectomy should be discussed. On the other hand some germ cell tumors have normal levels of AFP and β-hCG [17].

In conclusion, radical orchiectomy should be performed in cases of testicular mass where germ cell neoplasms cannot be definitively distinguished with the anamnesis, physical examination, laboratory and ultrasonography findings. Testicular protective surgical approaches can be selected in pediatric age group if only tumor markers are normal, radiologically there are typical findings of epidermoid cyst and the frozen section supports the diagnosis.

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Case report
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Paroxysmal nocturnal hemoglobinuria case presenting as cerebral venous sinus thrombosis

Serebral venöz sinüs trombozu ile başvuran paroksismal noktürnal hemoglobinüri vakası

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Abstract

Venous thromboembolism (VTE) is the leading cause of morbidity and mortality in paroxysmal nocturnal hemoglobinuria (PNH). Between 29% and 44% of PNH patients experience a clinically evident VTE that affects the liver, brain, gut or kidney. Cases of VTE have been reported in all major organs except the spinal cord and bone marrow. Cavernous venous sinus thrombosis (CVST) is rare, but it has been reported previously to occur late in the course of PNH. Here we describe a case of CVST in a 34-year-old female admitted to our hospital with severe left sided temporal headache, double vision and malaise as an initial manifestation of PNH. This is a rare case of CVST as a presenting manifestation of PNH. This case along with two other recent reports of CVST accompanied by haemolytic anaemia in patients with PNH encourages increased vigilance for PNH in patients without an associated thrombophilic condition.

Keywords: Paroxysmal nocturnal hemoglobinuria, Cavernous venous sinus thrombosis, Eculizumab

Öz

Venöz tromboembolizm (VTE), paroksismal nokturnla hemoglobinuri'de (PNH) morbidite ve mortalitenin önde gelen nedenidir. PNH hastalarının %29 ila %44'ü, karaciğer, beyin, bağırsak veya böbrekleri etkileyen ve klinik olarak belirgin bir VTE deneyimi yaşamaktadır. Bugüne kadar, omurilik ve kemik iliği dışındaki tüm ana organlarda VTE vakaları bildirilmiştir. Kavernöz venöz sinüs trombozu (KVST) nadirdir, ancak daha önce PNH seyrinde geç ortaya çıktığı bildirilmiştir. Burada, hastanemize ciddi sol taraflı temporal başağrısı, çift görme ve başlangıçta PNH'nin ilk belirtisi olarak görülen halsizlik, kırgınlık şikâyeti ile başvuran 34 yaşında bir kadın hastada bir KVST vakasını sunduk. Vakamız PNH'ın klinik tabloları içinde nadir görülen bir KVST hastasıdır. Bu vaka, PNH'lı hastalarda hemolitik aneminin eşlik ettiği diğer iki KVST vakası gibi PNH ilişkili sık gözlenen trombofilik durumu olmayan hastalarda PNH için farkındalığı teşvik etmektedir.

Anahtar kelimeler: Paroksismal nokturnal hemoglobinuria, Kavernöz venöz sinüs trombozu, Eculizumab

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal hematopoietic stem cell disorder. Clinical manifestations of the disease can be defined as thrombophilia broadly, intravascular hemolysis, smooth muscle dystonia and bone marrow failure [1]. PNH arises because of the nonmalignant clonal expansion of one or several hematopoietic stem cells that have acquired a somatic mutation of the X chromosome gene PIGA, which is required for synthesis of the glycosyl phosphatidylinositol moiety that anchors some proteins to the cell surface [2].

Venous thromboembolism (TE) is the leading cause of morbidity and mortality in PNH. Between 29% and 44% of PNH patients experience a clinically evident VTE affecting the liver, brain, gut or kidney. To date, venous thrombosis has been reported in all major organs except the spinal cord and bone marrow [3], and is particularly common in the hepatic, portal, splenic and cerebral venous system. Cavernous venous sinus thrombosis (CVST) is rare, but when it does occur in PNH patients it has previously been reported to appear late on in the disease course [3-5]. Here we describe a case of CVST as an initial manifestation of PNH [3,4].

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Case presentation

A 34-year-old female admitted to our hospital for severe left sided temporal headache, double vision and malaise. Physical examination revealed mild tachycardia (heart rate: 104 beats per minute) and lethargy as well as pain in right upper quadrant. Cranial nerve examination showed no paralysis and ophthalmological examination indicated bilateral advanced papilledema.

