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Relationship between Helicobacter pylori and thiol-disulfide homeostasis: A prospective observational study

Helicobacter pylori ve tiyol-disülfid homeostazı arasındaki ilişki: Prospektif, gözlemsel bir çalışma

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Abstract

Aim: Helicobacter pylori (HP) infection causes inflammation and oxidative stress at a cellular level. In the present study, we aimed to evaluate the possible relationship between HP and thiol-disulfide homeostasis (TDH), a novel indicator of oxidative stress.

Methods: Medical data of a total of 53 patients admitted with persistent dyspepsia and undergoing gastroscopy were evaluated prospectively. The patients were divided into two groups, based on the result of gastric biopsy, as HP-positive (+) and HP-negative (-). Demographic data, ferric-reducing ability of plasma (FRAP), ischemia-modified albumin (IMA), native thiol, total thiol, disulfide, and malondialdehyde (MDA) levels of the patients were recorded and compared between the two groups.

Results: The native thiol (451.03 mmol/L vs. 407.03mmol/L, p=0.005) and total thiol (493.20 mmol/L vs. 456.40 mmol/L, p=0.027) levels were significantly higher in the HP (+) group than in the HP (-) group. The disulfide levels and disulfide/native thiol, disulfide/total thiol and native thiol/total thiol ratios were similar between the HP (+) and HP (-) groups. Although the FRAP was lower in the HP (+) group than in the HP (-) group, this difference was not statistically significant (0.94 mmol/L vs. 1.10 mmol/L). No statistically significant difference was found between the groups in the IMA and MDA levels..

Conclusion: In this study, oxidative status of HP patients was evaluated in several different methods. Among them, only elevated native thiol and total thiol levels were found in HP-induced gastritis. There is a need for further studies involving a larger number of patients and a subgroup analysis to examine whether elevated serum thiol-disulfide levels in HP infection suggest an antioxidant or pro-oxidant status.

Key words: Helicobacter pylori, homeostasis, thiol, disulfide, oxidative stress

Öz

Amaç: Helicobacter pylori (HP) enfeksiyonu, hücresel düzeyde inflamasyona ve oksidatif strese neden olur. Bu çalışmada, oksidatif stresin bir göstergesi olan tiyol-disülfid homeostazı (TDH) ve HP arasındaki olası ilişkiyi değerlendirmeyi amaçladık.

Yöntemler: Dispepsi yakınması ile başvuran ve gastroskopi uygulanan toplam 53 hastanın tıbbi verileri prospektif olarak değerlendirildi. Hastalar gastrik biyopsi sonucuna göre HP-pozitif (+) ve HP-negatif (-) olarak iki gruba ayrıldı. Hastaların demografik verileri, plazma ferik indirgeme kabiliyeti (FRAP), iskemi modifiye albümin (IMA), native tiyol, total tiyol, disülfid ve malondialdehit (MDA) düzeyleri kaydedildi ve iki grup arasında karşılaştırıldı.

Bulgular: Doğal tiyol (451,03 mmol/L ve 407.03 mmol/L, p=0.005) ve toplam tiyol (493.20 mmol/L ve 456.40 mmol/L, p=0,027) seviyeleri HP (+) grubunda HP (-) grubuna göre anlamlı olarak daha yüksekti. Disülfid düzeyleri ve disülfid / native thiol, disülfid/total tiyol ve native tiyol / total tiyol oranları HP (+) ve HP (-) grupları arasında benzerdi. FRAP, HP (+) grubunda HP (-) grubuna göre daha düşük olmasına rağmen, bu fark istatistiksel olarak anlamlı değildi (0,94 mmol/L ve 1,10 mmol/L). IMA ve MDA düzeylerinde gruplar arasında istatistiksel olarak anlamlı bir fark saptanmadı.

Sonuç: HP kaynaklı gastrit gibi oksidatif stresin arttığı koşullar altında serum tiyol-disülfid düzeylerinin yükselmesi görülebilir. HP enfeksiyonunda yüksek serum tiyol-disülfid düzeylerinin antioksidan veya pro-oksidan durumu gösterip göstermediğini incelemek için daha fazla sayıda hasta ve alt grup analizi içeren çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Helicobacter pylori, homeostaz, tiyol, disülfid, oksidatif stres

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Introduction

Helicobacter Pylori (HP) is a spiral gram-negative, microaerophilic bacterium, highly adapted, that selectively colonizes the human stomach [1]. It is transmitted by fecal-oral, gastro-oral and oral-oral routes, assuming that the infection is mainly in childhood. According to statistics, it affects around 3-4 billion people worldwide, with the rate of infection in developing countries very high, reaching up to 80% [2]. During the host colonization process, HP induces a strong inflammatory response, characterized histologically by superficial epithelial degeneration and infiltration of the gastric mucosa by inflammatory cells [3].

HP results in reactive oxygen species (ROS) and reactive nitrogen species (RNS) production from the gastric mucosa. Low and moderate amounts of ROS have a beneficial effect on several physiological processes including the killing of invading pathogens, wound healing and tissue regeneration processes [4]. Although immune system is capable of creating an immune response to the infection, it usually fails to clear HP. The inability of the host to clear HP results in a chronic inflammation with continued oxidative stress within the gastric tissue. Determination of oxidative stress in gastric inflammation may be necessary for a better understanding of its pathophysiology [5].

Oxidative stress plays an important role in the pathogenesis of inflammation, the level of which is measured based on such parameters as FRAP, IMA, MDA, and thiol-disulfide

[6-9]. Moreover, a relationship between oxidative stress and the development of HP infection has been demonstrated in many studies [5, 10-12]. Elevated serum thiol-disulfide levels can be seen under conditions with increased oxidative stress such as HP-induced gastritis. In the present study, we aimed to evaluate the possible relationship between HP and thiol-disulfide homeostasis, a novel indicator of oxidative stress.

Material and methods

Medical data of a total of 53 patients who were admitted to hospital between April 2018 and June 2018 with persistent dyspepsia, and had undergone gastroscopy, were evaluated prospectively. Detailed information about the procedure and study was supplied to all patients and written informed consent was obtained. The study protocol was approved by the local Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the hospital's ethical committee (2011-KAEK-25 2018/06-06).

Inclusion and Exclusion Criteria

This study included 53 literate patients with chronic dyspeptic complaints (lasting more than three months), aged between 18 and 70 years, who agreed to participate in the study. Patients with varicose, inflammatory or active ulcerous lesions in the upper gastrointestinal tract that could cause hemorrhage and those with a previous history of gastric surgery were excluded.

Interventions

Gastroscopic interventions were performed under sedation by a single endoscopist in the endoscopy unit. A biopsy was obtained from four different quadrants in the antral mucosa. difference between the groups (p=0.388). FRAP was also lower in the HP (+) group, although the difference between the two groups was not statistically significant (p=0.059). The mean A 5-mL blood sample was withdrawn into two separate tubes before the gastroscopic intervention, and the samples were centrifuged at 4,000 rpm for 10 min. The sera were stored in the Eppendorf tubes at -80°C.

After the measurement of weight and height according to the standard protocol, body mass index (BMI) was calculated using the following formula: BMI (kg/m^2) = weight (kg) / height^2 (m^2). Blood pressure measurements were performed at the out-patient clinics of the general surgery department according to the standard protocol.

Grouping

The patients were divided into two groups, as 27 patients with HP infection (HP-positive) or 26 patients without HP infection (HP-negative), based on the results of a pathological examination of gastric biopsies. Participants who never smoked were recorded as smoking (-) patients and active smokers were the smoking (+) group.

Outcomes

Demographic data, the ferric reducing ability of plasma (FRAP), ischemia-modified albumin (IMA), native thiol, total thiol, disulfide, and malondialdehyde (MDA) levels of all patients were recorded. IMA levels were analyzed spectrophotometrically according to the method described by Bar Or et al. [10]. Serum TDH was analyzed by a novel automated method [13]. Total antioxidant capacity (TAC) was measured with the FRAP method which measures all available antioxidants aside from thiols [7].

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 software (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to evaluate whether the variables were normally distributed. The data were expressed in mean ± standard deviation (SD) or median (min-max) and number and frequency. Based on the results of the normality test, either an independent samples t-test or Mann-Whitney U-test was used to compare the groups. The categorical variables were compared using a chi-square test. A binary logistic regression analysis was carried out to examine the independent risk factors affecting the occurrence of HP. A p value of <0.05 was considered statistically significant.

Results

Of the study patients, 28.3% were males and 71.7% were females with a mean age of 46.28 ± 9.57 years and a mean body mass index of (BMI) of 28.03±5.6 kg/m^2. Comparisons of HP groups with baseline demographic and clinical characteristics of patients are shown in Table 1. There was no significant difference between the two groups in terms of age, sex, BMI, systolic and diastolic blood pressure, and smoking status.

The laboratory data of the patients in the HP groups are presented in Table 2. The native thiol and total thiol levels were significantly higher in the HP (+) group than in the HP (-) group (p=0.005 and p=0.027, respectively) (Table2 and Figure 1 and Figure2).

There was no significant difference between the groups in terms of the disulfide levels, disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol ratios. The mean IMA value was 0.81-absorbance unit (au) in the HP (+) group and 0.84 au in the HP (-) group, indicating no statistically significant

MDA level was 3.9 mol/L in the HP (+) group and a slightly lower 3.8 mol/L in the HP (-) group, although not statistically significant.

Table 1: Comparisons of general characteristics in Helicobacter Pylori groups.

Variable	HP (+)	HP (-)	p
Age (years) †	43.85±8.80	48.81±9.85	0.059
Sex (F/M) ‡	20 (74.1)/7(25.9)	18 (69.2)/8(30.8)	0.696
BMI (kg/m^2) ¶	27.34 (19.53-46.07)	26.72 (17.58-52.79)	0.838
Systolic BP (mmHg) ¶	126.50 (102-210)	138 (110-187)	0.332
Diastolic BP (mmHg) ¶	82.50 (65-122)	86 (70-137)	0.248
Smokers ‡	4 (14.8)	7 (26.9)	0.277

†: mean ± standard deviation, ‡: n (%), ¶: median (min-max).
HP: Helicobacter pylori; BMI: body mass index, BP: blood pressure.

Table 2. Comparisons of the laboratory results in Helicobacter Pylori groups.

Variable	HP (+) (n=27)	HP (-) (n=26)	P
Albumin (g/dL) ¶	4.30 (2.80-5.20)	4.10 (1.70-5.30)	0.161
IMA (AU) ¶	0.81 (0-0.97)	0.84 (0.61-0.96)	0.388
IMA/Albumin ¶	0.19 (0-0.32)	0.20 (0.11-0.53)	0.168
Native thiol (mmol/lt) †	451.03±55.95	407.03±52.19	0.005
Total thiol (mmol/lt) ¶	493.20 (411.80-675.20)	456.40 (344.90-548)	0.027
Disulfide (mmol/lt) ¶	21.95 (5.30-37.25)	22.63 (14.40-41.25)	0.612
SS/native thiol (%) ¶	4.95 (0.90-7.33)	5.59 (3.45-10.72)	0.068
SS/total thiol(%) ¶	4.50 (0.90-7.33)	5.03 (3.23-8.83)	0.070
Native/total thiol (%) ¶	90.99 (85.35-98.21)	89.95 (82.34-93.54)	0.070
FRAP (µmol/L) ¶	0.94 (0.64-2.07)	1.10 (0.61-1.87)	0.059
Malondialdehyde (µmol/L) †	3.9±1.0	3.8±1.0	0.610

†: mean ± standard deviation, ¶: median (min-max).
HP: Helicobacter pylori, IMA: ischemia-modified albumin, FRAP: ferric reducing ability of plasma, AU: absorbance unit, SS: disulfide.

Discussion

In this study, the possible relationship between HP and thiol-disulfide homeostasis was evaluated. The native thiol and total thiol levels were significantly higher in the HP (+) group than in the HP (-) group. No significant differences between the groups were observed in FRAP, IMA, MDA and disulphide levels. The FRAP levels was lower in the HP (+) group, but the difference between the two groups was not statistically significant.

A study conducted in humans showed higher MDA levels in the gastric mucosa of HP-infected patients, compared to healthy tissues, and that MDA levels returned to normal after HP eradication [8]. Remarkably increased serum MDA, catalase, and superoxide dismutase levels were demonstrated in patients with HP infection [14], although, in the present study, we found no statistically significant difference between the MDA levels of the two groups. IMA increases in oxidative stress conditions associated with ischemia and is considered a biomarker of oxidative stress, which is, in turn, associated with chronic kidney disease, hypercholesterolemia, and type2 diabetes mellitus [15-17]. In the present study, we found no statistically significant difference in IMA and albumin levels or IMA/albumin ratios.

FRAP is one of the most widely used technique for the measurement of total antioxidant capacity [7]. Several studies have reported total oxidant status, total antioxidant capacity, and oxidative stress index to be significantly higher in HP-infected patients than in non-HP infected patients [18]. However, in our study, we found no statistically significant difference between the FRAP levels of the two groups.

Interestingly, contrary to expectations, a comparison of the native thiol and total thiol parameters of the HP (+) and HP (-) groups revealed significantly higher levels in the HP (+) group in our study. Thiols are considered to be the main antioxidant buffer, and play an important role in protecting against the detrimental effects of ROS [19]. Proteins containing thiol groups act as an antioxidant buffer, but are also involved in the regulation of the redox system [20]. Thiols are both antioxidant and pro-oxidant molecules, and although thiols are mostly considered antioxidant molecules, they may act as pro-oxidant molecules, depending on the physical status of the organism [21, 22]. The level of oxidative stress in an organism is the determinant of the behavior of thiols, and this is maintained with a dynamic balance in the body. Naja et al. has found no significant difference in the plasma thiol level in HP infected patients compared with controls [23]. Baykan et al. reported that there was no difference between the total thiol, native thiol, disulphide/native thiol and dissulphide/total thiol ratios of the HP (+) patients and control group [24]. They claimed severity of inflammation affected their results. In the present study, disulfide levels, disulfide/native thiol ratio, and disulfide/total thiol ratio were found to be similar between the two groups, suggesting that TDH is not impaired in the HP (+) group.

Nonetheless, there are some limitations to the present study. First, our sample size was relatively small. Second, it was conducted in a single center. Therefore, the results cannot be generalized to other populations or settings. Smokers are another limitation of the study since smoking may interfere with the results. We recommend further large-scale, multi-center, prospective studies to establish a definitive conclusion.

In conclusion, we evaluated oxidative status of HP patients in several different methods. Among them, only elevated native thiol and total thiol levels were found in HP-induced gastritis. There is a need for further studies involving a larger number of patients and a subgroup analysis to examine whether elevated serum thiol-disulfide levels in HP infection suggest an antioxidant or pro-oxidant status.

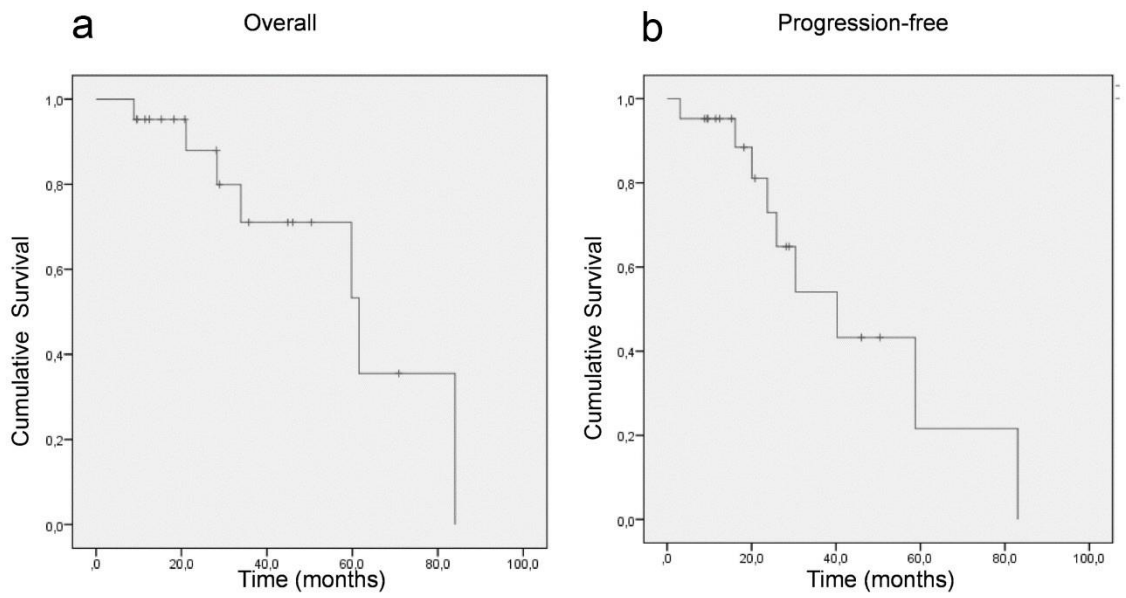

Figure1. Relationship between native thiol (mmol/lt) and Helicobacter pylori.
HP: Helicobacter pylori.

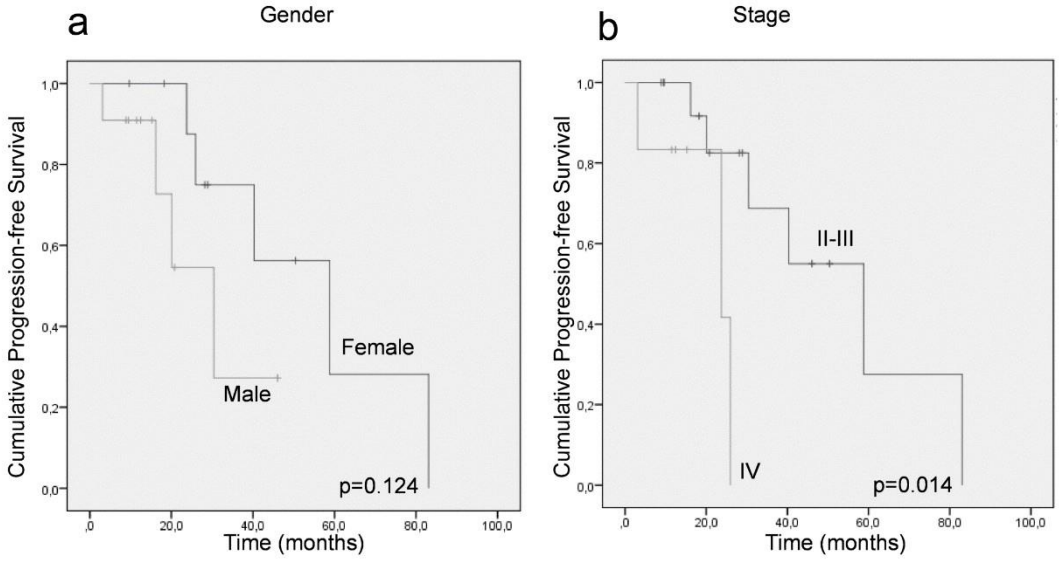

Figure2. Relationship between total thiol (mmol/lt) and Helicobacter pylori.
HP: Helicobacter pylori.

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The clinical significance of preoperative neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in patients with gastric or colorectal cancer

Mide ve kolorektal kanserli hastalarda preoperatif nötrofil/lenfosit ve trombosit / lenfosit oranlarının klinik önemi

Berrin Papila Kundaktepe [1]

Abstract

Aim: Gastrointestinal-related cancers, gastric cancer (GC) and colorectal cancer (CRC), have become major public health problems. Preoperative evaluation in such cases is very important to determine initial treatment strategies. This study was conducted to evaluate the possible clinical significance of the preoperative neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in patients with GC or CRC.
Methods: This retrospective study included 50 consecutive patients with GC, 50 consecutive patients with CRC, and 60 consecutive age-matched healthy subjects (control group). Routine preoperative blood examination results detailing neutrophil, platelet, and lymphocyte counts were obtained from the patients' medical records.
Results: NLR and PLR values were significantly higher in both GC and CRC patients compared to the control group (both $p<0.001$). PLR values were also significantly higher in CRC patients compared to GC patients ($p<0.01$). NLR and PLR levels were significantly higher in both GC and CRC stage 4 patients compared to stage 3 patients (both $p<0.001$). The NLR was negatively related to lymphocyte count but positively related to neutrophil count, platelets, and PLR in both GC and CRC patients.
Conclusion: NLR and PLR may be significant predictive biomarkers in GC and CRC. As such, the NLR and PLR can be used as simple, feasible, inexpensive, and useful parameters to predict clinical significance in patients with GC and CRC. These promising results should be validated in further large-scale clinical studies.

Key words: Gastric cancer, colorectal cancer, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio

Öz

Amaç: Gastrik kanser (GK) ve kolorektal kanser (KRK) gibi gastrointestinal ilişkili kanserler, önemli bir halk sağlığı problemi haline gelmiştir ve preoperatif değerlendirme, ilk tedavi stratejilerinin belirlenmesinde oldukça önemlidir. Bu çalışma, GK ve KRK hastalarında preoperatif nötrofil-lenfosit oranı (NLO) ve trombosit-lenfosit oranı (TLO)'nın olası prognostik değerini değerlendirmek için yapıldı.
Yöntemler: Bu retrospektif çalışmaya 50 GK, 50 ardışık KRK hastasını ve yaşları eşleştirilmiş 60 ardışık sağlıklı kişi (kontrol grubu) alındı. Preoperatif tam kan sayımı sonuçları (nötrofiller, trombositler ve lenfositler) hastanın tıbbi kayıtlarından alındı. Bulgular: NLO ve TLO değerleri hem GK hem de KRK hastalarında kontrol grubuna göre anlamlı olarak yüksek bulundu (her ikisi de $p <0.001$). KRK hastalarında TLO değerleri GK hastalarına göre anlamlı derecede yüksek bulundu ($p <0.01$). NLO ve TLO değerleri hem GK hem de KRK hastalarında kontrol grubuna göre anlamlı olarak yüksek bulundu (her ikisi de $p <0.001$). NLO ve TLO değerleri hem gastrik hem de kolorektal kanserin evre 4 hastalarında evre 3 hastalara göre anlamlı derecede yüksek bulundu (her ikisi de $p <0.001$). Hem GK hem de KRK hastalarında NLO, lenfosit sayısıyla negatif olarak ilişkiliyken, nötrofil sayısı, trombosit ve TLO ile pozitif olarak ilişkiliydi.
Sonuç: GC ve CRC'de, NLO ve TLO, önemli bir öngörücü biyobelirteç olabilir. NLO ve TLO değerlerinin, GK ve KRK hastalarında klinik önemi tahmin etmek için basit, uygulanabilir, ucuz ve kullanışlı parametreler olarak kullanılabileceği sonucuna varıldı. Sonuçlar klinik uygulamada daha geniş çaplı çalışmalarda doğrulanmalıdır.

Anahtar Kelimeler: Mide kanseri, kolorektal kanser, nötrofil-lenfosit oranı, trombosit-lenfosit oranı.

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Introduction

Cancer is a public health problem in our country as well as worldwide. Gastric cancer (GC) and colorectal cancer (CRC) are the most common cancers of the gastrointestinal system. Early diagnosis of GC and CRC is of great importance as it enables the provision of more effective treatments and reduced mortality and morbidity. Early diagnosis can be achieved with various screening and laboratory methods. A variety of biochemical biomarkers have been adopted for risk stratification of patients and prediction of survival outcomes [1].

Complete blood count (CBC) parameters are used as diagnostic biomarkers for many diseases associated with inflammatory processes. Abnormalities in peripheral blood cells such as neutrophilia, lymphopenia, and thrombocytosis, have been identified as responses to systemic inflammation [2,3]. Accumulating evidence indicates that inflammation is related to tumor development and progression [4]. Hematological parameters related to neutrophils, such as lymphocyte counts known to be important in the inflammatory process, are recommended as prognostic factors in several cancer types [5-9]. The relationships between cancer prognosis and hematologic parameters such as neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) have been studied in many cancers [10-13]. Various studies have demonstrated the prognostic significance of NLR, including evaluations in early-stage colon cancer, stage III colon cancer, and thrombocytosis in patients with GC. While PLR and NLR have been evaluated for early diagnosis and prognostic prediction in patients with resectable GC, limited information related to cross-comparisons of several easily accessible parameters is available for patients with GC and CRC [13-19].

Data regarding NLR, PLR, and their association with GC, CRC, and healthy people are lacking. Hence, the purpose of this study was to evaluate the possible clinical significance of preoperative NLR and PLR in patients with GC and CRC.

Material and methods

This study was approved by the ethics committee and conducted according to the principles described in the Declaration of Helsinki. Written informed consent was obtained from each subject after they were informed as to the purpose of the study.

Study design and patient selection

This was a retrospective case-control study conducted in the Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Department of General Surgery and Department of Medical Oncology. A total of 50 consecutive patients with GC, 50 consecutive patients with CRC, and 60 consecutive age-matched healthy subjects (control group) were enrolled in this study.

The patients' age, sex, medical history, and routine preoperative blood examination, detailing neutrophil, platelet, and lymphocyte counts, were obtained from the medical records. Postoperative histopathological reports regarding tumor, lymph node involvement, and metastasis (tumor-node-metastasis (TNM) staging) were also recorded from the records. Inclusion criteria were as follows: biopsy-proven rectal cancer and measurable disease as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Patients with incomplete follow-up data or active concurrent infections were excluded. Patients with a concomitant disease other than GC or CRC, a hematologic disease, or a history of blood transfusion were also excluded from the study. Healthy control subjects (n=60) had no demonstrated cancer, endocrine, cardiovascular, or inflammatory diseases.

Hematological analysis

Blood samples obtained before surgery were collected into standardized tubes containing ethylenediaminetetraacetic acid (EDTA) for CBC. Neutrophil (× 109/L), lymphocyte (× 109/L), and platelet (× 103/μL) counts obtained using an automatic hematology analyzer (Beckman Coulter, Brea, CA, USA) were transcribed from the patients' medical records.

Statistical analyses

The software program SPSS (Statistical Package for Social Sciences) 20.0 for Windows was used for statistical evaluations. Descriptive statistics were obtained and data were tested for normality using the Kolmogorov-Smirnov test for Gaussian distribution. For comparison of parameters with normal distribution, parametric tests were used and for comparison of parameters with abnormal distribution, non-parametric tests were used. One-way ANOVA, unpaired Student's-t test, Kruskal-Wallis, and Mann-Whitney U tests were used. Relationships between variables were assessed with Pearson's correlation coefficient. A p-value ≤ 0.05 was considered statistically significant.

Results

The demographic and hematologic parameters of the groups are shown in Table 1. There was no statistically significant difference between groups in terms of age and gender ($p > 0.05$). Neutrophil count and NLR were found to be significantly higher in patients with GC and CRC compared to the control group ($p<0.001$), while lymphocyte count was found to be significantly lower in patients with GC and CRC compared to the control group ($p<0.05$ and $p<0.001$, respectively). NLR and PLR were found to be significantly higher in patients with CRC compared to patients with GC (both $p<0.01$). There was no statistically significant difference between patients with GC and CRC with regard to neutrophil and lymphocyte counts. Platelet count and PLR were found to be significantly higher in patients with GC and CRC compared to the control group (both $p<0.001$). There was no statistically significant difference between patients with GC and CRC with regard to platelet count.

Table 1. Demographic and hematologic parameters.

	Control group (n=60)	Gastric cancer (n=50)	Colorectal cancer (n=50)
Age (years)	57.30± 5.18	58.62± 5.51	58.96± 5.36
Gender (F/M)	30/30	20/30	20/30
Neutrophil count ($\times 10^9$/L)	1.48±0.59	3.49±2.22[c]	5.01±3.26[c]
Lymphocyte count ($\times 10^9$/L)	3.02±0.73	2.42±1.32[a]	1.92±1.23[c]
NLR	1.48±0.59	3.49±2.22[c]	5.01±3.26[c,e]
Platelet count ($\times 10^3$/μL)	201.58±53.61	299.30±87.80[c]	311.08±99.61[c]
PLR	71.80±29.01	178.48±127.13[c]	257.92±172.00[c,e]

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio
Comparison with control group [a]p<0.05, [b]p<0.01, [c]p<0.001
Comparison with Gastric Cancer group [d]p<0.05, [e]p<0.01, [f]p<0.001

Neutrophil, platelet, and lymphocyte ratios according to the stage of GC and CRC are shown in Tables 2 and 3. Neutrophil count, NLR, platelet count, and PLR were found to be significantly higher in patients with stage IV cancer compared to stage III (all p<0.001), while lymphocyte counts were found to be significantly lower in patients with stage IV compared to stage III for both types of cancer (p<0.001).

Table 2. Neutrophil, platelet, and lymphocyte ratios according to gastric cancer stages.

	Stage III (n=20)	Stage IV (n=30)	p
Neutrophil count (× 10^9/L)	4.84±1.70	6.82±1.13	<0.001
Lymphocyte count (×10^9/L)	3.65±0.98	1.60±0.78	<0.001
NLR	1.45±0.63	4.85±1.82	<0.001
Platelet count (×10^3/μL)	237.75±86.91	340.33±61.00	<0.001
PLR	70.88±30.96	250.22±115.64	<0.001

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

Table 3. Neutrophil, platelet, and lymphocyte ratios according to colorectal cancer stages.

	Stage III (n=20)	Stage IV (n=30)	p
Neutrophil count (× 10^9/L)	5.32±1.24	6.77±1.13	<0.001
Lymphocyte count (× 10^9/L)	3.02±1.13	1.20±0.62	<0.001
NLR	2.52±2.57	6.61±2.59	<0.001
Platelet count (×10^3/μL)	229.75±77.30	363.55±74.14	<0.001
PLR	112.00±114.55	352.06±132.83	<0.001

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

The relationships of hematological parameters in patients with GC and CRC are shown in Tables 4 and 5. There were significant positive correlations between NLR, neutrophil count, platelet count, and PLR, but a significant negative correlation with lymphocyte count in both types of cancer.

Table 4. Correlations of hematological parameters in gastric cancer.

		Lymphocyte count (× 10^9/L)	NLR	Platelet count (×10^3/μL)	PLR
Neutrophil count (× 10^9/L)	r	-0.369	0.541	0.533	0.353
	p	0.008	<0.001	<0.001	0.012
Lymphocyte count (× 10^9/L)	r	-	-0.837	-0.447	-0.803
	p	-	<0.001	<0.001	<0.001
NLR	r	-0.837	-	0.554	0.939
	p	<0.001	-	<0.001	<0.001
Platelet count (×10^3/μL)	r	-0.447	0.554	-	0.650
	p	0.001	<0.001	-	<0.001

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

Table 5. Correlation of hematological parameters in colorectal cancer.

		Lymphocyte count (× 10^9/L)	NLR	Platelet count (×10^3/μL)	PLR
Neutrophil count (× 10^9/L)	r	-0.622	0.719	0.521	0.542
	p	<0.001	<0.001	<0.001	<0.001
Lymphocyte count (× 10^9/L)	r	-	-0.861	-0.690	-0.880
	p	-	<0.001	<0.001	<0.001
NLR	r	-0.861	-	0.524	0.889
	p	<0.001	-	<0.001	<0.001
Platelet count (×10^3/μL)	r	-0.690	0.524	-	0.769
	p	<0.001	<0.001	-	<0.001

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

Discussion

This study investigated the possible clinical significance of preoperative NLR and PLR values in patients with GC and CRC. NLR and PLR values increased in patients with GC and CRC. Our analysis suggests that NLR and PLR could be used as simple, feasible, inexpensive, and useful parameters to predict clinical significance in patients with GC and CRC. Systemic inflammation can be measured through inflammatory markers such as the NLR and PLR in patients with GC and CRC.

NLR has been reported as a simple marker of the systemic inflammatory response in GC and CRC patients [14-17]. Inflammation is a critical component of tumor progression. A systematic review and meta-analysis focused on high levels of inflammatory markers indicated that NLR appeared to be associated with worse overall survival (OS) for those with solid tumors. Evaluation of the NLR is a cost-effective method that is widely available in preoperative settings. Furthermore, it can effectively predict clinical significance, as high values of this biomarker are related to more aggressive tumor characteristics. This ratio can also be used for risk stratification in patients within the same disease stage and may be used to assist in planning individualized follow-up and treatment [18].

Lian et al. [19] investigated the application value of systemic inflammatory response markers PLR and NLR in early diagnosis and prognostic prediction in patients with resectable GC. Preoperative PLR and NLR levels were significantly higher in GC patients compared to healthy subjects. Low preoperative PLR and NLR levels correlated with better clinicopathological features, including decreased depth of invasion, less lymph node metastasis, and early tumor stage. Kaplan-Meier plots illustrated that patients with higher preoperative NLR and PLR had decreased OS and disease-free survival. Thus, PLR and NLR measurements can provide important diagnostic and prognostic results in patients with resectable GC.

In the current study, neutrophil count, NLR, and PLR were found to be significantly higher in patients with GC when compared to the control group. NLR and PLR were found to be significantly higher in patients with stage IV cancer compared to those with stage III, while lymphocyte counts were found to be

significantly lower in patients with stage IV compared to stage III in both types of cancer. As in our study, others have shown that a high NLR is clinically significant in GC patients [20-22]. Mellor et al. [23] showed that NLR is an important prognostic indicator associated with both OS and disease-free survival after R0 resection of GC, but the critical level is confusing. Similarly, an increased NLR was associated with tumor aggressiveness in patients with CRC [24–27]. Zhou et al. [24] indicated that these measurements may be used as a cost-effective way to evaluate the systemic inflammatory response. NLR may provide available information in the differential diagnosis of CRC, adenomatous polyps, and healthy people. Palin et al. [25] reported that preoperative NLR is an inexpensive, easily performed, and useful clinical tool to aid in the prediction of outcome in emergency CRC patients. Silva et al. [26] evaluated the prognostic value of nutritional status and NLR in CRC patients and determined that NLR, weight loss, and body mass index assessments are promising prognostic indicators of CRC. Eto et al. [27] reported that preoperative NLR appears to be a useful predictor of bowel obstruction as a result of CRC growth.

Similarly, recent studies have shown that elevated PLR predicted poor prognoses and clinicopathological characteristics in CRC and that PLR is a convenient and low-cost blood-derived prognostic marker for CRC [28, 29]. However, the clinical significance of PLR in CRC is controversial and has not been confirmed [30-34]. Azab et al. [35] evaluated patients with stages I-IV categorized into an equal tertile based on PLR, and results showed that PLR was significantly related to tumor stage. Other researchers have shown a significant association between PLR and tumor stage and pT category [36, 37]. Emir et al. [38] showed that there was no significance of NLR between those with neoplastic colorectal polyps and healthy individuals. Further studies are needed to assess the clinical significance of PLR in CRC using optimal multivariable analysis or adjustment [39].

We found that a high PLR was more important in GC risk increase and a high NLR was more important in CRC risk increase. We also found that high NLR and PLR together increased the risk of both GC (12.86 fold) and CRC (14.23 fold). The fact that the risk increases significantly shows that NLR and PLR can be used as evaluation criteria by being included in routine tests. Systemic and local immune response indexes allow stratification of patients in different OS and recurrence-free survival risk groups.

This study has some limitations. First, the study population is relatively small. Second, this study is retrospective in design, thus some important clinical features could not be recorded. Third, since there were no survival data included in the study, we could not use prognostic values.

The results of the study suggest that lymphocyte count was decreased, and neutrophil count, NLR, and PLR were elevated in patients with GC and CRC. Platelets play an important role in inflammatory conditions related to cancer. Chronic inflammation is also known to induce platelet activation. Platelet function may be modified by the systemic inflammation associated with GC and CRC. A low lymphocyte count can be used as a negative acute phase reactant in the evaluation of cancer. NLR and PLR may be significant predictive biomarkers in GC and CRC.

In conclusion, NLR and PLR could be used as simple, feasible, inexpensive, and useful parameters to predict clinical significance in patients with GC and CRC. These results should be validated in further large-scale studies in clinical practice.

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Impact of status of ER, PR, HER2 and Ki-67 index on axillary lymph node metastasis of breast cancer

Meme kanserinin aksiller metastazlarında ER, PR, HER2 ve Ki-67 indeksinin etkisi

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Abstract

Aim: Axillary status evaluation and, if present, the number of metastatic lymph nodes is important in staging and adjuvant therapy planning of breast cancer. A number of clinical and pathological variables were analyzed to detect factors affecting nodal status.
Methods: A total of 298 women with unilateral breast cancer operated with axillary lymph node dissection or sentinel lymph node biopsy, were retrospectively analyzed for age, localization, BIRADS category, pathological features, subtypes as Luminal A, Luminal B, HER2 positive, triple negative, Ki-67 index and number of lymph nodes involved.
Results: The mean age was 54.7 years. BIRADS 5 was the most detected category in 208 (69.8%) patients. The most common pathological type was invasive ductal carcinoma in 265 patients (88.9%). The most detected tumor grade was grade 2 in 160 (31.2%). Luminal B was the most common subtype and detected in 173 patients (58.1%). Ki-67 indexes were detected between 0-14% in 69 patients (23.3%), between 15-19% in 31patients (10.4%) and above 20% in 198 patients (66.4%).
Conclusions: HER2 positivity, Ki-67 index, and progesterone receptor negativity are the most significant factors affecting axillary lymph node metastasis.

Key Words: Breast cancer, axillary lymph node metastasis, hormonal status.

Öz

Amaç: Aksiller lenf nodu metastazı değerlendirmesi ve varsa lenf nodu sayısı meme kanserinin evrelemesi ve adjuvan tedavi planlamasında önemlidir. Amacımız lenf nodu metastazını etkileyen faktörleri saptamak için bir dizi klinik ve patolojik değişkeni araştırmaktır.
Yöntemler: Aksiller lenf nodu diseksiyonu veya sentinel lenf nodu biyopsisi ile opere edilen tek taraflı meme kanseri olan 298 kadın hastanın yaş, lokalizasyon, BIRADS kategorisi, patolojik özellikler, Luminal A, Luminal B, HER2 pozitif, tripl negatif subtipleri, Ki-67 indeksi verileri ile metastatik lenf nodu sayısı arasındaki ilişkisi analiz edildi.
Bulgular: Yaş ortalaması 54,7 yıl idi. BIRADS 5, 208 (% 69,8) hastada en fazla saptanan kategori idi. En sık görülen patolojik tip 265 hastada (% 88,9) invaziv duktal karsinomdu. En fazla saptanan tümör evresi 2 olup, 160 hastada (% 31,2) tespit edildi. Luminal B en sık görülen subtipti ve 173 (% 58,1) hastada tespit edildi. Ki-67 indeksi 69 hastada (% 23,3) % 0-14, 31 hastada (% 10,4) % 15-19 ve 198 hastada (% 66,4) % 20'nin üzerinde saptandı.
Sonuçlar: HER2 pozitifliği, Ki-67 indeksi ve progesteron reseptör negatifliği aksiller lenf nodu metastazını etkileyen en önemli faktörlerdir.

Anahtar Kelimeler: Meme kanseri; aksiller lenf nodu metastazı; hormonal durum

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Introduction

Breast cancer (BC) is one of the most common cancers in women and its incidence increases every year. The prognosis and life expectancy is closely related to axillary lymph node metastasis (ALM) and the number of metastatic lymph nodes. Axillary status is also important in staging and for planning postoperative chemoradiotherapy. Therefore, every effort should be done for accurate assessment of the axilla [1].

Hormonal receptor status of the tumor as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and Ki-67 proliferation index are important for ALM, subtyping and choice of treatment modality [1,2]. Other prognostic factors, also for ALM, are age, tumor subtypes as Luminal A (LA), Luminal B (LB), HER2 positive, and Triple negative (TN) according to St. Gallen Consensus 2013 [1, 3], histological and nuclear grade, tumor size, multifocality, lymphovascular invasion and the stage of the tumor [4,5].

The aim of this study is to find out the factors affecting the number of ALM in our series.

Material and methods

Our study was approved by the Haseki Research and Training Hospital Ethical Committee on October 10th, 2017/555 with full compliance to Helsinki declaration, as revised by 2000. Informed consent was obtained on the first day of hospitalization from all individual participants included in the study.

Age, localization, and BIRADS category reports were recorded. The axillary status evaluation was made by mammography, ultrasonography and, if needed, by other imaging modalities. A detailed pathological examination was made on the terms of type, tumor diameter, histological grade, lymphatic invasion, perineural invasion, number of metastatic lymph nodes (1-3, 4-9, >10), hormonal status as ER, PR, HER2, Ki-67 index analysis (in the range of 0-14, 15-19, >20 as percentages) and subtypes LA, LB, HER2 positive, TN.