Laboratory test findings included: leucocyte count 7800/mm^3; hemoglobin 5.26 g/dl; hematocrit 16.3%; differential leucocyte count 88% neutrophils, 11% lymphocytes and 1% monocytes; platelet count 180,000/mm^3; C-reactive protein 15.0 mg/dL; d-dimer 54.8 mg/dL. Liver function tests showed elevated total and direct serum bilirubin (3.09/1.23 mg/dL), lactate dehydrogenase (LDH; 1281 U/L), and alanine/aspartate aminotransferases (AST/ALT; 204/191 IU), while alkaline phosphatase was within normal range. The total serum protein level was 4.9 g/dl, and serum albumin was 2.9 g/dl. Serum electrolytes and renal function tests were within normal limits; serum uric acid was 4.9 mg/dl.

Abdominal ultrasonography revealed mild hepatosteatosis, calculous cholecystitis and splenomegaly. A lateral sub capsular splenic infarct measuring 2.5 x 2.0 cm was also detected. Cerebral venography identified a filling defect consistent with a partially recanalized or small thrombus (Figure 1). Cerebral magnetic resonance imaging revealed focal ischemic focus in the left cerebellar hemisphere (Figure 2). Color Doppler studies of the carotid, vertebral, hepatomesenteric and portal vessels gave normal findings.

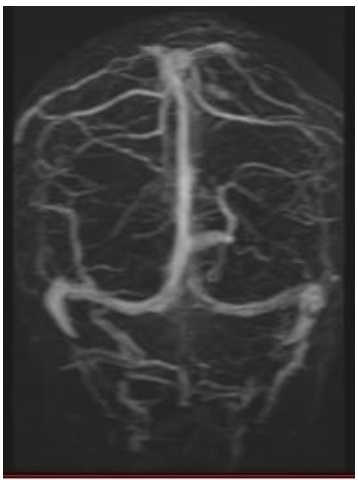

Figure 1: Cerebral venography: filling defect

The patient initially received enoxaparin 0.6 cm^3 twice daily. A peripheral blood smear revealed hemolysis. Negative findings were detected by direct and indirect Coombs testing, and we looked for thrombophilia based on the apparent thrombosis. Factor 5 homozygous Leiden mutation was normal; antithrombin 3, and Protein-C and -S levels were within normal limits. Anti-nuclear antibody was negative the reticulocyte count was 1.4%. We therefore suspected PNH based on the presence of Coombs-negative hemolytic anemia and VTE. FLARE-based (Fragment Length Analysis using Repair Enzymes) assays revealed a PNH clone size of 85% in granulocytes and 80% in monocytes.

The patient's abdominal pain decreased, and after 48 hours she was able to tolerate oral intake; her bowel sounds returned to normal. Enoxaparin was later switched to warfarin. However, her clinical picture was complicated by right hemiplegia, central facial paralysis and aphasia after 5 days under enoxaparin and warfarin therapy. Cerebral CT revealed a suspicious ischemic focus at the internal capsule and putamen (Figure 3). During follow up, right hemiplegia and aphasia regressed. Eculizumab was initiated. The patient was discharged from the hospital on day 27 with oral warfarin. Eculizumab therapy, 600 mg IV infusion for the first 4 weeks after 1 week 900 mg for the fifth dose then 900 mg for every 2 weeks was started at outpatient clinic. At the last outpatient clinic visit she is on eculizumab and warfarin therapy with no thrombotic events during 9 months of follow up. Her general health status has quietly improved with only a slight anemia and no need for any blood transfusions; she currently receives eculizumab every other week. Her plasma LDH at the time of writing is 160U/L, and the patient has gained weight. Written informed consent is obtained from the patient who participated in this study.

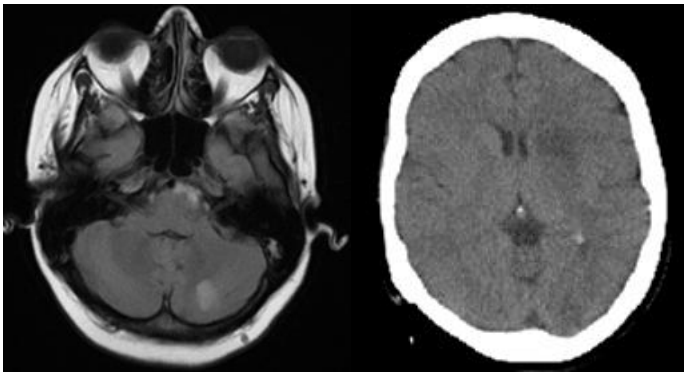

Figure 2: Cerebral MRI: partially re-canalized or small thrombus

Figure 3: Cerebral CT: ischemic focus at the internal capsule and putamen

Discussion

To the best of our knowledge, this is among the few cases of PNH in which the patient has presented with CVST as an initial disease manifestation. Two other cases of CVST in PNH have been described recently. Sharma et al described a patient with PNH who presented with thrombosis of the superior sagittal and right sigmoid sinuses, who was diagnosed 9 months later when the patient developed hepatic venous thrombosis [4]. More recently, the diagnosis of a patient 11 months after an initial episode of cerebral venous sinus thrombosis was described in India [3].