Two hundred and ninety-eight BC cases operated with axillary lymph node dissection or sentinel lymph node biopsy (SLNB) between March 1st, 2009 and March 1st, 2017 were retrospectively analyzed. For the scope of this study, 298 BC patients met the inclusion criteria. The patients with male gender, bilateral BC, having other cancers previously or at the time of BC diagnosed, and the patients taking neoadjuvant chemotherapy were excluded.

All patients underwent local excision of the tumor or mastectomy according to tumor/breast ratio for better cosmetic results. Axillary lymph node dissection was done directly in patients with positive lymph nodes on imaging. SLNB was done in other patients. At least 3 lymph nodes were excised. If positive, they also underwent axillary dissection. If negative, they were accepted as ALM negative.

Outcomes were searched whether variables/parameters affect ALM and number of lymph nodes or not.

Statistical analysis

SPSS 15.0 (SPSS Inc. Chicago, USA) program for Windows was used for statistical analysis. Descriptive statistics, number and percentage for categorical variables, means, standard deviation, minimum, maximum for quantitative variables were given. To compare the rates in independent groups, the Chi-square test was used. Relations between ratios in groups were studied by linear-by-linear association. The relations of ordinal variables were analyzed by Spearman's correlation analysis. A p-value <0.05 was taken to be statistically significant.

Results

The results of demographic, radiologic and pathologic features of the patients are presented in Table 1 and Table 2.

Table 1: Demographic and pathologic features (N=298).

		n	%
Localization	Right	142	47.7
	Left	156	52.3
Type	Invasive ductal carcinoma	265	88.9
	Invasive lobular carcinoma	9	3.0
	Mucinous carcinoma	16	5.4
	Ductal carcinoma in situ (with invasive foci)	5	1.7
	Papillary carcinoma	3	1.0
Subtype	Luminal A	65	21.8
	Luminal B	173	58.1
	HER2 positive	27	9.1
	Triple negative	33	11.1
T stage	T1	92	30.9
	T2	168	56.4
	T3	30	10.1
	T4	8	2.7
Grade	1	45	15.1
	2	160	53.7
	3	93	31.2
BIRADS Category	0	27	9.1
	3	10	3.4
	4	32	10.7
	5	208	69.8
	6	21	7.0

Table 2. Detailed pathological examination.

		n	%
Metastatic lymph node	Negative	141	47.3
	≤3 positive	104	34.9
	4-9 positive	32	10.7
	10 and more	21	7.0
Lymphatic Invasion	Yes	200	67.1
Perineural Invasion	Yes	145	48.7
Estrogen Receptor	Positive	240	80.5
Progesterone Receptor	Positive	229	76.8
HER2	Positive	86	28.9
Ki-67 index (percentage)	0-14	69	23.2
	15-19	31	10.4
	20 and more	198	66.4

Table 3. Correlation of clinical parameters and axillary lymph node metastasis relationship.

		Metastatic lymph node (n(%))				
		Negative	≤3 positive	4-9 positive	>10 positive	p
Localization	Right	62 (44.0)	53 (51.0)	19 (59.4)	8 (38.1)	0.289
	Left	79 (56.0)	51 (49.0)	13 (40.6)	13 (61.9)	
Type	Invasive ductal	126 (89.4)	91 (87.5)	28 (90.3)	20 (95.2)	0.985
	Invasive lobular	4 (2.8)	5 (4.8)	0 (0)	0 (0)	
	Mucinous	8 (5.7)	5 (4.8)	2 (6.5)	1 (4.8)	
	Ductal Carcinoma in Situ (with invasive foci)	2 (1.4)	2 (1.9)	1 (3.2)	0 (0)	
	Papillary	1 (0.7)	1 (1.0)	1 (0.03)	0 (0)	
Subtype	Luminal A	35 (24.8)	20 (19.2)	6 (18.8)	4 (19.0)	0.062
	Luminal B	81 (57.4)	58 (55.8)	24 (75.0)	10 (47.6)	
	HER2 Positive	12 (8.5)	8 (7.7)	2 (6.3)	5 (23.8)	
	Triple Negative	13 (9.2)	18 (17.3)	0 (0)	2 (9.5)	
T stage	T1	55 (39.0)	17 (16.3)	14 (43.8)	6 (28.6)	0.927 *
	T2	67 (47.5)	72 (69.2)	14 (43.8)	15 (71.4)	
	T3	14 (9.9)	12 (11.5)	4 (12.5)	0 (0)	
	T4	5 (3.5)	3 (2.9)	0 (0)	0 (0)	
Grade	1	12 (15.6)	15 (14.4)	8 (25.0)	0 (0)	0.736 *
	2	69 (48.9)	65 (62.5)	15 (46.9)	11 (52.4)	
	3	50 (35.5)	24 (23.1)	9 (28.1)	10 (47.6)	
BIRADS	0	11 (7.8)	10 (9.6)	5 (15.6)	1 (4.8)	0.570 *
	3	5 (3.5)	5 (4.8)	0 (0)	0 (0)	
	4	20 (14.2)	12 (11.5)	0 (0)	0 (0)	
	5	95 (67.4)	73 (70.2)	24 (75.0)	16 (76.2)	
	6	10 (7.1)	4 (3.8)	3 (9.4)	4 (19.0)	

* Linear-by-Linear Association

All of the patients were women with unilateral breast cancer. The mean age was 54.7 ± 12.9 years (range: 27-92). BIRADS 5 category was the most commonly observed category with a rate of 69.8% in 208 patients. Invasive ductal carcinoma was detected in 265 (88.9%). The most common tumor diameter detected was T2 in 168 patients (56.4%).

Mean harvested lymph node number in axillary dissection was 15 (range 13-17). Axillary status was negative in 141 (47.3%) patients and positive in 157 patients (52.7%). Positive metastatic lymph nodes were 3 or less in 104 patients (34.9%), between 4 to 9 in 32 (10.7%) and 10 or more in 21 patients (7.0%). Molecular subtype luminal B had the highest number in 173 patients (58.1%).

The results of statistical analysis between parameters and ALM are shown in Table 3 and 4.

Table 4. Correlation of tumoral parameters and axillary lymph node metastasis.

		Metastatic lymph node (n(%))				
		Negative	<3 positive	4-9 positive	>10 positive	p
Lymphatic invasion	Yes	82 (58.2)	84 (80.8)	22 (68.8)	12 (57.1)	0.243*
	No	59 (41.8)	20 (19.2)	10 (31.3)	9 (42.9)	
Perineural invasion	Yes	59 (41.8)	55 (52.9)	21 (65.6)	10 (47.6)	0.065*
	No	82 (58.2)	49 (47.1)	11 (34.4)	11 (52.4)	
Estrogen receptor	Positive	117 (83.0)	78 (75.0)	32 (100.0)	13 (61.9)	0.419*
	Negative	24 (17.0)	26 (25.0)	0 (0)	8 (38.1)	
Progesterone receptor	Positive	114 (80.9)	80 (76.9)	24 (75.0)	11 (52.4)	0.012*
	Negative	27 (19.1)	24 (23.1)	8 (25.0)	10 (47.6)	
HER 2	Positive	31 (22.0)	23 (22.1)	19 (59.4)	13 (61.9)	<0.001 *
	Negative	110 (78.0)	81 (77.9)	13 (40.6)	8 (38.1)	
Ki-67 index	0-14 %	50 (35.5)	17 (16.3)	2 (6.3)	0 (0)	<0.001 *
	15-19%	22 (15.6)	6 (5.8)	1 (3.1)	2 (9.5)	
	>20 %	69 (48.9)	81 (77.9)	29 (90.6)	19 (90.5)	

* Linear-by-Linear Association

There was no significant difference for the number of ALM affected by tumor type, tumor diameter, histological grade and molecular subtypes (p=0.886, p=0.927, p=0.736 and p=0.062, respectively). The presence of lymphovascular invasion and perineural invasion were detected in 200 (67.1%) and 145 patients (48.7%), respectively. But both were not found to increase significantly ALM (p=0.243 and p=0.065, respectively).

HER2 receptor was positive in 86 patients (28.9%) and negative in 212 (71.1%). Ki-67 proliferation index was found to be in the range of 0-14% in 69 patients, in 31 patients (10.4%) in the range of 15-19% and in 198 patients (66.4%) in the range of >20%. Most of the patients were in the range of >20%. PR was positive in 229 (76.8%) and negative in 69 patients (23.2%). ER positivity was seen in 240 patients (80.5%).

Statistical analyses resulted as HER2 positivity, Ki-67 index and PR negativity increase the number of ALM showing a statistically significant difference (p<0.001, p<0.001 and p=0.012, respectively).

Discussion

In this study, we present an article to find out which factors affect ALM in BC patients in our series. ALM is important for expected survival rate. If predictive variables for axillary involvement are known, the treatment may be more specific and oncologic safety is maintained as well as surgical morbidity. Similar articles in the literature give various factors and their effects.

There was no significant difference for ALM and number of lymph nodes affected among any of the tumor types (p=0.886). The most detected tumor type was invasive ductal carcinoma (89.9%). This result was consistent with some

literatures [3, 6, 7] and inconsistent with some of the literature with the largest population of breast cancer series [1, 8]. 623 and 380 patients were included in these two published studies, respectively, and they found tumor type-histology was significantly related to ALM ($p<0.001$ and $p=0.003$, respectively). Tumor diameter (T1-T4) was not found to have an effect for ALM significantly in our series. In fact, it is logic to think, as the tumor size increases, ALM occurs more, especially with the existence of lymphovascular invasion. So, this result was found in the literature [1, 8, 9]. Lymphovascular invasion was found in 67.1% of the patients in this study, but it was not significant for ALM, whereas it is claimed that lymphovascular invasion is significantly associated with ALM [4]. Grade 2 was the most commonly found histological in our study. But, the grade of the tumor was not correlated with ALM significantly.

Hormonal receptor status and Ki-67 proliferation index are studied for biological behavior of primary tumor [3]. Related to ER, PR, HER2, and Ki-67 index, molecular subtypes LA, LB, HER2 positive, and TN are formed. Most studies demonstrated that ER, PR, HER2, Ki-67 provided independent prognostic information in BC patients [10]. In our study, we didn't find such correlation between subtypes and ALM.

PR, HER2 and Ki-67 are mostly discussed for ALM and choosing treatment modalities. There are disagreements for progesterone receptor status correlation with ALM in the literature. Tan et al. [8] found a correlation between progesterone receptor positivity and lymph node metastases. Also, some other authors [11, 12] claimed this association. Viale et al. [13] demonstrated an inverse relationship, some studies showed no correlation [14]. Progesterone receptor expression negativity significantly affected ALM in our study.

HER2 is related with tumor proliferation and tumor progression. For ALM, its status is controversial. In the study of Emma Aitken et al. [1], no significant association was found for HER2 status with ALM. In our study, HER 2 was positive in 28.9% of the patients and negative in 71.1%. Its expression demonstrated a statistical significance for ALM. HER2 positive BC patients benefit from hormone therapy and/or antiHER2 or other targeted therapy.

The Ki-67 level is important for discrimination of LA and LB. As a prognostic factor, it is routinely studied for BC [5, 14]. Cheang et al. [2] identified that the ideal cut-off value of Ki-67 distinguishing LA and LB subtypes as 14%. It entered clinical use in 2011 St. Gallen International Expert Consensus on the Primary Therapy of Early BC [15]. In the study of Jin et al. [16], they concluded that Topo II α and Ki-67 expression were well correlated with the number of metastatic lymph nodes. So, that the positive expression of Ki-67 in BC tissues can be regarded as a determinant for prognosis. Costa et al. [17] claimed that Topo II α and Ki-67 together were beneficial to the prognosis determination of BC and postoperative therapeutic regimen is well selected, and Topo II α and Ki-67 together predict chemotherapeutic efficacy. In the present study, Ki-67 index was found significantly affecting ALM.

As the limitation of the study, some data was missing, such as number of excluded cases and radiologic imaging modalities' reports other than ultrasonography/ mammography.

In conclusion, HER2 positivity, Ki-67 index, and progesterone receptor negativity affect ALM significantly. HER2 and Ki-67 as prognostic markers may play an important role in the choice of treatment and may give survival benefits.

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Retrospective cohort analysis of 101 patients who underwent surgery due to spinal tumors: A single-center experience

Spinal tümörler nedeniyle ameliyat edilen 101 hastanın retrospektif kohort analizi: Tek merkez deneyimi

Serkan Kitiş [1], Meliha Gündağ Papaker [1]

Abstract

Aim: To evaluate the clinical and surgical outcomes of the spinal tumors operated in our clinic in order to provide an overview of the treatment strategies and outcomes of spinal tumors with the literature.
Methods: We retrospectively reviewed 101 spinal tumors patients who underwent microsurgical resection at our institution between January 2015 and January 2020. Data were collected consisting of the patients' clinics, demographic information, imaging methods, surgical approaches, neuropathological diagnosis, postoperative follow-up and complications, and postoperative neurological statuses. Frankel skore was used to assess neurological status of patients.
Results: 47 male and 54 female patients were followed-up for a mean period of 14.2 months. Intradural extramedullary (51.5%), extradural (36.6%) and intramedullary tumors (11.9%) were seen, respectively. The most common localization was thoracic (n=47), followed by lomber region (n=26). The most frequent histopathological diagnosis was schwannoma (n=27), meningioma (n=19), metastasis (n=19), ependymoma (n=11). According to the Frankel Scale, there was a decrease in the grades of two cases, an increase in the grades of 26 cases and no change in the grades of 73 cases. During follow-up with magnetic resonance imaging, it was observed that there were residual tumors, recurrence, and progression in 32.7%, 5.9% and 5.9% of the cases, respectively.
Conclusion: Despite the developing preoperative diagnostic methods, technological developments in peroperative tools and equipment, and the development of surgical techniques, the preoperative neurological status remains the strongest predictor of postoperative function for spinal tumors. It is also important to determine the recurrence and progression rates of early magnetic resonance imaging examinations performed in patients during postoperative follow-up.

Keywords: Spinal tumor, Frankel Scale, histopathological diagnosis, magnetic resonance imaging.

Öz

Amaç: Spinal tümörlerin tedavi stratejileri ve sonuçlarına genel bir bakış sağlamak amacıyla kliniğimizde opere edilen spinal tümör olgularının klinik ve cerrahi sonuçlarını literatür eşliğinde değerlendirmektir.
Yöntemler: Ocak 2015 - Ocak 2020 tarihleri arasında kurumumuzda mikrocerrahi rezeksiyon uygulanan 101 spinal tümör hastası retrospektif olarak incelendi. Hastaların klinikleri, demografik bilgileri, görüntüleme yöntemleri, cerrahi yaklaşımlar, nöropatolojik tanı, postoperatif takip ve komplikasyonlardan oluşan veriler ve postoperatif nörolojik durumlar hakkındaki veriler toplandı. Hastaların nörolojik durumlarını değerlendirmek için Frankel skalası kullanıldı.
Bulgular: 47 erkek ve 54 kadın hasta ortalama 14.2 ay takip edildi. Yerleşim yerlerine göre intradural ekstramedüller (% 51.5), ekstradural (% 36.6) ve intramedüller tümörler (% 11.9) oranda görüldü. En sık yerleşim yeri torasik (n = 47), ardından lomber bölgeydi (n = 26). En sık görülen histopatolojik tanı schwannoma (n = 27), menenjiyom (n = 19), metastaz (n = 19) ve ependimoma (n = 11) idi. Frankel skalasına göre, iki olgunun derecesinde azalma, 26 olgunun derecesinde artış olmuştu ve 73 olgunun derecesinde ise değişiklik olmamıştı. Hastaların magnetik rezonans görüntüleme takiplerinde % 32.7 rezidüel tümör, % 5.9 rekürrens ve % 5.9 progresyon olduğu görüldü.
Sonuç: Gelişen preoperatif tanı yöntemleri, peroperatif araç ve gereçlerdeki teknolojik gelişmeler ve cerrahi tekniklerin gelişmesine rağmen, preoperatif nörolojik durum spinal tümörler için postoperatif fonksiyonun hala en güçlü prediktörü olmaya devam etmektedir. Ayrıca postoperatif takip sırasında hastalara yapılan erken magnetik rezonans görüntüleme incelemelerinin de nüks ve progresyon oranlarını belirlemede de önemlidir.

Anahtar Kelimeler: Spinal tümör, Frankel skalası, histopatolojik tanı, manyetik rezonans görüntüleme.

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Introduction

Spinal tumors are major spinal pathologies that lead to significant morbidity and mortality, by causing radicular or local pain and neurological deficits such as limb dysfunction. These rare tumors affect a small proportion of the population. Although the most common symptom in patients is pain, the clinical presentation is often not disease specific. Most patients may confuse these tumors with degenerative spinal disease or intervertebral disc hernia. Accurate diagnosis and rapid treatment of spinal tumors are important because they can lead to significant morbidity in terms of pain and neurological deficits as well as death [1-3]. Regarding the differential diagnosis, the patient's age, topographic localization of the mass, and morphological features of the lesion shown by radiological examinations play an important role [4]. Preferred treatment is the microsurgical radical resection. The main goal in surgery is to make maximum neural tissue decompression and diagnose tissue while preserving neurological functions and stability.

The purpose of this study was to evaluate the clinical and surgical outcomes of the spinal tumor cases operated in our clinic in order to provide an overview of the treatment strategies and outcomes of spinal tumors with the literature. In addition to the clinical demographic information of the patients, their functional neurological status was investigated to evaluate the patients' quality of life after surgery.

Material and methods

Patient Data, Study Design, and Study Criteria:

We retrospectively reviewed 121 patients with spinal lesions who underwent microsurgical resection at our department between January 2015 and January 2020. This retrospective study was approved by the local medical ethics committee of Bezmialem University (2020-7228).

The medical data and demographic features of all the patients were collected according to the hospital records. The patients' clinics, demographic information, imaging methods, surgical approaches, neuropathological diagnosis, postoperative follow-up and complications, and postoperative neurological statuses were investigated.

The inclusion criteria were, all the patients who were diagnosed based on magnetic resonance imaging (MRI) findings and who underwent surgical resection due to a spinal tumor and which was proven pathologic diagnosis by histopathological examination. In addition age restrictions were not applied to the patients.

The excluded criteria were, patients undergoing diagnostic biopsy, patients who underwent resection of the spinal tumors determined using computerised tomography (CT) and not preoperative MRI. Also, patients who were not surgically treated, who were only diagnosed with radiological diagnosis and directed to oncological treatment were also excluded.

As a result, the study continued with 101 patients who met our criteria.

All of the cases were evaluated using MRI in the preoperative period. After surgical resection, the residual tumor was evaluated by performing an early postoperative MRI (in the first 24 hours). During the postoperative follow-up, control MRIs were performed and relapses were evaluated by a specialist radiologist and neurosurgeon.

The neurological status of each patient at presentation, early postoperative period and at the last follow-up were graded based on International Frankel Scale (FS) (Table 1). Functional result (FR) was obtained by comparing the FS values of the patients' preoperative and follow-up control examinations.

Table 1. Frankel Scale

Class		Severity
A	Complete	No motor or sensory function below level of lesion
B	Sensory only	No motor function, but some sensation preserved below level of lesion
C	Motor useless	Some motor function without practicl application
D	Motor usefull	Useful motor function below level of lesion
E	Recovery	Normal motor and sensory function, may have reflex abnormalities

Functional status of the patients were evaluated according to the increase or decrease in the scores they received in FS.

The patients were operated under general anesthesia with a posterior, posterolateral, or anterior approach. We performed simple decompression, intradural tumor excision with laminoplasty, posterior stabilization with decompression, corpectomy and posterior stabilization using the posterior approach, and anterior corpectomy. Intraoperative neurophysiological monitoring (IONM) was use in necessary cases. Postoperative physical therapy protocol was applied to all patients. The necessary patients underwent oncological treatment (chemotherapy and/or radiotherapy) procedures.

Statistical analysis

SPSS 21.0 statistics program was used in our study. In addition to descriptive statistical methods, frequency, percentage, mean, standard deviation, and crosstabs analysis were used to describe the demographic characteristics of the cases. Data with normal distribution were evaluated by independent sample t test. The normality of the distribution was assessed using the Kolmogorov Smirnov test. Pearson correlation test was used for correlation analysis. P values less than 0.05 were considered statistically significant.

Results

Demographic and clinical features

Of the 101 patients, 47 were males (46.5%) and 54 were females (53.5%). The youngest patient was 4 months old while the oldest was 82 years old (Mean 46.56 ± 19.05). Ninety two patients (91%) were adults while 9 patients (9%) were children (<18 years of age).

The time between the onset of symptoms and admission ranged from 1 day to 4 years. The patients were re-evaluated after an average of 14.7 months of follow-up.

The most common symptom was local pain (neck, back or low back pain) (63.3%) and radicular pain (upper or lower limb pain) (37.6%). 52 patients (51.4%) presented with neurological deficits and 41 patients (40.5%) presented with paresthesia. Sphincter dysfunction were present in 14 patients (13.8%). Pathological reflexes, clonus and abnormality of deep tendon reflexes were found in 14 patients (13.8%).

Surgical treatment

Sixty-five (64.4%) patients underwent simple decompression, 21 (20.8%) underwent intradural tumor excision with laminoplasty, 7 (6.9%) underwent posterior stabilization with decompression, 3 (3%) underwent corpectomy and posterior stabilization using the posterior approach, and 5 (4.9%) underwent anterior corpectomy.

Histopathological and localization features

Regarding the localization of the tumors, 1 was craniocervical, 18 were cervical, 1 was cervicothoracic, 47 were thoracic, 7 were thoracolumbar, 26 were lumbar and 1 was lumbosacral. It was observed that the most common location were intradural extramedullary (50.5%), then extradural (36.6%), and intramedullary (12.9%).

According to the histopathological diagnosis, the most common pathology was Schwannoma (n: 27, 26.7%) (Figure 1), then meningioma (n: 19, 18.8%), metastasis (n: 19, 18.8%) (Figure 2) and ependymoma (n: 11, 10.9%). The detailed histopathological analysis of the tumors are shown in Table 2.

Table 2. Histopathological Features of tumors

Pathology	n=101, n (%)
Schwannoma	27 (26.7)
Meningioma	19 (18.8)
Psammomatous meningioma	10 (9.9)
Transitional meningioma	4 (4)
Atypical meningioma	4 (4)
Anaplastic meningioma	1 (1)
Ependymoma	11 (10.9)
Myxopapillary ependymoma	5 (4.9)
Subependymoma	1 (1)
Ependymoma (WHO grade 2)	3 (3)
Anaplastic Ependymoma	2 (2)
Metastasis	19 (18.8)
Lung cancer	4 (4)
Breast cancer	4 (4)
Renal cell carcinoma	2 (2)
Prostate cancer	3 (3)
Cholangiocarcinoma	1 (1)
Hepatocellular carcinoma	1 (1)
Leiomyosarcoma	1 (1)
Endometrial carcinoma	1 (1)
Adenoid cystic carcinoma	1 (1)
Nasopharyngeal carcinoma	1 (1)
Lymphoma	6 (5.9)
Plasmacytoma	3 (3)
High grade gliomas (WHO grade 4)	2 (2)
Anaplastic astrocytomas (WHO grade 3)	1 (1)
Neurofibroma	2 (2)
Ganglioglioma	1 (1)
Ganglioneuroma	1 (1)
Epidermoid cysts	1 (1)
Myeloid sarcoma	1 (1)
Malignant peripheral nerve sheath tumor	1 (1)
Neuroblastoma	1 (1)
Immature teratoma	1 (1)
Angiolipoma	1 (1)
Ewing sarcoma	2 (2)
Dermoid cysts	1 (1)

Early postoperative evaluation

When the early postoperative evaluations of the patients were examined, the mean hospitalization duration was 7.06 ± 9.24 days. Although the neurological examination of 80 patients did not change in comparison to the preoperative situation, those of 16 patients was found to be better compared to the preoperative situation, those of 5 patients got worse compared to the preoperative period, while one patient with mild paresis improved with physical therapy.

Three patients were reoperated due to postoperative hemorrhage and although a neurological function regression was observed in these 3 patients before the hemorrhage, improvements were observed after reoperation. These same three patients later developed postoperative surgical site infections and were reoperated and treated with appropriate antibiotherapy. Postoperative cerebropsinal fluid (CSF) fistula developed in one case and was treated with lumbar external drainage. No deaths were record due to the surgeries.

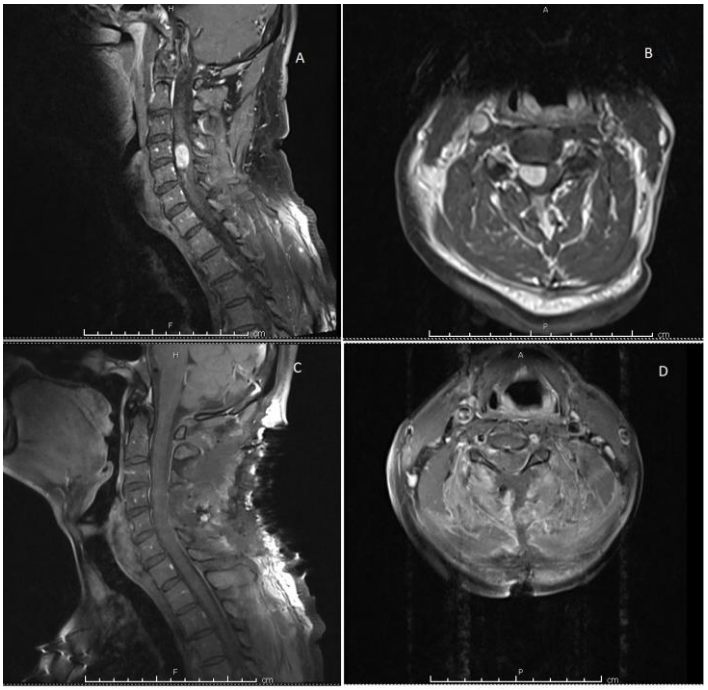

Figure 1. Cervical magnetic resonance images of a 62 year old male patient. Histopathological diagnosis Schwannoma. (a) Preoperative sagittal contrast enhanced T1 weighted image sequence showed that heterogeneous contrast enhancement lesion and (b) Preoperative axial T1 weighted image of heterogeneous contrast enhancement lesion. (c) Postoperative T1 weighted image sequence and (d) postoperative axial T1 weighted image appear to have a total removal of the lesion.

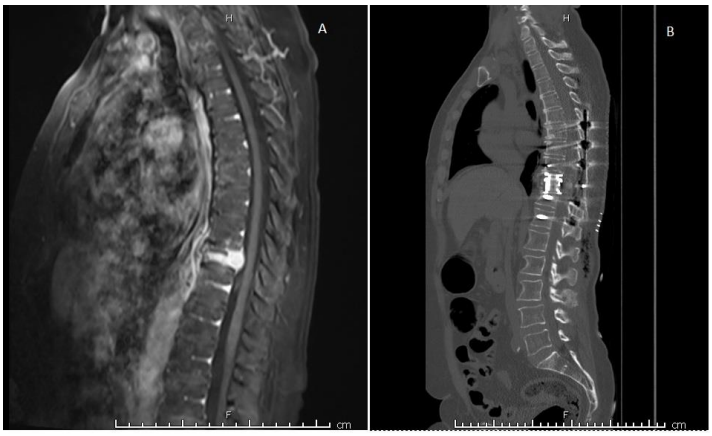

Figure 2: 44 year old female patient. Histopathological diagnosis hepatocellular carcinoma. (a) Preoperative sagittal contrast enhanced T1 weighted thoracic magnetic resonance images showed that T10 burst fracture compressed the spinal cord. (b) Postoperative computed tomography sagittal image showed that corpectomy and posterior stabilization using the posterior approach.

Radiological evaluation

MRI results of the patients in the early postoperative period were compared with the control MRI results in the follow-up period. In the early postoperative period, 68 (67.3%) patients had no residual tumor, while 33 (32.7%) had residual tumors. On examination of the control MRIs performed during the patient follow-up, it was observed that recurrence occurred in 6 of 68 (5.9%) patients without residual tumors and 2 of them were reoperated. It was observed that 24 (23.8%) of 33 patients had stable residual tumors during follow-up, while 6 (5.9%) had progressing tumors, 4 of which were. In 3 (3%) patients (2 lymphomas and 1 ewing sarcoma), tumor regression was observed when they received oncological treatment after surgery (Table 3).

Frankel scores and functional results

When the preoperative Frankel scores were examined, 6 were grade A, 9 were grade B, 15 were grade C, and 22 were grade D and 49 were grade E. At the follow-up control, six were grade A, three were grade B, eight were grade C, and 26 were grade D and 58 were grade E. The preoperative neurological status was significantly related with the late postoperative outcome (p <0.001).

Table 3. Analysis of Functional Result and Radiological Evaluation according to histopathological changes

Pathology	Functional Result					Radiological Evaluation				Total
	+2	+1	0	-1	-2	Rc	P	S	Rg	
Schwannoma		4	22	1				27		27
Psammomatous meningioma	1	1	8			1		9		10
Transitional meningioma		2	2					4		4
Atypical meningioma		1	3					4		4
Anaplastic meningioma		1					1			1
Myxopapillary ependymoma			5					5		5
Subependymoma			1					1		1
Ependymoma (WHO grade 2)			3			1		2		3
Anaplastic ependymoma			2				1	1		2
Metastasis	1	5	13				2	17		19
Lymphoma	1	2	3					4	2	6
Plasmacytoma		2	1					3		3
High grade gliomas (WHO grade 4)			2				2			2
Anaplastic astrocytomas (WHO grade 3)		1						1		1
Neurofibroma			2			1		1		2
Ganglioglioma					1			1		1
Ganglioneuroma			1					1		1
Epidermoid cysts			1			1				1
Myeloid sarcoma		1						1		1
Malignant peripheral nerve sheath tumor			1			1				1
Neuroblastoma	1							1		1
Immature teratoma			1			1				1
Angiolipoma			1					1		1
Ewing sarcoma	1		1					1	1	2
Lymphoma		1						1		1
Total	5	21	73	1	1	6	6	86	3	

Rc: Recurrence, P: progressing, S: stable, Rg: regression

Functional result (FR) was obtained by comparing these Frankel Scale values of the patients' preoperative and control examinations. When the patients were re-evaluated of follow-up, according to the Frankel Scale, there was a decrease in the grade of two patients and an increase in the grade of 26 patients. There was no change in the grade of 73 patients (Figure 3). Two cases (2%) whose FR deteriorated were intramedullary. In the examination of the 73 patients whose FR did not change, it was observed that patients with intradural extramedullary location maintained their status at a rate of 40.6%, those with an intramedullary location at a rate of 8.9%, and patients with an extradural location at a rate of 22.8%. Of the patients with improved FR, 10.9% were found to be intradural extramedullary, 1% were intramedullary, and 13.9% were extradural (Figure 4). When the patients' tumor location were compared with preoperative FS (p<0,001), follow-up FS (p=0.014) and FR (0.001), tumor location was associated with the clinical presentation of the patients. However, the relationship between the FR and the tumor level (p=0.430) were not statistically significant. Likewise, there was no statistically significant relationship between the FR and the the patients' gender (p=0.992) and age (p=0.907).

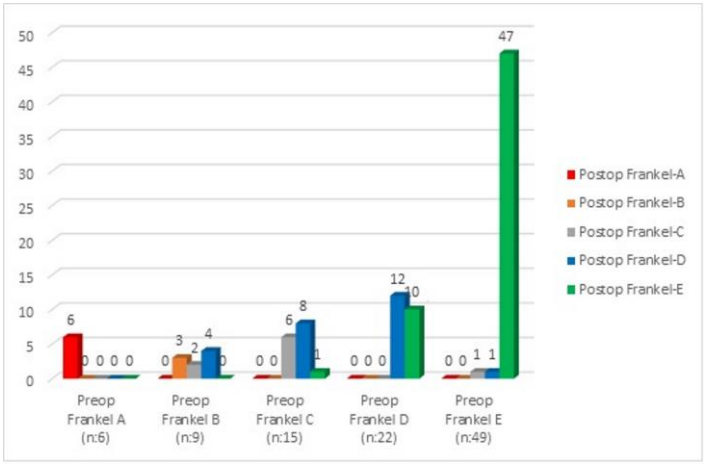

Figure 3. Preoperative (Preop) and postoperative (Postop) change of patients' Frankel Scores. According to this graph, all 6 patients with preop grade A all maintained their status as grade A during their follow-up. While 3 of 9 patients with preop grade B retained their status as grade B, 2 increase to grade C and 4 to grade D. While 6 of 15 patients with preop grade C retained their status as grade C, 8 increase to grade D and 1 to grade E. While 12 of 22 patients with preop grade D remained as grade D, 10 increase to grade E. 1 of 49 patients with preop grade E decrease to grade C and 1 to grade D.

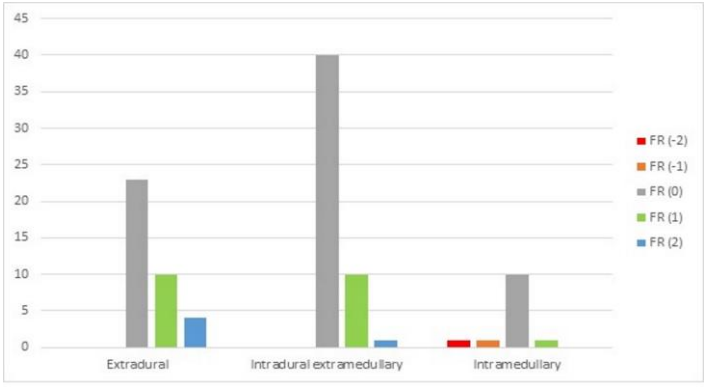

Figure 4. Relationship between tumor location and Functional result (FR) of patients.

While 23 of 37 patients with extradural tumors maintained their status, 10 of them increased 1 grade and 4 of them increased 2 grades. While 40 of 51 patients with intradural extramedullary tumor maintained their status, 10 of them increased 1 grade and 1 of them increased 2 grades. While 10 of 13 patients with intramedullary tumor maintained their status, 1 of them decrease of two grade and 1 of them decrease of one grade.1 of them increased 1 grade.

Discussion

Spinal tumors are rare lesions that are common in neurosurgical practice. They are life-changing and destructive conditions associated with ongoing disability, addiction, psychological stress, and financial burden [5, 6]. It is importantly recommended to use clinical scores based on the neurological function to evaluate the prognosis after surgery. Some studies have shown that the most important prognostic factor is the initial functional state at the time of treatment [7, 8]. In this study, we used the Frankel Scale to evaluate the functional result of patients before and after treatment. We found that the preoperative neurological status was significantly related with the late postoperative outcome. Also tumor location of patients was found to be related to functional result.

Neurological conditions of patients and sphincter functions are the most important factors affecting their quality of life. Therefore, early diagnosis of these lesions and appropriate treatment are important for the functional status of patients in the future. Pain, weakness, and sensory disturbances were found to be the most common symptoms and signs in these patients with spinal tumors. However, sphincter, bladder, and intestinal functions are impaired at a later stage [9-12]. Local pain (63.3%) were the most common symptoms in our patients. In some studies, motor deficit was observed in 66-82% of cases, while it was observed in 51.5% of the patients in our study [6]. The incidence of urinary dysfunction (13.9%) in our study was not as high as previously reported [10-12].

Today, with the advances in imaging methods, these lesions are better diagnosed and more information about the neurovascular structures is obtained. MRI is the gold standard method, which is at the center of radiological examinations for the classification of tumors by location [13]. Comparing the patients' early MRI with the control MRI is an important marker of relapse/rogression [14]. In our study, we found that how important early MRI examinations to patients were determining recurrence and progression rates in postoperative follow-up.

In general, secondary (metastatic) tumors are the most common spinal tumors and are most often are extradural. The spinal region is the third most common involvement site for metastatic tumors after the lung and liver [15]. Due to the prolonged life span of most cancer patients (20-40%), the incidence of spinal metastasis increases during their illness and approximately 20% of these patients become symptomatic [16, 17]. In our study, extradural tumors were seen with a second rate of 36.6% and metastatic tumors were the second most common with 18.8%. According to the literature, the most important reason why metastatic tumors are in the second place is that patients who did not undergo surgery, who underwent biopsy with interventional techniques, and who received oncology/radiation oncology treatment were not included in the study.

Patients with primary spinal tumors are relatively rare. It has been reported that intradural extramedullary tumors are more common than intramedullary tumors [18- 20]. In our study, 50.5% of the cases were intradural extramedullary and 12.9% of them were intramedullary in location. Schwannomas (26.7%) and meningiomas (18.8%), which are intradural extramedullary lesions, were common while ependymomas (10.9%), which are among the intramedullary lesions, also occured frequently.

It has been reported in the literature that resection is the most effective treatment for well-limited benign intraspinal tumors and that surgical biopsy plays an important role in obtaining the histological diagnosis. It is not useful to perform a total resection in patients with malignant spinal cord tumors or in patients with a high probability of neurological injury. The purpose of surgery in partial resection is to obtain tissue for the definitive diagnosis, open the spinal cord as safely as possible, and to stabilize the spine in case of instability [21-24]. Decompressive laminectomy is one of the most used approaches in the treatment of spinal tumors. Several recent studies have shown that laminoplasty is superior to decompressive laminectomy in terms of prognosis and outcomes [25, 26]. Instability may occur during the surgical treatment of spinal tumors and methods requiring stabilization should be used [27-29]. Therefore, more aggressive surgical strategies are sometimes required in the presence of severe instability and/or deformity [30-32]. We performed laminoplasty in 21 of 64 intradural tumors and simple decompression in 42 tumors, while one was decompressed with posterior stabilization. Of the five cases that underwent anterior corpectomy, four were cervical and one was thoracic in location, which were extradural tumors.

The limitation of our study is that it was a retrospective study in a relatively small group, since it only included spinal cases that were treated surgically and had only pathological diagnosis. Prospective studies with large and long follow-up are needed to systematically investigate these findings.

In conclusion, despite the increasing preoperative diagnostic methods, technological developments in peroperative tools and equipment, and the development of surgical techniques, the preoperative neurological status remains the strongest predictor of postoperative function for spinal tumors. It is also important to determine the recurrence and progression rates of early MRI examinations performed in patients during postoperative follow-up.

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Capsule and Ablation Tract Related Features of Local Recurrence in Ultrasound Guided Microwave Ablation of Liver Metastases

Karaciğer Metastazlarında Ultrason Eşliğinde Yapılan Mikrodalga Ablasyon Tedavisi Sonrası Gelişen Lokal Nüksün Kapsül ve Ablasyon Traktı ile İlişkisi

Serkan Arıbal [1], Eyup Kaya [1]

Abstract

Aim: We aimed to evaluate the capsule and ablation tract related features of local recurrence after ultrasound (US) guided percutaneous microwave ablation (MWA) of the liver metastases independently.
Methods: Between February 2016 and December 2019, 101 patients with US-guided percutaneous MWA of the liver metastases were analyzed. Nineteen patients having thirty-two ablated lesions with local recurrence (LR) were included in the study. Histopathologic type of tumor, pre-ablative features of the lesions and the ablation procedure data were noted. Tumor size, the closest distance between the lesion and the liver capsule was measured. The site of LR related to the liver capsule and related to ablation tract and the shape of the LR were noted.
Results: The median time of LR was 8.46±4.54 months (range, 3-20). The patient (n=19) and the ablated lesion (n=32) depended LR rates were 19% and 20% respectively. All LR of the parenchymal localized metastatic lesions originated from either tip or the side of the ablation tract and this relationship was found as statistically significant (p=0.035). No statistically significant relationship was found between vessel closeness and shape of LR (p=0,704) and between the site and the shape of LR (p=0.683).
Conclusion: We demonstrated that the LR arising from parenchymal localized metastatic lesions were from either the tip or the side of the ablation tract. We also defined some features of LR related to the ablation tract and liver capsule independently.