It is recommended that patients with a Coombs-negative hemolytic anemia, aplastic anemia, refractory anemia, and unexplained thrombosis in conjunction with cytopenias or hemolysis should be screened for PNH [6]. VTE merits special attention as it is considered the leading cause of PNH-related death, accounting for two-thirds of all mortalities in patients with this disease [2]. VTE is a relatively common complication during the course of PNH, with 29–44% of patients experiencing a clinically evident embolic event affecting the liver, brain, gut or kidney [2]. Among these sites, the hepatic vein is the most frequent location of thrombosis in PNH, accounting for the majority of deaths. CVST is the second most common type of thrombosis. There is a particular propensity for involvement of

hepatic and cerebral veins but the reason for this is not fully understood [7].

Hall et al reported that risk factors for thrombosis in patients with PNH include hemolytic anemia and hemoglobinuria, and PNH granulocyte clones >60% [7]. A more recent data from a Korean Registry showed that LDH≥1.5 ULN combined with clinical symptoms such as abdominal pain, chest pain, dyspnea or hemoglobinuria would be a better risk predictor for VTEs than clone size [8].

The exact pathophysiologic mechanism of VTE associated with PNH is yet to be clarified. A number of potential mechanisms include platelet activation by complement due to nitric oxide consumption because of intravascular hemolysis and endothelial damage by the intravascular hemolysis. Complement activation is recognized as a major contributor to vascular inflammation and is known to play a role in ischemia/reperfusion injury [9].

In the present case, PNH was suspected due to recurrent VTE, despite the absence of any other hereditary or acquired thrombophilic disorder. Moreover, the presence of hemolytic anemia, which was initially considered as a consequence of menorrhagia, also led to diagnosis of PNH.

VTE is a significant complication that constitutes an indication for the treatment of PNH in an otherwise asymptomatic patient [7]. Since thrombosis occurs frequently in visceral veins where morbidity and mortality is significant, careful anticoagulation is essential in such cases. Based on a retrospective study of 67 patients with PNH who did not receive prophylactic anticoagulation, Hall et al reported a VTE rate of 3.7 events per 100 patient-years, while no single VTE event was observed in 117.8 patient-years in 39 patients with PNH treated with anticoagulants (as primary prophylaxis) [9]; there were two serious hemorrhages in more than 100 patient-years of warfarin therapy in this study. The authors concluded that primary prophylaxis with warfarin in PNH prevents VTE with acceptable risks. However new VTE events or progression of initial VTE events have been reported in patients who are currently on anticoagulation in other reports [10-13]. Moreover, frequent occurrence of thrombocytopenia can increase the risk for fatal hemorrhage in patients with PNH [12,13].

Eculizumab is a humanized monoclonal antibody that specifically targets the terminal complement protein C5 [2]. It is the first treatment for PNH that effectively inhibits complement-mediated intravascular hemolysis, thereby preventing subsequent morbidities such as VTE. In a study by Hillmen et al. 2013, the reduction of the incidence of VTE from 11.3 events per 100 patient-years to 2.14 events per 100 patients-years, a relative risk reduction of 81.8% [14]. Our patient received eculizumab along with oral warfarin for 9 months. Follow up at 3-month intervals showed significant reduction in hemolysis, and there were no new VTE events or hemorrhages.

In conclusion, this is a rare case of CVST as a presenting manifestation of PNH. This case along with two other recent reports of CVST accompanied by hemolytic anemia in patients with PNH encourages increased vigilance for PNH in patients without an associated thrombophilic condition.

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Surgically managed gunshot injury of the heart; Bullet in the right coronary artery

Kalbin ateşli silah yaralanmasında cerrahi yönetim; Sağ koroner arterde kurşun

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Abstract

Gunshot injuries are one of the penetrating traumas of the heart and that require urgent intervention. Localization of the cardiac injury is important in terms of appropriate treatment approach. For this reason, rapid diagnosis and surgical intervention is life-saving in such patients. In our study, we present a surgical intervention of a patient with lesion on the right coronary artery that doesn't allow blood flow in coronary angiography due to cardiac injury with gunshot injury.