Keywords: Local recurrence, microwave ablation, ablation tract, liver metastasis, liver capsule

Öz

Amaç: Çalışmamızda karaciğer metastazlarında ultrason eşliğinde yapılan mikrodalga ablasyon tedavisi sonrası gelişen lokal nüksün karaciğer kapsülü ve ablasyon traktı ile ilgili özelliklerinin değerlendirilmesi amaçlanmıştır.
Yöntemler: Şubat 2016 ile Aralık 2019 tarihleri arasında mevcut karaciğer metastazına US rehberliğinde perkutan mikrodalga abalasyon tedavisi yapılan 101 olgu retrospektif olarak değerlendirildi. Toplam 32 lokal nükse sahip ablate lezyonu bulunan 19 hasta çalışmaya dahil edildi. Metastazların histopatolojik tipleri, ablasyon öncesi özellikleri ve ablasyon işlemine ait bilgiler not edildi. Tümörün boyutları ve tümör ile karaciğer kapsülü arasındaki en kısa mesafe ölçüldü. Lokal nüksün karaciğer kapsülüne ve ablasyon tarktına göre tarafı ve yerleşimi ile şekil özellikleri değerlendirildi.
Bulgular: Ortanca lokal nükssüresi 8.46±4.54 ay (3-20 aralığında) olarak bulundu. Hasta ve lezyon bağımlı lokal nüks oranları sırasıyla 19% ve 20% idi. Parankim içi yerleşimli lezyonlara ait lokal nükslerin tümü ablasyon traktının ucu ya da yanında yerleşimli olarak bulundu ve bu ilişki istatistiksel olarak anlamlıydı (p=0.035). Damar yakınlığı ile lokal nüksün şekli ve lokal nüksün tarafı ile şekli arasında istatistiksel olarak anlamlı ilişki saptanmadı (sırasıyla p=0.704 ve 0.683).
Sonuç: Çalışmamızda parankimal yerleşimli lezyonlardan gelişen lokal rekürrensin hepsinin ablasyon traktının uç ve yan kesimlerinden geliştiği ortaya konulmuştur. Ayrıca lokal rekürrensin karaciğer kapsülü ve ablasyon traktı ile ilişkili bir takım özellikleri ve bu bulguların birbiri ile ilgili ilişkileri ortaya konuldu.

Anahtar Kelimeler: Lokal rekurrens, mikrodalga ablasyon, ablasyon trakt, karaciğer metastazları, karaciğer kapsülü

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Ethics Committee Approval: The study was approved by Prof. Dr. Cemil Taşcıoğlu State Hospital ethical authority (02.06.2020/ No: 215).

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Introduction

Because of being quite often site for the distant metastasis of the primary tumors, especially for colorectal metastasis (CRM), the liver takes an important place in the treatment strategies of cancer to have good long-term outcomes (1-3). Surgical resection is the first-line and the gold standard therapy for patients with liver metastasis (4,5). However, only one-fourth of the cases are deemed resectable at presentation (6). Apart from systemic therapies, local and regional treatment options have been a good alternative for these patients. When compared to surgery, locoregional procedures are minimally invasive treatment choices and the most prominent advantage over surgery is being a less adverse effect on liver functions by their hepatocyte sparing features. Nevertheless, the biggest disadvantage is their inferior local tumor control rates resulting recurrence (7).

There are many risk factors for local recurrence (LR) such as tumor size, histopathologic type, ablation zone, segmental distributions, presence of an adjacent vessel, ablation method used, described and analyzed in previous studies (8,9). As might be expected, subcapsular tumor localization is another significant and independent factor associated with LR (10,11). On the other hand, there are also a couple of studies suggesting that the subcapsular localization is not a significant factor for LR and poor survival rates (12,13). To the best of our knowledge, there is no study focused on the capsule and ablation tract features related to LR following the thermal ablation (TA) of liver metastasis.

The purpose of this study was to evaluate the capsule and ablation tract related features of local recurrence after ultrasound (US) guided percutaneous microwave ablation (MWA) of the liver metastases independently.

Material and methods

This retrospective study was approved by the local ethics committee. Informed consent has been obtained from all patients. It is confirmed by the author that the study is appropriate for the Declaration of Helsinki Standards.

Study Population: Between February 2016 and December 2019, 101 patients with US-guided percutaneous MWA of the liver metastases were analyzed with both their patient files including the whole follow–up information and all radiological images on local Picture Archiving and Communication System (PACS). All thermal ablation treatment decisions of the liver tumors are taken by the multidisciplinary local tumor board formed by the specialist in medical oncology, hepatopancreatobiliary surgery, nuclear medicine, radiation oncology, radiology and interventional radiology. The only inclusion criterion is to be having at least one lesion with MWA after a single session of TA. Among them, nineteen patients having thirty-two ablated lesions with LR were included in the study. Seventy-one patients having one hundred and five ablated lesions with no LR, seven patients having ten ablated lesions with residual tumor rather than LR after MWA and four patients having six ablated lesions with a short follow-up period (< 3 moths after MWA) due to non-follow up or death are excluded from the study population. In addition, the patients in the study group had also four thermal ablated lesions with no evidence of LR (Figure 1).

Pre-procedural Assessments: Every single patient decided to perform percutaneous TA was referred to interventional radiology service for further evaluation. The patients underwent ultrasound and doppler ultrasound evaluation to plan the ablation and the procedures accompanied by the

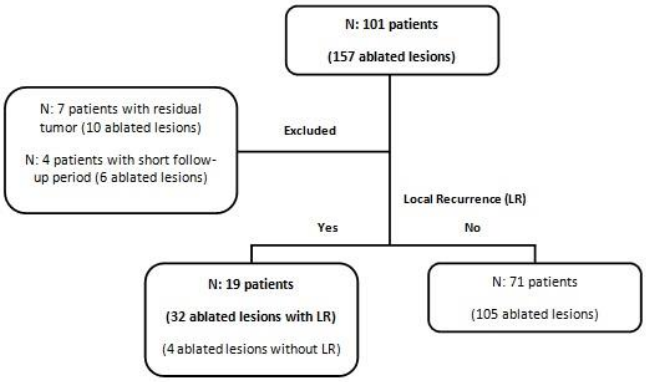

Figure 1: Study flow chart.

findings of contrast-enhanced (CE) triphasic liver computed tomography (CT) or dynamic CE liver magnetic resonance (MR) scans which were obtained within 1 month before the TA procedure. Identifications of metastases in the patients whose primary tumor was known were made according to imaging findings such as contrast wash-out throughout the dynamic series wiyhout any biopsy procedure. Depending on the localization of the tumor, the thermal ablation suitability criteria were accepted as follow: solitary tumors of up to 5 cm and up to 3 tumor measuring <3 cm. The general condition of the patients was evaluated according to Child-Pugh classification and Eastern Cooperative Oncology Group (ECOG) performance scale to make the final decision for the procedure. Additional findings such as ascites, adjacent structures (vascular, colon, gall bladder, etc.) were documented to plan all steps of procedures in detail. After exhaustive information about the TA procedure and taking some blood samples including whole blood count, bleeding and coagulation parameters, they were directed to anesthesia service for the convenience of anesthesia.

Thermal Ablation Procedure: All thermal ablation procedures were performed with percutaneous MWA using only US guidance under general anesthesia. 15-gauge electrodes with 2.45 GHz Solero and Acculis MWA generators (Angiodynamics, New York, USA) was the MWA systems used during the procedures. Aplio 500 ultrasound system (Toshiba Medical Systems Corporation, Tochigi, Japan) had been used with 3-6 Mhz convex or 4-9.2 Mhz linear array transducers for ablation guidance. In the presence of acid, percutaneous drainage was applied just before the procedure. Following the local and subcapsular anesthesia and a skin puncture, the ablation probe was advanced towards the center of the targeted lesion. Once the probe tip was positioned at the intended ablation zone, two interventional radiologists checked whether the lesion had been centralized or not from different plans by ultrasound probe maneuvers. After ensuring the probe centralization by consensus, the TA process was begun with general anesthesia. The ablation energy and duration were selected according to the targeted tumor ablation size and location using standard algorithms by aiming at least 5 mm of each margin around the tumor. Immediately after the ablation period was accomplished, the procedure was completed by performing tract ablation for the section up to the liver capsule

Follow-up: All patients were followed by triphasic liver CT scans or dynamic CE MR imaging performed on the first day after ablation, quarterly in the first 2 years, and biannually thereafter for follow up. Besides, the US and Doppler US imaging were performed at the time of each follow-up admissions and patient files were examined in detail. LR was

defined as the pathologic contrast enhancement at any site of ablated lesion in the control CT or MR imaging after 3 months. Any lesion before this period was accepted as residual tumor rather than LR. We didn't perform biopsy procedure to make definitive diagnosis according to our hospital's tumor board decisions. In the case of suspicious imaging findings for LR, diffusion-weighted (DW) MR and Positron Emission Tomography (PET) scans were also applied.

Definitions and Data Obtaining: Age and gender of the patients were recorded. All ablated lesions were assessed prospectively in terms of the histopathologic type of primary tumor, pre-ablative tumor size and volume, post-ablative tumor size and volume at the first day after ablation and at the time of LR, presence of blood vessel proximity and the diameter of the vessel(s), liver segmental location, the closest distance to the liver capsule, type of LR, capsule and ablation tract related features of LR.

Histopathologic type of tumor, ablation procedure data, the segmental localization of the tumor according to Couinaud classification system and time of post-ablation LR were noted. Tumor size was measured in three dimensions; width (W), length (L) and height (H) using multiplanar reconstructed (MPR) CT or axial and coronal MR images and the volume (V) of the lesions was calculated using the following formula $V = W \times L \times H \times \pi/6$. The vessels closer than 10 mm to the lesions and their diameters were recorded. The closest distance in any image plan (axial, coronal or sagittal images) between the lesion and the liver capsule was measured. Subcapsular location was defined as a tumor lying within 10 mm of the liver capsule. Otherwise, it will be accepted as a parenchymal lesion. The site of LR related to the liver capsule was classified as capsular and noncapsular according to a straight line passing through the center of the lesion and parallel to the liver capsule (Figure 2A). The site of LR related to the ablation tract was classified as entry, tip and side (Figure 2B). Lastly, the shape of the LR was categorized into two patterns: nodular, crescentic (Figure 2C,D).

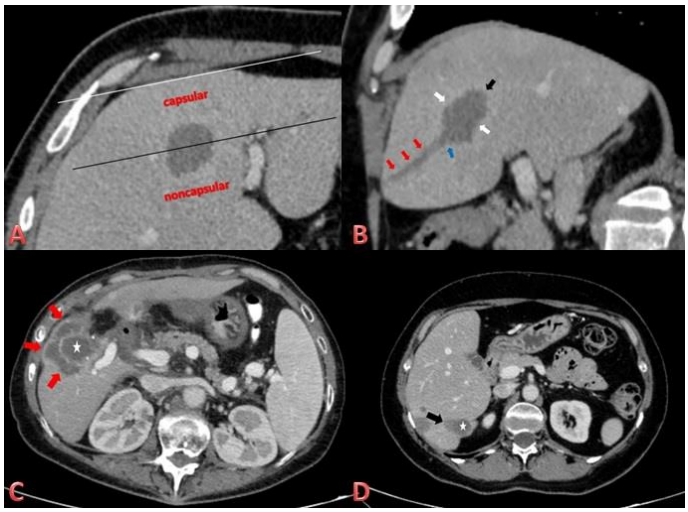

Figure 2: The classification of the local recurrence site as capsular and noncapsular according to liver capsule (A). The lesion was accepted as capsular side in case the large part of the LR was located within the capsular side of the straight line passing through the center of the lesion and parallel to the liver capsule. Otherwise it was accepted as noncapsular side. The classification of the local recurrence site (B) as entry (blue arrow), tip (black arrow) and side (white arrows) according to ablation tract (red arrows). Entry is accepted as the site which the ablation probe first enters to the lesion. Tip is accepted as the site which the ablation probe's last position immediately before the ablation and the side is defined as the both sides of the ovoid ablation zone. The shape of local recurrence (C,D) as nodular (black arrow) and crescentic (red arrows). White stars indicate the ablation zones of each lesions.

Statistical Analysis

The parametric data were presented as mean ± standard deviation values. Analysis of categorical variables was performed using the Chi-square test. Fisher Exact test was applied when more than 20% of the expected values were below 5. All the results were evaluated in the 95% confidence interval and the statistical significance level was defined as p-value < 0.05. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL) version 21.0 for International Business Machines (IBM) statistical package.

Results

The characteristics of the study population and the ablated metastatic lesions are presented in detail in table 1. About one third (35%) of the LR was located in segment 6 (n=11/32). Figure 3 represents the Couinaud's segmentation of the metastases with LR. Fourteen new liver metastases were detected in the follow-up imaging when the LR was detected in eight of nineteen patients. Of thirty-two ablated metastases with LR, sixteen lesions (50%) showed the presence of blood vessel proximity and the mean distance between the lesions and vessels was 1.04±1.90 mm. The median time of LR and follow-up were 8.46±4.54 months (range, 3-20) and 19.62±10.26 (range, 6-40) months respectively. The patient (n=19) and the ablated lesion (n=32) depended LR rates were 19% and 20% respectively. The capsule and ablation tract related features of the LR were detailed in table 2. The ratio for the LR arising from subcapsular localization was found as 69%. Also, 72% of the LR from the subcapsular located metastatic lesion was found in the capsular side (Figure 4). But we couldn't find the statistically significant relationship between the subcapsular LR occurrence and the subcapsular localization of the metastatic lesions (p=0.683, table 3). All LR of the parenchymal localized metastatic lesions originated from either tip or the side of the ablation tract and this relationship was found as statistically significant (p=0.035, table 4). No recurrence was detected from the ablation tract entry of these lesions. The LR was developed on the side of the vessel in eight of sixteen metastatic lesions (50%) with vascular closeness before MWA ablation (p=0.315) (Figure 5). In addition to these, no statistically significant relationship was found between vessel closeness and shape of LR (p=0,704) and between the site and the shape of LR (p=0.683) (table 5). None of the patients with LR had major complications after the procedure. Focal subcapsular hematoma in one patient, reactive perihepatic fluid in three patients and ipsilateral reactive minimal pleural effusion in two patients were noted. None of the minor complications described in these patients required any additional treatment and further evaluation.

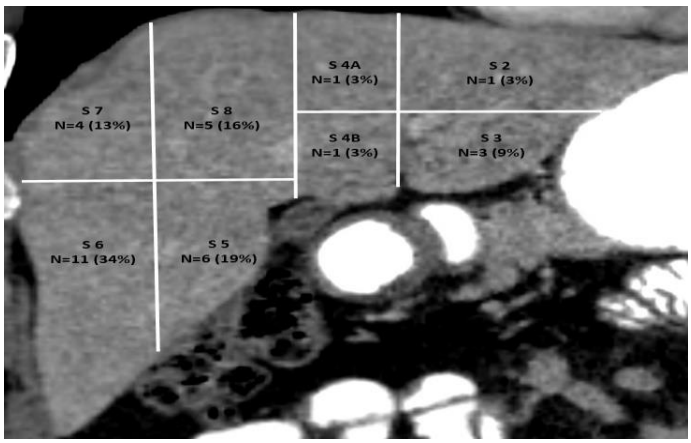

Figure 3: Couinaud's segmentation of the metastases with LR

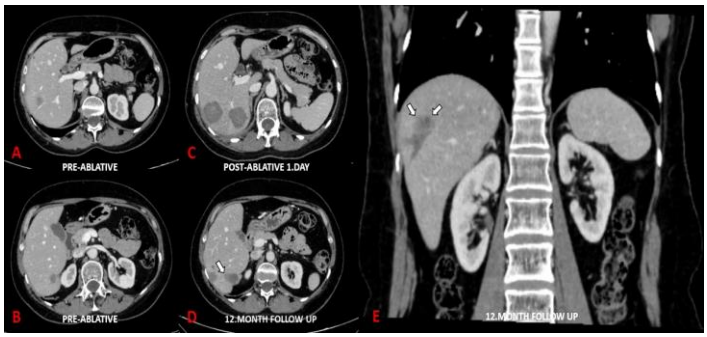

Figure 4: 46-years-old female patient with liver metastases of breast cancer. There are two metastatic lesions located in segment 6 (A and B). Computed tomography (CT) image on the first day after microwave ablation showed the ablation zones with no evidence of residual tumor(C). But in 12th month control, axial (D) and coronal (E) CT images demonstrated the local recurrence. Nodular shaped LR at the entry zone of ablation tract with noncapsular site localisation (white arrow in D) and nodular shaped LR at the side zone of ablation tract with capsular site localisation (white arrows in E).

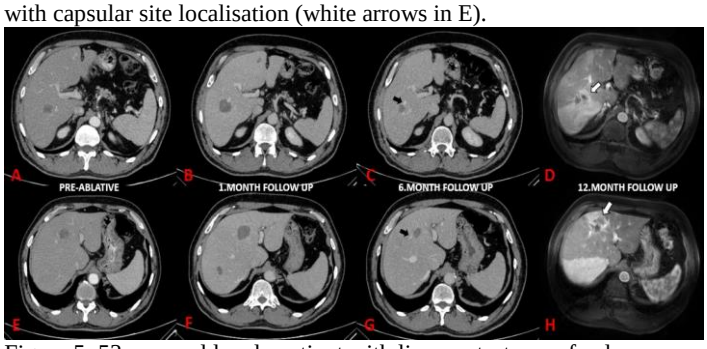

Figure 5: 53-years-old male patient with liver metastases of colon cancer. Pre and post-ablative computed tomography (CT) and magnetic resonance (MR) images of two metastatic lesions located in segment 6 (A-D) and segment 4A (E-H). There was no evidence of local recurrence (LR) for both lesions in 1st and 6th months follow-ups. In addition to this, the CT images showed the volume reduction of two lesions. But, control contrast-enhanced liver MR images at the time of 12th month follow-up showed the crescentic shaped LR on noncapsular site for the lesion in segment 6 (white arrow in D) and crescentic shaped LR on capsular site for the lesion in segment 4A (white arrow in H). Note that, while the LR in segment 6 developed from the site of vascular proximity (black arrow in C), the LR in segment 4A developed from the other site of the adjacent vascular structure (black arrow in G).

Table 1: The characteristics of the study population and ablated metastatic lesions.

Variables	Total / Mean±SD
Patient (total)	19
Male/Female	13/6
Lesion (total)	32
Male/Female	20/12
Age (years)	56.21±10.84
Female Age (years)	48.50±8.36
Male Age (years)	61.30±9.78
Primary malignancies	32
Colorectal	25 (79%)
Breast	2 (6%)
Lung	2 (6%)
Liver/Biliary	3 (9%)
Subcapsular localisation	17 (53%)
Parenchymal localisation	15 (47%)
Tumor volume (pre-ablative, mm³)	5.14±5.09
Tumor volume (post-ablative 1st day, mm³)	21.48±12.60
Tumor volume (at the time of LR, mm³)	22.45±23,48
Time of LR (months)	8.46±4.54

SD : Standart Deviation, LR: Local Recurrence

Table 2. The capsule and ablation tract related features of the local recurrence.

Variables	Total N= 32 (%)
Shape	
Nodular	22 (69%)
Crescentic	10 (31%)
Tract Features	
Entry	8 (24%)
Side	12 (38%)
Tip	12 (38%)
Capsular Features	
Capsular site	22 (69%)
Non-capsular site	10 (31%)
Vessel Proximity	
No	16 (50%)
Portal Vein	7 (22%)
Hepatic Vein	9 (28%)

Table 3. Relationship between the lesion localization and the site of local recurrence.

Lesion Localization	Local Recurrence (site)		Total	P value
	Capsular	Noncapsular		
Subcapsular	16	6	22	0.683
Parenchymal	6	4	10	
Total	22	10	32	

Table 4. Relationship between the lesion and the ablation tract localizations of local recurrence.

Lesion Localization	Local Recurrence (Tract)		Total	P value
	Tip + Side	Entry		
Subcapsular	14	8	22	0.035
Parenchymal	10	0	10	
Total	24	8	32	

Table 5. Relationship of the shape of local recurrence between the lesion localization and the vascular closeness.

	Local Recurrence (shape)		Total	P value
Lesion Localization	Nodular	Crescentic		
Subcapsular	17	5	22	0.683
Parenchymal	5	5	10	
Total	22	10	32	
Vascular Closeness				
No	12	4	16	0.704
Yes	10	6	16	
Total	22	10	32	

Discussion

We have demonstrated in our study that there was not a specific shape and side features of LR related to both the liver capsule and the ablation tract. To the best of our knowledge, the present study was the first one which was evaluated the ablation tract and the liver capsule related features of LR after US-guided percutaneous MWA of the liver metastases independently.

When it is considered that the large part of the liver metastases is technically inappropriate for surgical resection, locoregional treatment strategies have been taken their place in the management of these patients as a minimally invasive choice (6,14). However, when compared to surgery, the prominent disadvantage of these locoregional procedures is their inferior

local tumor control rates resulting in recurrence (7). There are several studies reporting that the thermal ablation methods showed similar results to surgical treatment in patients with colorectal cancer liver metastases less than 1 cm and even superior to surgery in noroendocrine tumor metastases (10,12,15). Apart from the patient status such as systemic treatments and the primary tumor depended features, it is important to understand the local environmental changes and features of the LR to improve the thermal ablative treatment procedures and to obtain some new treatment strategies related to approach and the ablation zone.