Keywords: Gunshot injury, Cardiac trauma, Surgery

Öz

Ateşli silah yaralanmaları, kalbin penetran travmalarından biridir ve acil müdahale gerektirmektedir. Kardiyak hasarın lokalizasyonu uygun tedavi yaklaşımı açısından önemlidir. Bu sebeple bu hastalarda hızlı tanı ve cerrahi müdahale hayat kurtarıcıdır. Çalışmamızda ateşli silah yaralanmasına bağlı kardiyak yaralanma nedeniyle koroner anjiyografide kan akışına izin vermeyen sağ koroner arter lezyon olan bir hastanın cerrahi müdahalesini sunduk.

Anahtar kelimeler: Ateşli silah yaralanması, Kardiyak travma, Cerrahi

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Introduction

Penetrating cardiac traumas are rarely seen and life-threatening clinical situations. Rapid and correct diagnose and intervention are important. Although prognosis and outcome is often not good in cardiac gunshot injuries, here we presented a successful surgical management of right coronary injury due to gunshot.

Case presentation

A 42-year-old man was transferred our hospital with multiple penetrating wounds from a shotgun. The patient was conscious at the time of admission and physical examination revealed multiple pellet injuries in the skull, face, chest, abdomen and upper and lower extremities. The electrocardiogram showed changes indicating an acute inferior wall myocardial infarction. Multiple pellets in the chest and abdomen, including one in the heart was seen in CT images. Two-dimensional echocardiography showed minimally pericardial effusion near lateral wall. Emergent coronary angiography was performed to the patient and it was seen that there was a complete occlusion of the distal right coronary artery with a pellet embedded in the heart (Figure 1).

As the worsening of the vital signs urgent operation was decided. Aorto-right coronary bypass with saphenous vein was done. Bullet was untouched because for being deeply settled and the patient was discharged from hospital postoperatively 12th day without any cardiac problem.

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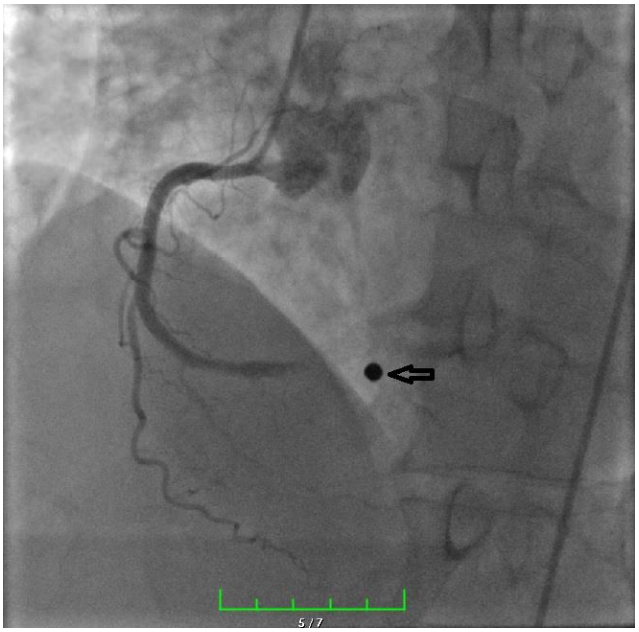

Figure 1: A foreign material caused total occlusion of right coronary artery in coronary angiography

Discussion

Traumas result to cardiac injury can be classified as penetrating and nonpenetrating. Penetrating cardiac trauma is rarely seen and intravascular and intracardiac bullets are a diagnostic and therapeutic challenge. Myocardial rupture, contusion, laceration, pericardial insult, coronary injury, valvular damage, arrhythmias and conduction abnormalities can be seen after these traumas. Stab or gunshot wounds are the most frequent penetrating injuries [1]. Penetrating injury to the heart may result in intracardiac injury in different sites; the right ventricle is the most common (43%), followed by the left ventricle (33%), right atrium (15%), left atrium (6%) and intrapericardial great vessels (6%) [2].

Similarly in our case, various case studies reveal that trauma is one of the nonatherosclerotic factors associated with acute myocardial infarction [3]. Although there are few reports related to a gunshot injury to a coronary artery managed conservatively that ended with a favorable outcome, our patient had total occlusion of the right coronary artery, caused complicated inferior myocardial infarction, needed to surgery [4].

Although penetrating cardiac traumas are rarely seen, there is a short time lag to keep the patients alive [5]. Approximately 80-90% of the patients with gunshot wounds of the heart cannot be reached to the hospital [6]. Wall et al reported the hospital mortality of complex cardiac injuries (coronary, septal, valvular) up to 53% [7]. The most common causes of mortality are cardiac tamponade or bleeding [1].

Management decision depends on the cardiac chamber involved, the patients' symptoms and the projectile's size, shape and location within the chamber [8]. Small pericardial and myocardial wounds with tamponade can be treated by pericardiocentesis, but larger wounds of the pericardium and myocardium due to the bullets should be managed by thoracotomy and sternotomy [6].

Cardiac foreign bodies are challenging clinical entities with varied manifestations that all surgeons should be aware of so, acute operations for complex injuries are important and necessity for saving lives.

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Case report
Olgu sunumu

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Spontaneous pneumothorax as an uncommon complication of herpes zoster infection

Herpes zoster enfeksiyonunun nadir bir komplikasyonu olarak spontan pnömotoraks

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Abstract

Varicella zoster virus (VSV) is a neurotropical alpha-herpesvirus. Although many complications may be observed in VZV infections during adulthood, pneumothorax is one of its rare complications. It should be kept in mind that the easiest way to protect the patient from a complication that may be mortal, such as tension pneumothorax, is prompt diagnosis using physical examination and chest x-ray and immediate removal of air in the pleural cavity.

Keywords: Pneumothorax, Varicella zoster, Herpes zoster

Öz

Varisella zoster virüsü (VSV), nörotropizm gösteren alfa-herpes virüslerindendir. Erişkin yaş grubundaki VZV enfeksiyonlarında birçok komplikasyon gözlenmekle birlikte pnömotoraks, VZV'nin ender rastlanan komplikasyonlarından biridir. Tansiyon pnömotoraks gibi mortal seyredebilecek bir komplikasyondan hastayı korumanın en kolay yolu ise, akciğer grafisi ve fizik muayene ile bu tanıyı hızlıca koyup, mevcut havanın tahliyesi olduğu akıldan çıkarılmamalıdır.

Anahtar kelimeler: Pnömotoraks, Varisella zoster, Herpes zoster

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Introduction

Varicella zoster virus (VSV) is a neurotropical alpha-herpesvirus. Varicella, which is the primary infection of VZV causes vesicular skin lesions during childhood period. Following primary infection, the virus remains latent in neuron ganglia. Secondary infection, known as Herpes Zoster (HZ), is an infection that occurs years after the primary infection. It occurs due to the viral reactivation in the ganglion. HZ presents as painful vesicular lesions along the associated neuronal dermatome, usually occurring in adulthood [1,2]. Although many complications may be observed in VZV infections during adulthood, pneumothorax is one of its rare complications. In this article, we present a male patient diagnosed with unilateral spontaneous pneumothorax that developed secondary to VZV.

Case presentation

A 47-year-old male patient admitted to our emergency department with the complaint of right-sided chest pain beginning 2 days ago. His medical history revealed that it was a sudden onset pain with pleuritic character. Dyspnea accompanied the pain. On physical examination, bilateral respiratory sounds were diminished particularly on the right side. His blood pressure was 135/80 mm Hg, fever was 36.1 °C and pulse was 89 / min. The patient's past medical history revealed that he was prescribed 500 mcg fluticasone + 50 mcg salmeterol discus 2x1, tiotropium bromide inhaler 18 mcg 1x1 for chronic obstructive pulmonary disease (COPD) and he was an active smoker for 30 pack*years. Patient was consulted with our clinics with the pre-diagnosis of right-sided spontaneous pneumothorax after posterior-anterior (PA) chest radiographs were analyzed. Our physical examination revealed crusted millimetric multiple lesions that were located on the intersection of right 5th intercostal space (ICS) and posterior axillary line (Figure 1).