We found the patient-depended LR rate as 19% and lesion-depended LR rate as 20% in our study. Xu et al. reported that LR was discovered after ultrasound-guided MWA treatment in half of the patients in their study about ultrasound-guided percutaneous microwave ablation for intrahepatic cholangiocarcinoma (16). Although the reported LR rate was higher than our results, we think this was due to the prognostic feature of this specific tumor type in their study. In another study about the laparoscopic ultrasound-guided MWA for multifocal primary liver cancer, the LR ratio was reported as 12.5% which was lower than our result (17). In a very recent study which was about the comparison between the percutaneous and laparoscopic approaches in MWA, it is mentioned that the local tumor progression rates were 21.1% and 7.7% in percutaneous and laparoscopic approaches respectively (18). Therefore, it is clear that the laparoscopic thermal ablation methods are technically superior to percutaneous methods in terms of LR occurrence. On the other hand, Lorentzen et al. reported that the LR rates can be reduced up to 9.6% when contrast material usage is added to ultrasound guidance (19).

The basic mechanism of MWA is the transmission of electromagnetic energy produced by the generator to the active tip of the probe which is positioned within the lesion throughout the tract to produce intratumoral adequate heat which denatures the intracellular proteins and cell membranes. The heat is dissipated centrifugally around the probe tip resulting in the formation of ablation zones (20). Considering this basic principle of the thermal ablation procedure, the features of the ablation zone and the ablation tract could give some ideas about the local tumor progression. Although we couldn't find a statistically significant relationship between the data, most of the LR was occurred either in the tip (38%) or the side (38%) of the ablation tract rather than the entry zone (24%) of the ablation tract in the present study. When considered that the occurrence of the ablation zone (depending on the MWA system) first starts at the active tip of the probe and radiates towards both sides and posteriorly throughout the ablation probe settled in the ablation tract, the idea of positioning the ablation probe a little further by considering the safety limits and planning the ablation zone a little wider than the accepted standards can be discussed. We also found that almost all of the LR developed from the tip of the ablation tract were nodular in shape.

In thermal ablation practice, especially with US-guidance, both the subcapsular lesions and the sections of the lesion close to the liver capsule are sometimes disadvantageous places for the performer in terms of approaches and manipulations (21). The physicians usually prefer to use some assistive techniques such as hydrodissection to protect the liver capsule for an undesired and extrahepatic ablation (22). However, sometimes this discreet approach may cause the tip of the ablation probe not to be advanced and positioned well enough. Supportively, it is reported in some studies that the subcapsular tumors are associated with a higher rate of local tumor progression after thermal ablation because of the inability to achieve required tumor-free ablation margin (11,23). However, it is also reported that there is no definitive evidence about the increase of local progression rate after thermal ablation in the capsular side of a peripheral tumor (24,25). We demonstrated in our study that about three out of four (69%) of the LR were seen at the capsular side of the ablation zone.

Another definition that could cause some technical problems directly effective on the ablation success is the "heat sink effect" due to the adjacent vessel (26). The blood flow with a relatively lower temperature within the lumen of the vascular structure near the ablation zone reduces the heat which is radiating through the ablation zone. In another word, it creates a cooling effect that will result in inadequate ablation. In this case, the development of a possible local recurrence will not be a surprise at all. This effect is more likely to be in radiofrequency ablation rather than the MWA (27). On the other hand, some authors did not report an association between the heat sink effect and MWA (28,29). Although we didn't determine any statistically significant relationship, the presence of blood vessel proximity was demonstrated in half of the ablated lesion with local recurrence in our study.

There are several limitations to our study that should be noted. First and the main limitation was the small sample size. Although we demonstrated some valuable results in percentages, it will be needed a larger sample size to have statistically significant data in future studies. Second, we only evaluated the patients who underwent the thermal ablation with only the MWA system and using only ultrasound guidance. No other imaging modalities and thermal ablation methods were analyzed. Third, no further evaluations were made related to histopathological types of lesions due to the small sample size. Forth, the performer dependent properties of the ablation procedure were not evaluated. Last, since we aimed to define the ablation tract and the liver capsule related features of LR which has been already occurred rather than evaluating the predisposing factors of LR occurrence, we didn't note the clinical parameters such as systemic chemotherapy treatment, presence of other distant metastases. In future studies, relationship between the features of LR and the clinical status of the patiens could be evaluated.

In conclusion, we have discussed and defined some features of LR related to the ablation tract and liver capsule independently such as the relation between the recurrence and the blood vessel proximity, side of the LR throughout the ablation tract and its relation with the liver capsule. In future studies, defining these features detailly with large cohorts would offer an insight into the development of the thermal ablation methods and treatment strategies.

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Arch Clin Exp Med 2020;5(2):64-68. e-ISSN: 2564-6567

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The effect of nutrition, depression, activity scores on mortality in patients with geriatric hip fractures

Geriatrik kalça kırığı hastalarında beslenme, depresyon, aktivite skorlarının mortalite üzerine etkisi

Savaş Çamur [1], Çağrı Özcan [1], Mehmet Mesut Sönmez [2], Sefa Giray Batıbay [3]

Abstract

Aim: Hip fracture causes high mortality rates in elderly patients. Here we investigate the relationship between serum laboratory parameters, bone densitometers, malnutrition, depression and pre-fracture survival activity scores of patients who died within 24 months after surgery for hip fracture.

Methods: 121 patients who underwent surgery for hip fracture between 2013 and 2016 and who met the study criteria were evaluated retrospectively. The patients who died within the first 24 months after surgery were evaluated as Group 1, and the patients who died after 24 months or who were still alive were evaluated as Group 2. Serum parameters before surgery, hip and vertebra bone densitometry were examined. The Barthel and Lawton Life Scale was completed, Mini nutritional assesment (MNA), geriatric depression scala short form (GDS-SF) and preoperative length of stay and BMI were evaluated.

Results: Comparing the parameters between groups, we detected no significant difference between age, BMI, vertebral BMD preoperative length of stay. Albumin, total protein, hip BMD, barthel score, and the lawton scoring system, GDS-FM, MNA showed significant differences between the two groups (P<0.05). According to the regression analysis, Albumin, total protein, MNA, GDS-SF, Barthel Score and Lawton Scoring Systems showed a significantly correlation in patients with mortality in the first 24 months (P<0.05).

Conclusion: Geriatric hip fractures have many factors that determine the risk of mortality within the first 24 months. According to our study, low albumin, total protein , malnutrition, high depression as well as low pretreatment activity scores, indicate high mortality risk in the 24 months.

Keywords ; Hip fractures, depression , nutrition, geriatric mortality, bone densitometry

Öz

Amaç: Kalça kırığı yaşlı hastalarda yüksek mortalite oranlarına sebep olur. Bu çalışmada kalça kırığı nedeniyle ameliyat sonrası 24 ay içinde ölen hastaların serum laboratuvar parametreleri, kemik dansitometreleri, yetersiz beslenme, depresyon ve kırık öncesi sağkalım aktivite skorları arasındaki ilişkiyi araştırdık.

Gereç ve Yöntem: 2013-2016 yılları arasında kalça kırığı nedeniyle ameliyat edilen ve çalışma kriterlerini karşılayan 121 hasta retrospektif olarak incelendi. Ameliyattan sonraki ilk 24 ay içinde ölen hastalar Grup 1, 24 ay sonra ölen veya halen hayatta olan hastalar Grup 2 olarak değerlendirildi. Ameliyat öncesi serum parametreleri, kalça ve vertebra dansitometrisi ölçüldü. Barthel ve Lawton Aktivite Skorları, Mini beslenme değerlendirmesi (MNA), geriatrik depresyon skala kısa formu (GDS-SF) ve preoperatif yatış süresi ve BMİ değerlendirilmiştir.

Bulgular: Gruplar arasındaki parametreleri karşılaştırarak yaş, BMİ, vertebra dansitometresi, preoperatif yatış süresi arasında anlamlı bir fark saptanmadı. Albümin, total protein, kalça dansitometresi, Barthel ve Lawton Aktivite Skorları, GDS-FM, MNA iki grup arasında anlamlı farklılıklar gösterdi (P <0.05). Regresyon analizine göre, albumin, total protein, MNA, GDS-SF, Barthel ve Lawton Aktivite Skorları ilk 24 ayda mortalitesi olan hastalarda anlamlı bir korelasyon gösterdi (P <0.05).

Sonuç: Geriatrik kalça kırıkları ilk 24 ay içinde mortalite riskini belirleyen birçok faktöre sahiptir. Çalışmamıza göre, düşük albümin, total protein, yetersiz beslenme, yüksek depresyon ve düşük aktivite skorları geriatrik kalça kırıklarında ilk 24 ayda yüksek mortalite riskini göstermektedir.

Anahtar Kelimeler; Kalça kırıkları, depresyon, beslenme, geriatrik mortalite, kemik Dansitometrisi

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Introduction

Hip fractures are often seen in elderly patients, with high mortality and morbidity rates. The average life expectancy in elderly people treated for hip fractures is shorter than those not treated from hip fractures [1]. Many factors play a role in postoperative mortality and morbidity in elderly patients[2]. Whether regional or general anesthesia methods are selected, mortality and morbidity cannot be reduced beyond a certain level[3]. In these patients, concomitant diabetes, hypertension, cardiovascular insufficiency, and lung problems increase the mortality and complications after surgery in these patients [4]. More than 50% of patients with old hip fractures have three or more chronic diseases[5]. In the literature, several studies had addressed morbidity and mortality in hip fractures, investigating various potentially contributing factors.

Some studies have shown that patients with high potassium, low albumin, and low hemogram have a relatively high mortality[6]. Other studies have reported that osteosarcopenia, muscle imbalans, activity scores are associated with mortality.

Depression is a pathological process that affects the daily activities of patients and reduces the quality of life[7]. This process affects the recovery of patients after surgery. Depression, especially associated with malnutrition, adversely affects the rehabilitation, healing process of the patient after surgery.

In our study, we evaluated malnutrition, depression scale and activity score of patients who were operated for hip fractures and investigated the relationship between the values of mortality and the risk of mortality in the first 24 months. We hypothesized that malnutrition, depression, albumin, total protein, activivity scores and osteoporosis affect mortality in these patients during the first 2 years after surgery.

Material and methods

Our study was approved by the Ethical Committee of our Institute (Number: 2019/1133). Between 2013 and 2016, 267 patients who were admitted to our hospital due to hip fracture were evaluated retrospectively. The study inclusion criteria were: Patients between the ages of 65 and 100 years, patients with an ASA score of 3 and above, patients who were admitted to our hospital within the first 24 h after a fracture, PFN Proksimal Femoral Nail, TST Rakor Medical Instruments Inc., Istanbul, Turkey), or patients with hip fractures treated with hemiarthroplasty with cemented and cementless(TST Rakor Medical instruments Co., Istanbul, Turkey). Cement application decision was decided according to hip dorr index. According to Dorr index, those with type A were treated with cementless, type B and C with cemented prosthesis. The exclusion criteria were: patients in the intensive care unit preop followed, patients with a fracture of the hip with another fracture, oncology patients, patients with preop or postop dialysis requirements, patients with pathological fractures, patients with a previous hip fracture, patients who have undergone another surgery within the last month, patients using immunosuppressive agents, patients with died during surgery, Patients with less than 24 months follow-up, and patients who have to wait for surgery for more than 7 days.

A total of 121 patients who met the study criteria were evaluated retrospectively. Relatives of the patients were reached from the hospital records. The exact days of death were asked. The patients who died within the first 24 months after the surgery were classified as Group 1, and the patients who died or survived after 24 months were Group 2. All patients were evaluated by a single anesthesiologist. ASA scores were determined. In the first 24 hour after the fractures, venous blood samples were taken, and laboratory parameters were evaluated. In laboratory parameters, albumin, and total protein levels were evaluated in all patients.(Coulter LH 780 Hematology Analyzer, California, USA) All patients' BMIs (Body Mass Indexes) were calculated by asking the patients or their relatives. In the preoperative period, albumin supplements were applied to patients with albumin below 2.5. However, preoperative initial values were included in the study. No special supplements were used in the postoperative period. Densitometry was performed from the intact hips and vertebra. The patient's intact hip was measured with 25 degrees of internal rotation following the following parameters (QDR Series Hologic, Inc., Bed- 97 ford, MA USA): (hip FOV: 113 × 112; neck FOV: 49 98 ×15; total BMD CV: 1.0 %; TH: 4.5). The Barthel and Lawton scores were calculated. Preop malnutrition disorders were evaluated by Mini nutritional assesment (MNA) [8]. The results of the MNA score were categorized into 3 groups. Malnourished patients were defined as having a MNA score less than 17 points (It was categorized as 1), risk for malnutrition patients the MNA score was between 17 and 23.5 points (It was categorized as 2) and Patients with good nutrition had a MNA score above 23.5 points (It was categorized as 3). Preop depression condition was evaluated by geriatric depression scale short form (GDS-SF) were evaluated[9] . The results of the GDS-SF score were categorized into 4 groups. Patients with a score of 0-4 were diagnosed with no depression (It was categorized as 0), mild depression with a score of 5-8 (It was categorized as 1), moderate depression with a score of 9-11 (It was categorized as 2), and major depression with a score of 12-15(It was categorized as 3).. According to the anesthesiologist's assessment, 40 patients underwent general and 92 patients underwent spinal anesthesia. PFN or hemiarthroplasty was performed according to the type of fracture. All patients were mobilized on the first postoperative day. All patients were given cephazolin (1 g IV) for the prophylaxis of infection on the first day and enoxaparin sodium embolism for the first 4 weeks. The patients were contacted by telephone every month in the postoperative follow-up, and their mortality status was questioned.

Statistical analysis

While evaluating the findings of the study, IBM SPSS Statistics 22 (IBM SPSS, USA, New York) program was used for statistical analysis. The normal distribution was evaluated by Shapiro-Wilks test. The Mann-Whitney U test was used to evaluate the parameters that did not show a normal distribution.. When the parameters were evaluated by Shapiro-Wilks test, it was seen that the parameters were not distributed homogeneously. The values between the two groups were evaluated by the Mann Whitney U test.

A multivariate logistic regression analysis was used to determine the relationship between the parameters used and mortality in our study. Results of multivariate analyzes were reported as adjusted odds ratios (OR) with 95% confidence intervals (CI) with a threshold significance at $p < 0.05$.

Results

One hundred twenty one patients included in the study, 63 were Group 1 and 58 were Group 2. Of 121 patients, 50 were male, and 71 were female. PFN was performed in 70 patients, and hemiarthroplasty was performed in 51 patients. Femoral neck fracture in 46 patients, subtrochanteric fracture in 17 patients, intertrochanteric fracture in 58 patients was seen. Cemented hemiarthroplasty was performed in 37 patients, and cementless hemiarthropasty in 14 patients.

The mean age of the patients in Group 1 was 82.32 (65-103). The mean preoperative BMI was 24,55 (18,14-37,10). Bone densitometry in spine was measured as -2.54 (0.80- -6.60). Bone Densitometry in hip at -3.08 (0.70- -4.90). When the laboratory parameters of the patients in Group 1 are evaluated, the values were: albumin 2.86 g/dL (2.1-4.78); total protein, 5.58 g/dL (3.70-7.93);. The Barthel score of the patients in Group 1 was 2,54 (1-3), and the Lawton score was 2.28 (0-5). The mean preoperative hospitalization time of the patients in Group 1 was 2.4 (1-6) days. According to GDS-SF there were no depression in 4 patients, mild depression in 22 patients, moderated depression in 30 patients and major depression in 7 patients. According to MNA scores, 12 patients had good nutrition and 35 patients had risk for malnutrition and 16 patients had malnutrition in Group 1

The mean age of the patients in Group 2 was 78.80 (65-90). The mean preoperative BMI was 25.95 (18.17-35.70). The mean spine densitometry was -2,18 (0.90--5.2) and hip densitometry was -2.5 (0.6--4.30). When laboratory parameters of the patients in Group 2 are evaluated, the values were: mean albumin, 3.16 g/dL (2-4.6); total protein, 6.12 g/dL (4.9-7.76) The mean Barthel score of the patients in Group 2 was 3.42 (1-5) and the Lawton score was 4.94 (0-8). The mean preoperative hospitalization period of the patients in Group 2 was 2.1 (1-7) days. When GDS-SF was examined in Group 2 patients, 21 patients had no depression, 25 patients had mild depression and 10 patients had moderated depression. There was no major depression sign in group 2 patients. According to MNA scores, 42 patients had good nutrition, 14 had risk for malnutrition and 2 had malnutrition in group 2 patients.

The parameters between the two groups were evaluated using the Mann Whitney U test. We detected no significant difference between age, BMI, vertebra BMD, preoperative hospitalization (all P>0.05). albumin, total protein, Hip BMD, MNA, GDS-SF, the Barthel Score, and the Lawton scoring system showed significant differences between the two groups (p<0.05) (Tables 1 and 2).

Table 1. Demographic findings, serum parameters, bone measurements of both groups, Preop Hospitalization.

	Total	Group 1	Group 2	P Value*
AGE	80,45 ± 8,06 (65-103)	82.32 ± 5,99 (68-100)	78,80 ±6,96 (65-90)	0,107
BMI	25,29 ±4,17 (18,14-37,10)	24,55 ±4,08 (18,14-37,10)	25,95 ±4,17 (18,17-35,70)	0,089
ALBUMIN	3,01±0,53 (2,00-4,78)	2,86 ± 0,51 (2,1-4,78)	3,16 ±0,5 (2-4,60)	*0,001*
TOTAL PROTEIN	5,86 ±0,79 (3,70-7,93)	5,58 ±0,84 (3,7-7,93)	6,12 ±0,65 (4,90-7,76)	*0,001*
SPINE BMD	-2,35 ± 1,57 (0,90--6,60)	-2,54 ±1,64 (0,80--6,60)	-2,18 ±1,49 (0,90--5,2)	0,25
HIP BMD	-2,7 ± 0,92 (0,70--4,90)	-3,08 ±0,86 (0,7- --4,9)	-2,5 ±0,89 (0,6--4,30)	*0,001*
Preop Hospitalization (Day)	2,3 ± 0,89 (1-7)	2,4 ± 0,87 (1-6)	2,1 ±0,92 (1-7)	0,48

Body Mass Index (BMI); Bone Mineral Density (BMD), * Mann Whitney U test p <0.05 statistically significant.

According to the Multinomial Logistic Regression Analysis after correcting various covariates (age, gender, BMI, preoperative hospitalization, surgery procedure, fracture type, ASA scores) the parameters examined in the study. Albumin, total protein, MNA, GDS-SF, the Barthel Score, and the Lawton scoring systems were significantly different in patients with mortality in the first two years (p<0.05). (Table 3) There was no significant relationship between bone densitometry and mortality in the first 2 years according to regression analysis.

Table 2. Functional scores, Mini nutritional assessment (MNA) and geriatric depression scala short form (GDS-SF) of both groups.

	Total	**Group 1**	**Group 2**	**P Value***
BARTHEL	3 ± 0,8 (1-5)	2,54 ± 0,61 (1-3)	3,42 ±0,91 (1-5)	***0,001***
LAWTON	3,6 ± 2,3 (0-8)	2,28 ± 1,55 (0-5)	4,94 ±2,21 (0-8)	***0,001***
MNA**	2,45±0,7 (1-3)	2,12±0,5 (1-3)	2,9±0,8 (1-3)	***0,001***
GDS-SF***	1,2±0,4 (0-2)	1,61± 0,7 (0-2)	0,82±0,5 (0-2)	***0,001***

MNA: Mini nutritional assessment, GDS-SF: Geriatric depression scala short form, * Mann Whitney U test p <0.05 statistically significant, **MNA score were categorized into 3 groups, ***GDS-SF score were categorized into 4 groups.

Table 3. Models adjusted for age, gender, BMI, preoperative hospitalization, surgery procedure, fracture type

	B	Std Error	Odd Ratio	%95 Confidence interval	P Value*
MNA	1,8	0,6	0,19	0,06-0,71	0,014
GDS-SF	1,55	0.33	1,12	1,3-1,1	0,044
BARTHEL	-1,7	0,41	1,18	1,08-1,40	0,001
LAWTON	-0,7	0,37	0,49	0,34-0,69	0,032
T.PROTEIN	-1,6	0,6	0,3	0,9-1,2	0,041
ALBUMIN	-0,2	0,8	0,9	1,1-1,5	0,022
SPINE BMD	1,1	0,6	1,2	0,8-21,5	0,08
HIP BMD	0,9	0,3	1,5	1,3-2,1	0,106

Std error: Standart Error, B: Coefficient of variables, MNA: Mini nutritional assessment, GDS-SF: Geriatric depression scala short form BMD: Bone Mineral Density, *: Multinomial Logistic Regression Analysis

Discussion

In recent years and because of advances in medicine, we are living longer, and the elderly population is increasing rapidly[1]. Thus, hip fractures are more common due to the increase in the elderly population. The comorbidities of these patients increase the difficulty of the surgery. In these patients, the mortality rates within the first year after surgery have been reported as 22%[10]. Franzo et al. reported the mortality rate in geriatric hip fractures in the first 6 months as 20%, and as 25% in the first year[11]. Roche et al. reported a mortality rate of 33% after 1 year[12]. These rates are altered according to the comorbidities of these patients and the time before surgery [13]. Pre-fracture functional status and muscle activity are the factors determining the post-surgical mortality rate[14].

Malnutrition in geriatric patients is an important factor affecting mortality[15]. In a meta-analysis study by Li et al., low serum albumin levels were found to be the most important predictors of hospital death risk and complication increase in geriatric hip fracture patients[16]. These authors also stated that the mortality rate was high in patients with low levels of malnutrition. In our study, albümin, total protein levels and MNA were found to be very low in the patients who were lost within the first 2 years. In these patients, improvement of albumin supplementation and malnutrition before and after

surgery might lead to a decrease in the mortality rates of patients. There are many publications in the literature that postoperative rehabilitation and patients recovery are more difficult in patients with poor nutritional status. A metaanalysis study by Peeters CM et al showed that patients with poor nutritional status had a very low return to pre-fracture health status [17] . Malafarina et al. In the metaanalysis study, malnutrition rate was 18.7% in patients evaluated with MNA score, whereas the prevalence was 45.7% in the case of malnutrition assessed by albumin protein and BMI rates in hip fracture[18]. İn this study although surgical techniques improved, 1-year mortality rate was 30% in these patients. In our study, especially in patients with low MNA scores, severe albumin and total protein decreased were observed in the group with a high mortality rate in the first two years. Van Wissen et al. Reported that 1-year mortality rate was 46% in patients with poor MNA scores and decreased to 7% in patients with good MNA scores in 226 cases of hip fracture patients[19]. In our study, a result consistent with the literature was observed.

In recent years, several studies have investigated the relationship between depression and hip fractures. In a study by Bi-Hua Cheng et al., They showed that 61% of patients with major depression had hip fractures more frequently than those without depression. However, in the same study, there was no significant difference between patients with less severe depressive disorder and without depressions[20] . According to our study, we think that depression is the cause of mortality in hip fracture. Andrade C showed that hip fracture was more common in patients with depression[21]. He questioned whether this was due to depression or antidepressant drugs. However, Branstrom et al showed that the risk of fracture was significantly lower after antidepressant use[22]. In a retrospective study by Maharlounei et al., Depression showed a significant effect on mobilization and recovery of patients within 6 months postoperatively. When these patients do not receive psychiatric support, they become more bedridden and patients recovery becomes more difficult in these patients [23]. In this case the depression scale of the patients more severe. It is especially important to recognize and treat depression in these patients. And we think that older osteoporotic hip fractures have more depression than expected.

GDS-SF was filled before surgical treatment in the patients included in the study. The high GDS-SF of these patients was found to be related to the mortality of patients after treatment. Depression is a pathological process that affects patients' daily care and quality of life. If the scale of depression is high in these patients, psychiatric support is required for this pathological process. In the meta-analysis study conducted by Shi TT et al., The incidence of hip fracture is more common in individuals with depression than in normal individuals. The mortality risk is also very high in these patients [24].

In our study, Barthel and Lawton's scoring system was used to evaluate the daily life activities of patients before hip fracture. Living activities prior to fracture show muscle imbalance of patients. This causes faster recovery and mobilization of the patient after surgery. Muscle imbalance also varies proportionally to bone density [25]. Türkmen et al. reported that bone density and gluteus maximus muscle mass were correlated with hip fracture in geriatric patients, and they show that bone density decreased in patients with low muscle mass [26]. In our study, daily life activity scores were significantly lower in patients who died within the first 24 months. In our study, no significant effect of osteoporosis on mortality was observed in the first two years. Osteoporosis increases the risk of fracture. However, since osteoporosis treatment indirectly increases activity in these patients, we think that it increases muscle imbalance and activity scores. Although there is no significant mortality, osteoporosis treatment should be given after fracture in these patients. Additionally preoperative muscle activation and strengthening of the muscle gives a better result after surgery [27].

Based on these data, we think that improved nutrition, treatment of patients with signs of depression, psychological rehabilitation and early physiotherapy would likely decrease the mortality rate during the early period postoperative period.

Limitations of this study include its retrospective design. Also, comorbidities were not investigated in the study group. Comorbidities might affect the mortality rate of patients, regardless of laboratory values [28,29]. Laboratory values are likely affected by multiple different factors. Therefore, we attempted to apply strict exclusion criteria in our study. We found that the number of patients studied in both groups was adequate based on comparison to similar studies in the literature.

Based on our findings, we propose that, low albumin, and total protein levels, depression, low malnutrition in elderly patients with hip fractures are important risk factors affecting mortality in the first 2 years. In addition, the preoperative activity status of the patient is related to mortality in the first 2 years.

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Efficacy of Genetic Sonogram For Predicting Aneuploidy In a High-Risk Pregnancy Population

Yüksek Riskli Gebelik Popülasyonunda Anöploidi Tahmin Etmede Genetik Sonogramın Etkinliği

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Abstract

Aim: This study evaluates the efficacy of genetic sonogram for predicting aneuploidy in high-risk pregnancies.
Material-Methods: This retrospective study included 1363 pregnant women who underwent a second trimester genetic sonogram due to high-risk pregnancy. Sensitivity, specificity, odds ratio, (+) and (-) likelihood ratios were calculated for each of the ultrasonography markers.
Results: Among the high-risk pregnancy study population, there was no significant difference regarding advanced maternal age, presence of a relative with Down Syndrome, history of anomaly in the previous pregnancy, hyperechogenic bowels, pyelectasis, nuchal fold thickness > 5 mm, ventriculomegaly, choroid plexus cyst, single umbilical artery or presence of right echogenic intracardiac focus between the control and aneuploidy groups (p>0.05). Tricuspid regurgitation, hypoplasia/absence of nasal bone, short femur, short humerus and left echogenic intracardiac focus were associated with increased risk of aneuploidy (p<0.05). The risk of aneuploidy was increased by 14.45 fold (95% CI 2.90-71.85) in cases with tricuspid regurgitation, 18.01 (5.46-59.32) fold by hypoplasia/absence of nasal bone, 9.74 (3.70-25.65) fold by presence of short femur, 11.42 (4.30-30.30) fold by presence of short humerus, and 4.20 (1.39-12.64) fold with the presence of left echogenic intracardiac focus. Analysis of combined markers showed that hypoplasia/absence of nasal bone + short humerus + tricuspid regurgitation resulted in the highest risk (OR = 11.20, LHR = 7.53).
Conclusion: In countries where NIPT could not be used as a screening test, genetic sonography is recommended for Down syndrome risk modification in high-risk pregnancies.

Keywords: Genetic sonography, Aneuploidy, Pregnancy

Öz

Amaç: Bu çalışmanın amacı yüksek riskli gebeliklerde anöploidi öngörmede genetik sonogramın etkinliğini değerlendirmektedir.
Gereç ve Yöntem: Bu retrospektif çalışmaya yüksek riskli gebelik nedeniyle ikinci trimester genetik sonogram uygulanan 1363 gebe dahil edildi. Her bir ultrasonografi markerı için spesifite, sensivite, odds ratio, pozitif ve negatif olabilirlik oranları hesaplanmıştır.
Bulgular: Çalışmada yüksek riskli gebelik popülasyonunda; ileri anne yaşı, Down Sendromlu bir akrabanın varlığı, önceki gebelikte anomali öyküsü, hiperekojenik bağırsak, pyelektazi, ense kalınlığı > 5 mm, ventrikülomegali, koroid pleksus kisti, tek umbilikal arter varlığı, sağ ekojenik intrakardiyak odak açısından kontrol ve anöploidi grupları arasında anlamlı bir fark yoktu (p> 0.05). Triküspit yetersizliği, burun kemiği hipoplazisi/yokluğu, kısa femur, kısa humerus ve sol ekojenik intrakardiyak odak artmış anöploidi riski ile ilişkili bulunmuştur (p <0.05). Anöploidi riski, triküspit yetersizliği olan olgularda 14.45 kat (% 95 CI 2.90-71.85), burun kemiği yokluğunda/hipoplazisinde 18.01 (5.46-59.32), kısa femur varlığı ile 9.74 (3.70-25.65), kısa humerus varlığında 11.42 (4.30-30.30), sol ekojenik intrakardiyak odak varlığında 4.20 (1.39-12.64) kat artmaktadır. Kombine markerların analizinde,burun kemiği hipoplazisi, kısa humerus ve triküspit yetersizliğinin birlikteliği en yüksek riskle sonuçlandığını gösterilmiştir (OR =11.20, LHR =7.53).
Sonuç: NIPT'nin iyice yayılmadığı bazı ülkelerde, yüksek riskli gebeliklerde Down sendromu risk modifikasyonu için genetik sonografi önerilir.

Anahtar Kelimeler: Genetik Sonogram, Anöploidi, Gebelik

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Introduction

Prenatal diagnosis refers to the detection of fetal chromosomal anomalies and other fetal malformations and diseases during the intrauterine period. Biochemical tests and ultrasonography (screening at 11th-14th weeks for nuchal translucency, screening at 18th-23rd weeks for soft markers) have become standard procedures for screening fetal chromosomal abnormalities [1,2]. Diagnosis of fetal aneuploidy requires invasive prenatal diagnostic procedures. These invasive diagnostic methods can lead to abortions in 1-2% of cases and are therefore recommended to those who have a high risk of chromosomal anomaly [3]. One of the methods to determine risk is second trimester ultrasonographic evaluation. This evaluation should identify abnormal ultrasonographic findings including major structural anomalies as well as minor (soft) markers that can aid in distinguishing aneuploid fetuses from euploid ones [4].

Ultrasonography is a highly efficient method for detection of trisomy 13 and 18 due to the high frequency of major anomalies (83-100 %). However, major fetal anomaly is observed in only 25 % of cases with trisomy 21 [5]. Major fetal anomalies observed in the ultrasonographic examination of fetuses with Down syndrome include cardiac defects (AVSD, Membranous VSD, Coarctation of Aorta, Double Outlet Right Ventricle, Tetralogy of Fallot), duodenal atresia, cystic hygroma, and hydrops fetalis. When these findings are detected, fetal karyotyping is recommended without the need for any additional risk modification [6]. On the other hand, some minor ultrasonographic changes are used for Down syndrome risk modification. These changes are often seen in normal fetuses, are usually transient, and have no serious consequences on the prognosis of the fetus. However, some features are more common in fetuses with trisomy 21 and are considered ultrasonographic markers (soft markers) of Down syndrome [7]. The most commonly used markers include nuchal fold thickness, hyperechogenic bowels, echogenic intracardiac focus, short extremities, pyelectasis, mild degree ventriculomegaly, wide pelvic angle, shortness of frontal lobe hypoplasia, clinodactyly, chorioid plexus cyst, and single umbilical artery. In recent years, attempts have been made to increase the sensitivity of this procedure by integrating additional measures, including absence or hypoplasia of nasal bone [8], frontomaxillary facial angle, prenasal edema [9], aberrant right subclavian artery [10], and tricuspid regurgitation [11]. The concept of "genetic sonography" can be described as the determination of aneuploidy risk via ultrasonography in order to identify patients with a high risk of trisomy 21. The goal is to reduce the number of unnecessary amniocentesis (and thus to reduce pregnancy loss associated with this procedure) without compromising sensitivity.

The number of genetic sonographic markers which are recommended for use in assessment of fetal anomalies has increased substantially over the past 20 years. Utilization of a large panel of sonographic findings results in increased diagnostic sensitivity (50-93%) [12].

The aim of the present study is to determine the efficacy of genetic sonography for predicting aneuploidy among high risk pregnant women referred to the perinatology unit in Suleymaniye Maternity Hospital.

Material and methods

In our study, 2036 high-risk patients from 10942 patients who underwent genetic sonograms with second trimester (16th-24th gestational weeks) ultrasonography applied to the Perinatology Department of Suleymaniye Maternity Hospital Hospital between June 2000 and July 2011 were included. Approval of Education and Planning Board and Ethical Committee of the Suleymaniye Maternity Hospital was received (Date:01/06/2008, No: 352). This study has been conducted in accordance with the declaration of Helsinki.

The women were considered as high-risk and were referred to perinatology department due to one or more of the following criteria: advanced maternal age, history of baby with anomaly in the previous pregnancy, presence of a relative with trisomy 21, high biochemical risk, anomaly detected by ultrasonography, presence of a marker suggestive of aneuploidy. We attempted to contact all 2036 cases during the postpartum period to confirm the diagnosis. We could not reach 643 (31.06%) cases due to incorrect phone number, missing hospital records, or change of address. We successfully contacted 1393 cases. 30 subjects were excluded due to intra-uterine demise before 40th week of gestation. Therefore, the study included 1363 (66.94%) cases. Table 1 shows the reason for referral among high-risk pregnant women.

Table1: Reason for referral among high-risk pregnant women

Reason of referral	Count (%)
Advanced maternal age	290(14.24%)
Advanced maternal age + High calculated biochemical risk[a]	196 (9.62%)
Advanced maternal age + Presence of an ultrasonographic finding	92 (4.51%)
Advanced maternal age + High calculated biochemical risk[a]+ Presence of an ultrasonographic finding	45 (2.21%)
Advanced maternal age +History of a baby with anomaly in the previous pregnancy	6 (0.29%)
Advanced maternal age +Presence of a relative with trisomy 21	1 (0.04%)
Advanced maternal age+ History of a baby with anomaly in the previous pregnancy+ Presence of an ultrasonographic finding	1 (0.04%)
Advanced maternal age+ Presence of a relative with trisomy 21+ High calculated biochemical risk[a]	1 (0.04%)
History of a baby with anomaly in the previous pregnancy	11(0.54%)
History of a baby with anomaly in the previous pregnancy+ Presence of an ultrasonographic finding	4(0.19%)
History of a baby with anomaly in the previous pregnancy+ High calculated biochemical risk[a]	2(0.09%)
Presence of a relative with trisomy 21	1(0.04%)
Presence of a relative with trisomy 21+ Presence of an ultrasonographic finding	4(0.19%)
High calculated biochemical risk[a]	317(15.56%)
High calculated biochemical risk[a]+ Presence of an ultrasonographic finding	192(9.43%)
Presence of an ultrasonographic finding	873(42,87%)
Total	2036 (%100)

In our perinatology department, genetic sonography was performed using a 3-7 MHz abdominal convex probe with a General Electric Voluson E730 ultrasonography device or a 3-5 MHz abdominal convex probe with a General Electric Logic 400 ultrasonography device. All measurements and evaluations were performed by an experienced perinatologists in the unit following a standardized protocol. Examinations included fetal biometric measurements and detailed investigation for major and minor markers of aneuploidy. Examinations were carried out in the supine position at 2-3 MHz frequency, allocating 20 minutes of time per patient on average. Short femur was defined as the proportion of measured length to the expected length smaller < 0.91 and short humerus was defined as the proportion of measured length to the expected length < 0.90. Mild degree ventriculomegaly was defined as lateral ventricle atrial diameter of the fetal head measured in transverse axial section between 10 and 15 mm. Echogenic intracardiac focus was defined as the presence of one or more round hyperechogenic appearances in

the ventricles in a four chamber section of the heart with similar or higher echogenicity compared to bones. Likewise, echogenic bowel was defined as bowels showing the same or higher echogenicity compared to bone structures such as the tibia or iliac bones. Criterion for renal pyelectasis was defined as bilateral renal pelvis anteroposterior diameter greater than 3 mm. Nasal hypoplasia was defined as fetal nasal bone length ≤ 2.5 mm. Increased nuchal fold thickness was defined as thickness ≥ 5 mm. Sensitivity, specificity, odds ratio, (+) and (-) likelihood ratios were calculated for each of the markers observed by ultrasonography.

Statistical analysis

As statistical methods mean, standard deviation, frequency, the chi-square test and diagnostic screening tests were used. Statistical analyses were performed with the SSPS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA) We assessed the overall diagnostic performance by weighted independent estimation of detection rate (sensitivity), true negative rate (specificity), positive likelihood ratio (LR; sensitivity / (1−specificity) and negative LR (1−sensitivity) / specificity). Results were evaluated within a 95% confidence interval, and level of significance was accepted as $p<0.05$..

Results

The study included 1363 high-risk cases presenting to the Perinatology Department of Suleymaniye Maternity Hospital, who underwent a second trimester genetic sonography and whose diagnosis was confirmed during the postpartum period. Maternal age of cases varied between 17 and 48 years, with a mean maternal age of 31.25 ± 6.64 years. In our study, maternal age was < 35 years in 862 (63.5%) cases, and ≥ 35 years in 496 (36.5%) cases. 1363 high-risk cases were provided with genetic counseling. 1363 high-risk cases were advised to undergo invasive procedures to reach a definitive diagnosis and for karyotyping. 336 cases did not choose to undergo the recommended procedure. Of the 1015 cases who agreed to undergo the recommended procedure, 966 cases (95.1%) underwent amniocentesis , 45 cases (4.43%) underwent cordocentesis, and 4 cases (0.4%) underwent chorionic villous sampling. No prenatal or postnatal karyotype anomalies were detected in 1338 (98.16%) cases. Aneuploidy was detected in 25 (1.84%) cases. Of these 25 cases with aneuploidy, 22 had trisomy 21, 1 had trisomy 2, 1 had trisomy 18, 1 had triploidy (69 XXY). 21 of the 22 cases with trisomy 21 were detected via invasive prenatal diagnostic tests.

The remaining case was advised to undergo amniocentesis due to detection of a bilateral intracardiac echogenic focus, bilateral choroid plexus cyst, and tricuspid regurgitation in the ultrasonography. However, the patient did not follow the recommendations of the medical staff and trisomy 21 was diagnosed in the newborn postnatally.

Among the 25 cases with aneuploidy, none had a relative with Down syndrome or history of anomaly in a previous pregnancy. Among the 1338 cases classified as the control group, 7 (0.5%) had a relative with Down syndrome, and 2 had a history of anomaly in a previous pregnancy. There was no significant difference between the control and aneuploidy groups regarding presence of a relative with Down syndrome or history of anomaly in a previous pregnancy ($p>0.05$).

Hypoplasia/absence of the nasal bone was significantly more frequent among cases with aneuploidy ($p=0.001$). Among 25 cases with aneuploidy, 4 had hypoplasia/absence of the nasal bone. The sensitivity and specificity of this marker were 16% and 98.95%, respectively. Hypoplasia/absence of the nasal bone increased the risk of aneuploidy by 18.01 (95% CI 5.46-59.32) fold. The likelihood ratio (+) was 15.30 and the likelihood ratio (-) was 0.84 (Table 2).

Short femur was significantly more common among cases with aneuploidy ($p=0.001$). Among the 25 cases with aneuploidy, 6 had short femur. The sensitivity and specificity of this marker were 24% and 98.86%, respectively. Presence of short femur increased the risk of aneuploidy by 9.74 (95% CI 3.70-25.65) fold. The likelihood ratio (+) was 7.64 and the likelihood ratio (-) was 0.78 (Table 2).

Short humerus was significantly more common among cases with aneuploidy ($p=0.001$). Among 25 cases with aneuploidy, 6 had a short humerus. The sensitivity and specificity of this marker were 24% and 97.31%, respectively. Presence of short humerus increased the risk of aneuploidy by 11.42 (95% CI 4.30-30.30) folds. The likelihood ratio (+) was 8.92; and likelihood ratio (-) was 0.78. (Table 2).