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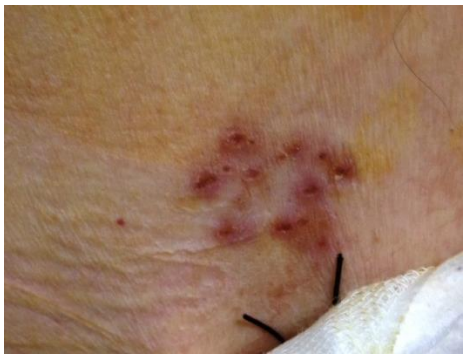

Figure 1: Skin lesions of the patient

His medical history revealed that those lesions appeared 2 weeks ago and they were severely painful. He also mentioned that he felt malaise and fatigue 1 week prior to the appearance of these lesions. Pulmonary auscultation revealed decreased pulmonary sounds on the right lung, and sub-total right sided pneumothorax was detected on chest x-ray. Tube thoracostomy was performed through the intersection of 6th ICS and mid-axillary line using a 32 Fr chest tube under local anesthesia (Figure 2). Case was consulted with the dermatology clinics for the differential diagnosis of the skin lesions. The dermatologic examination revealed that the skin lesions were concordant with VZV and no additional diagnostic tests were required. Chest tube was removed on the postoperative 4th day and the patient was discharged. Patient's physical examination at our outpatient clinics 1 week after his discharge was normal. He is admitting to our outpatient clinics regularly for follow up.

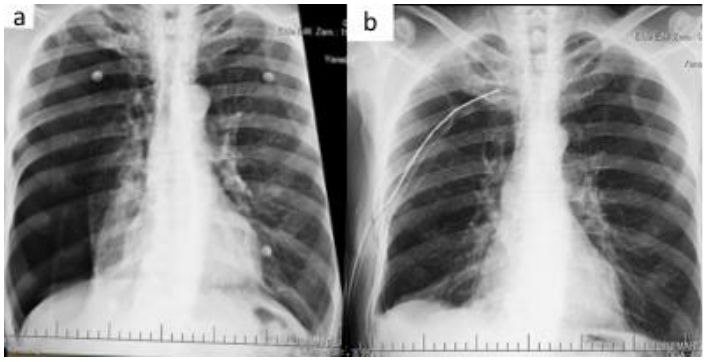

Figure 2: Chest x-ray before (a) and after (b) of the patient

Discussion

It has been reported that HZ secondary to VZV is diagnosed in about 1 million people in the United States of America (USA) annually. HZ is generally seen in adults and male to female ratio is equal [3]. The thoracic nerve ganglia are one of the regions where VZV remains latent and viral reactivations that cause HZ occur. Immunosuppression plays an important role in reactivation [4]. HZ vesicles appear attributable to the reactivation of VZV after a variable prodromal period.. This prodromal period may include symptoms of fatigue, headache, photophobia, as well as pain with variable frequency and severity. Vesicles are crusted in about one week. Contagiousness begins with the formation of HZ vesicles and ends with the crusting. However, the contagiousness of HZ is considered to be less than that of varicella due to the infrequent respiratory transmission [3,5]. No factor that could lead to immunosuppression as detected in our case. However, similar to the literature, the lesions appeared one week after the onset of fatigue and the resulting vesicles were crusted within one week period. Our case mentioned he had severe pain around the skin lesions lasting about one week, however he had no complaint of pain at the time of admission.

Typical skin lesions accompanied by characteristic signs and symptoms are usually adequate for the diagnosis of HZ. Laboratory tests are necessary for immunocompromised patients due to the presence of atypical findings [3]. Our patient was diagnosed with HZ because he presented with the typical signs and symptoms of HZ on admission.

Various complications of HZ infection such as pneumonia, keratitis, uveitis, pleuritis and cranial nerve paralysis have been reported. The likelihood of occurrence and severity of these complications increase with age [4,6]. Pneumothorax is also reported among the complications of HZ. Although the exact incidence is unknown, the majority of cases with secondary pneumothorax in HZ are those accompanied with VZV pneumonia and smoking. It has been argued that the development of pneumothorax secondary to VZV pneumonia is attributable to the rupture of subpleural necrotic nodules or the rupture of preexisting bleb due to inflammation caused by pneumonia [7]. In some cases, however, there is no examination or radiological findings to prove the presence of an underlying pneumonia [8]. In our case, clinical diagnosis of HZ could be established but the presence of pneumonia could not be clinically identified. However, we believe that inflammation due to HZ which is localized in the thoracic region may have caused the rupture of bullae secondary to the long-standing underlying COPD and active smoking and thus causing pneumothorax.

As a result, secondary spontaneous pneumothorax is a rare complication of HZ. It should not be forgotten that pneumothorax may develop rarely in these patients who present with dyspnea even with or without the presence of pneumonia. The easiest way to protect the patient from a complication that may be mortal, such as tension pneumothorax, is prompt diagnosis using physical examination and chest x-ray and immediate removal of air in the pleural cavity.

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