Tricuspid regurgitation was significantly more common among cases with aneuploidy ($p=0.001$). Among 25 cases with aneuploidy, 2 had tricuspid regurgitation. Sensitivity and specificity of this marker were 8% and 99.49%, respectively. Presence of tricuspid regurgitation increased the risk of aneuploidy by 14.45 (95% CI 2.90-71.85) fold. The likelihood ratio (+) was 13.37 and the likelihood ratio (-) was 0.92. (Table 2).

Clinodactyly was significantly more common among cases with aneuploidy ($p = 0.024$). Among 25 cases with aneuploidy, 1 had clinodactyly. Sensitivity and specificity of this marker were 4% and 99.48%, respectively. Presence of clinodactyly increased the risk of aneuploidy by 7.92 (95% CI 0.93-66.92) fold. However, this increase was did not meet the standard of statistical significance ($p<0.05$). The likelihood ratio (+) was 7.69 and the likelihood ratio (-) was 0.96. (Table 2).

The frequency of major cardiac anomaly was significantly higher among cases with aneuploidy ($p=0.035$). Among 25 cases with aneuploidy, 3 had major cardiac anomaly. Sensitivity and specificity of this marker were 12% and 99.33%, respectively. Presence of major cardiac anomaly increased the risk of aneuploidy by 20.13 (95% CI 5.10-79.47) fold. The likelihood ratio (+) was 17.91 and the likelihood ratio (-) was 0.88. (Table 2).

Presence of left echogenic intracardiac focus was significantly more common among cases with aneuploidy ($p=0.006$). Among the 25 cases with aneuploidy, 4 had left echogenic intracardiac focus. Sensitivity and specificity of this marker were 16% and 95.66%, respectively. The odds ratio was 4.20 (95% CI 1.39-12.64). The likelihood ratio (+) was 3.68 and the likelihood ratio (-) was 0.87. (Table 2).

In addition to isolated markers, we also examined the association between combinations markers and aneuploidy risk. Among all investigated combinations, the combination that was most strongly associated with aneuploidy was tricuspid regurgitation + hypoplasia/absence of the nasal bone + short humerus. The combination of tricuspid regurgitation + hypoplasia/absence of the nasal bone + short humerus was significantly more common among cases with aneuploidy ($p=0.001$). Among 25 cases with aneuploidy, 9 had at least one of the following conditions: tricuspid regurgitation, hypoplasia/absence of nasal bone, or short humerus combination. Sensitivity and specificity of this combination were 36% and 95.22%, respectively. The odds ratio was 11.20 (95% CI 4.76-26.31). The likelihood ratio (+) was 7.53 and the likelihood ratio (-) was 0.67.

Short femur + short humerus + hypoplasia of the nasal bone was the second most common combination among cases with aneuploidy ($p = 0.001$). Among 25 cases with aneuploidy, 8 exhibited at least one of the following traits: short femur, short

Table.2 :Odds ratios and Likelihood Ratios for Sonographic Markers: Statistically Significant* Associations With Down Syndrome

	Aneuploidy (n=25)	Normal (n=1338)	+p value	Sensitivity	Specificity	Odds Ratio		L ratio (+)	Li ratio (-)
	n (%)	n (%)		%	%		%95CI		
Hypoplasia/absence of the nasal bone	4 (16%)	14(1.0%)	0.001	16%	98.95%	18.01	5.46-59.32	15.30	0.84
Short femur	6 (24%)	42(3.1%)	*0.001*	24%	96.86%	9.74	3.70-25.65	7.64	0.78
Short humerus	6 (24%	36(2.7%)	*0.001*	24%	97.31%	11.42	4.30-30.30	8.92	0.78
Tricuspid regurgitation	2 (8%)	8 (0.6%)	*0.001*	8%	99.49%	14.45	2.90-71.85	13.37	0.92
Clinodactyly	1 (4%)	7 (0.5%)	*0.024*	4%	99.48%	7.92	0.93-66.92	7.69	0.96
Major cardiac anomaly	3 (12%)	9(0.7%)	*0.035*	12%	99.33%	20.13	5.10-79.47	17.91	0.88
Left echogenic intracardiac focus	4 (16%)	58(4.33%)	*0.006*	16%	95.66%	4.20	1.39-12.64	3.68	0.87
Ttricuspid regurgitation + hypoplasia/absence of the nasal bone + short humerus	9 (36%)	64(4.78%)	*0.001*	36%	95.22%	11.20	4.76-26.31	7.53	0.67
Short femur + short humerus + hypoplasia	8 (32%)	56(4.18%)	0,001	32%	95.81%	10.77	4.46-26.02	7.63	0.70

+ chi-square test p<0,05

humerus, or hypoplasia of the nasal bone. Sensitivity and specificity of this combination were 32% and 95.81%, respectively. Odds ratio was 10.77 (95% CI 4.46-26.02). The likelihood ratio (+) was 7.63 and the likelihood ratio (-) was 0.70. (Table 2).

There was no significant difference regarding presence of right echogenic intracardiac focus, hyperechogenic bowels, or the proportion of cases with nuchal fold thickness > 5 mm between the control and aneuploidy groups in the high-risk population (p=0.236; p=0.526; p=0.175). In addition, there was no significant difference between the normal and aneuploidy groups in the high-risk population regarding presence of right pyelectasis, or left pyelectasis, or bilateral pyelectasis, presence of right ventriculomegaly, or left ventriculomegaly, or bilateral ventriculomegaly, presence of right plexus cyst, or left choroid plexus cyst, or bilateral choroid plexus cysts, or absence of right umbilical artery, or left umbilical artery ([p=0.217, p=0.196, p=0.296]; [p=0.151, p=0.730, p=0.604]; [p=0.138, p=0.264, p=0.102]; [p=0.594, p=0.365], respectively) (Table 3).

Discussion

Genetic sonography relies on several ultrasonographic markers which are not strictly fetal anomalies. These features may also be observed in normal fetuses but are more common in fetuses with trisomy 21. In our study, we investigated cases who underwent genetic sonogram between the 16th and 24th weeks of gestation for examination of nuchal fold thickness, hyperechogenic bowel, echogenic intracardiac focus, short femur, short humerus, pyelectasis, ventriculomegaly, hypoplasia/absence of nasal bone, choroid plexus cyst, clinodactyly, single umbilical artery, tricuspid regurgitation and major cardiac anomaly. The patients were advised to undergo additional invasive diagnostic procedures because of presence of one or more significant ultrasonographic findings and another risk factor, such as advanced maternal age, increased calculated risk in triple test, history of anomaly in a previous pregnancy, or presence of a relative with Down syndrome.

According to our data, hypoplasia/absence of the nasal bone, short femur, short humerus, tricuspid regurgitation and left echogenic intracardiac focus were significantly more common among cases with aneuploidy (p<0.05).

Cicero et al. reported the LHR value for trisomy 21 in the presence of nasal bone hypoplasia as 50.5 [13]. Bromley et al. reported the LHR value in the absence of nasal bone as 83, stating that the absence of the nasal bone was the most significant marker in the genetic sonogram [14]. In our study, sensitivity and specificity of hypoplasia/absence of nasal bone were 16% and 98.95%, respectively. We found that hypoplasia/absence of nasal bone increased the risk of aneuploidy by 18.01 (5.46-59.32) fold.

Benacerraf et al reported the LHR value for short femur as 5.5, and the LHR value for short humerus as 13.4 [15]. Nyberg et al. calculated LHR of short femur as 1.2, and LHR of short humerus as 5.1 [16]. Johnson et al. reported the LHR of short humerus as 7.5, making this the third most important marker in the genetic sonogram [17]. In our study, we calculated sensitivity, specificity and LHR values of short femur as 24%, 96.86%, and 7.64, respectively. The presence of short femur increased the risk of aneuploidy by 9.74 (3.70-25.65) fold. As for short humerus, sensitivity, specificity and LHR values were 24%, 97.31% and 8.92, respectively. Short humerus increased the risk of aneuploidy by 11.42 (4.30-30.30) fold. Other studies also showed that in comparison to the presence of short femur, the presence of a short humerus was more significant for aneuploidy risk [18].

Faiola et al. examined the association between tricuspid regurgitation and chromosomal abnormalities [19]. Their study included a total of 1557 cases with high risk for Down syndrome (high biochemical risk, or increased nuchal translucency), and they examined tricuspid valve in 1538 (99%) cases. They detected trisomy 21 in 114 cases, trisomy 18 in 42 cases, and other chromosomal abnormalities in 59 cases, while 1323 cases were found to have no chromosomal abnormality. They observed tricuspid regurgitation in 67.5% of cases with trisomy 21, in 33% of cases with trisomy 18, in 15% of cases with other chromosomal abnormalities, and in 4.4% of cases without any chromosomal abnormality. Faiola et al. concluded that early detection of tricuspid regurgitation was not an appropriate screening method for the general population. They stated however, that since tricuspid regurgitation was frequently associated with chromosomal abnormalities in a high risk population, and because sensitivity was high, that this finding could serve as a useful marker. In our study, we found that tricuspid regurgitation was significantly more common among cases with aneuploidy (p=0.001). Among 25 cases with aneuploidy, 2 were found to have tricuspid regurgitation. Sensitivity and specificity of this marker were 8% and 99.49%, respectively. The odds ratio was 14.45 (95% CI 2.90-71.85). The likelihood ratio (+) was found as 13.37 and the likelihood ratio (-) was 0.92.

Roberts et al. reported the frequency of echogenic intracardiac focus among aneuploid fetuses as 16-39% [20]. Nyberg et al. and Benacerraf et al. reported LHR values for echogenic intracardiac focus between 1.4 and 5.4 [15,16]. In our study, the frequency of left echogenic intracardiac focus was significantly higher among cases with aneuploidy. Sensitivity,

specificity and LHR were 16%, 95.66% and 3.68, respectively, and this marker was found to increase the risk of aneuploidy by 4.20 (1.39-12.64) fold.

Table 3: Distribution of cases according to genetic sonogram results

	Aneuploidy (n=25) n (%)	Normal (n=1338) n (%)	*p value*
Right Echogenic Intracardiac Focus	1 (4%)	17 (1.27%)	*0.236*
Hyperechogenic Bowels	4 (16%)	284 (21.2%)	*0.526*
Nuchal Fold Thickness > 5 Mm	3 (12%)	81 (6.1%)	0.175
Right Pyelectasis	0	77 (5.75%)	*0.217*
Left Pyelectasis	0	84 (6.27%)	0.196
Bilateral Pyelectasis	0	56 (4.1%8)	*0.296*
Right Ventriculomegaly	2 (8%)	40 (3.0 %)	*0.151*
Left Ventriculomegaly	0	38 (2.8%)	*0.730*
Bilateral Ventriculomegaly	1 (4%)	32 (2.39 %)	*0.604*
RİGHT Choroid Plexus	5 (20%	143 (10.68%)	*0.138*
Left Choroid Plexus	4 (16%)	126 (10.16%)	*0.264*
Bilateral Choroid Plexus Cysts	4 (16%)	98 (7.32%)	*0.102*
Absence Of Left Umbilical Artery	1 (4%)	22 (1.64%)	0.365
Absence Of Right Umbilical Artery	0	15 (1.12%)	0.594

Vintzileos et al. (1997) and Deren et al. (1998) reported that clinodactyly was observed in 3.4% of normal fetuses, and in 18.8% of fetuses with trisomy 21. They reported the LHR value as 5.6 [21,22]. In our study, clinodactyly was significantly more common among cases with aneuploidy ($p<0.05$). Clinodactyly was calculated to increase the risk of aneuploidy by 7.92 (95% CI 0.93-66.92) fold. However, this increase was insignificant.

In our study, we found no significant difference regarding nuchal fold thickness, presence of hyperechogenic bowels, pyelectasis, ventriculomegaly, choroid plexus cyst, single umbilical artery, or right intracardiac focus between the normal and aneuploidy groups in the high risk population ($p>0.05$).

Studies that defined pathological nuchal fold thickness as ≥ 6 mm reported the sensitivity of this marker as 40% and false positivity as 0.1%. Smith-Bindman et al. Reported the LHR value of nuchal fold thickness as 17, and stated that it was the second most significant marker in the genetic sonogram [23]. Nyberg et al. proposed that the sensitivity of this marker would be increased without causing any abnormal increase in the false positivity rate by dropping the pathological threshold to 5m; using this definition, they, reported an LHR value of 38.7 [16]. In our study, we defined the pathological threshold for nuchal fold thickness as 5 mm. We found no significant difference between the normal and aneuploidy groups regarding the proportion of cases with increased nuchal thickness ($p=0.175$).

Benacerraf et al. and Nyberg et al. reported the LHR of hyperechogenic bowels as 22.5 and 6.7, respectively [15,16]. In their 2001 study, Smith Bindman et al. reported sensitivity, specificity, and LHR values of hyperechogenic bowels as 4%, 99%, and 6.1, respectively [23]. In our study, we found no significant difference in the high-risk population regarding frequency of hyperechogenic bowels between normal and aneuploidy groups ($p > 0.05$).

In the studies conducted by Mandell et al. and Benacerraf et al. pyelectasis was observed in 17-25% of fetuses with Down syndrome, and 2.8% of normal fetuses [15,24]. Mean LHR values of pyelectasis were reported in the range between 1.5 and 5.2 [15]. In their 2001 study, Smith Bindman et al. reported sensitivity, specificity and LHR values of pyelectasis as 2%, 99%, and 1.9, respectively [23]. We did not observe any cases of pyelectasis in the study group.

Hobbins et al. reported the sensitivity of mild degree ventriculomegaly between 5.7% and 14.5%, and false positivity rate as 0.1%. [25]. In our study, we found no evidence that ventriculomegaly has any meaningful sensitivity for the prediction of aneuploidy.

In a case control study published in 2002, Bromley et al. reported the LHR value of echogenic intracardiac focus for aneuploidy risk as 1.4 (95% CI 0.6-4.3) [26]. However, this result was not statistically significant26 .In our study, the frequency of left echogenic intracardiac focus was significantly higher among cases with aneuploidy ($p=0.006$). Among the 25 cases with aneuploidy, 4 were found to have left echogenic intracardiac focus. The sensitivity and specificity values were 16% and 95.66%, respectively. The odds ratio was 4.20 (95% CI 1.39-12.64). Likelihood ratio (+) The likelihood ratio (+) was 3.68 and the likelihood ratio (-) was 0.87.

Gross et al. reported the frequency of trisomy 18 in the presence of isolated choroid plexus cyst as 1/374 [27] .Smith Bindman et al. (2001) calculated the LHR value of choroid plexus cyst for trisomy 21 as 1.0, and stated that presence choroid plexus cyst was not a marker for trisomy 21 [23]. In our study, the frequency of choroid plexus cyst was not significantly different between the control and aneuploidy groups in a high risk population ($p>0.05$).

Budorick et al. found no significant association between isolated single umbilical artery and aneuploidy [28]. Similarly, we found no significant difference regarding frequency of a single umbilical artery between the control and aneuploidy groups in a high risk population ($p>0.05$). Nyberg et al. evaluated risk modification based on the genetic sonogram and found that the presence of a single marker increased the risk by 2 fold, the presence of two markers increased the risk by 10 fold, and presence of three markers increased the risk by 100 fold on average [18]. In our study, when we examined the effect of combinations of markers on aneuploidy risk, we found that the combination of hypoplasia/absence of nasal bone + short humerus + tricuspid regurgitation yielded the highest LHR value, with an odds ratio of 11.20.

Nowadays in most of the countries a highly sensitive non-invasive testing called NIPT is used as screening test for earlier detection of aneuploidy in high risk pregnant women. Pregnancies with high risk NIPT results are referred for genetic counselling to be evaluated for invasive procedures such as chorionic villus sampling, amniocentesis or cordosentesis. But still in some countries NIPT could not be used as routine screening method. In these cases, this study have clinical importance to guide obstetricians for efficacy of genetic sonogram for predicting aneuploidy in a high risk pregnancy population. The purpose of genetic sonogram is to reduce the number of unnecessary invasive procedures and to minimize the rate of false positivity without compromising the sensitivity for detection of anomalies in a high risk population. In conclusion, when performed following a standardized protocol in perinatology units by experienced per,natologists, genetic sonogram is characterized by high sensitivity, high specificity and low false positivity rates for Down syndrome screening. This procedure is recommended for Down syndrome risk modification in high or intermediate risk populations as determined by maternal age, first trimester screening or triple/quadruple tests.

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Clinical Approach to Renal Artery Thromboembolism

Renal tromboemboliye Klinik Yaklaşım

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Abstract

Aim: We aimed to reveal the clinical, laboratory, radiological findings of infarction in the renal artery and its branches due to thrombosis, its effects on renal functions and the measures to be taken.
Methods: The study sample included 8 patients who were admitted to the emergency department of Kutahya University of Health Sciences Evliya Celebi Training and Research Hospital between 2018-2020, and who were hospitalized with the diagnosis of acute renal infarction. Patients were retrospectively analyzed with clinical findings, CT angiography-abdomen, clinical observations, prognosis and complications.
Results: Of the patients, 5 were male and 3 were female. The mean age was 55.13 (29-69) years. One patient presented with bilateral renal infarction, while 7 had unilateral renal infarction. The etiology of the patients was idiopathic in 2, atrial fibrilation (AF) in 3 patients, and atherosclerosis in 3 patient. The mean serum creatinine of 1.24 (0.7-3.2) mg/dl and the mean blood leukocyte level of 16925 (11000-26000) mcL were determined. The mean length of hospital stay was 4.6 (3-7) days. Anticoagulant therapy was initiated in all patients for risk of recurrent renal infarction and thromboembolism.
Conclusion: We revealed that renal infarction, rarely seen in urology practice, has nonspecific clinical findings; therefore, it should be kept in mind in differential diagnosis for patients presenting with sudden-onset oblique or abdominal pain, and that diagnosis can be made using contrast-enhanced CT. We determined that AF and valvular heart diseases which cause atherosclerosis and cardiac thrombosis play an important role in the etiology.

Keywords: abdominal pain; computed tomography angiography; infarction; renal artery; thromboembolism

Öz

Amaç: Çalışmamızda renal arter ve dallarında izlenen trombüse bağlı infarktın; klinik, laboratuar, radyolojik bulgularını ve renal fonksiyonlara etkisi ile takibinde alınması gereken önlemlerin ortaya konulması amaçlandı.
Gereç ve Yöntem: Çalışmamıza 2018-2020 arasında Kütahya SBÜ Evliya Çelebi Eğitim ve Araştırma Hastanesi acil servisine başvuran ve akut renal infarkt tanısı konularak yatırılan 8 hasta dahil edildi. Hastalar retrospektif olarak incelenerek klinik bulguları, anjio batın tomografileri, klinik gözlemleri, renal fonksiyonlarda görülen değişimleri, takiplerinde gelişen komplikasyon ve prognozları değerlendirildi.
Bulgular: 8 hastanın 5'i erkek, 3'ü kadın idi. Yaş ortalaması 55,13 (29-69) yıl olarak saptandı. Bir hastada bilateral, 7 hastada tek taraflı renal infarkt alanı izlendi. Hastaların etiyolojisinde 2 hasta idiyopatik, 3 hastada atriyal fibrilasyon, 3 hastada ateroskleroz vardı. Serum kreatinin ortalaması 1.24 (0,7-3,2) saptandı. Kan lökosit ortalaması 16925 (11000-26000) olarak tespit edildi. Hastaların ortalama hastane yatış süresi 4.6 gün (3-7) idi. Tüm hastalara tekrarlayan renal infarkt ve tromboemboli riski için antikoagülan tedavi başlandı.
Sonuç: Çalışmamızda üroloji pratiğinde nadir olarak görülen renal infarktın klinik bulgularının nonspesifik olup bu nedenle ani başlayan yan veya karın ağrısı kliniği ile başvuran hastalarda ayırıcı tanıda mutlaka akılda tutulması gerektiği ve kontrastlı tomografi ile tanı konulabileceğini ortaya koyduk. Etiyolojide ateroskleroz ve kardiyak trombüse neden olan AF, kapak hastalıklarının önemli rol oynadığını belirledik.

Anahtar kelimeler: karın ağrısı; anjio batın tomografi; infarct, renal arter tromboemboli

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Introduction

Renal infarction (RI) is a rare (0.004-0.007%) disease with high morbidity [1, 2]. The renal artery divides into segmental arteries in the kidney after originating from the aorta. Obstruction of the renal artery or the segmental arteries with thrombosis may lead to infarction in the kidney, which is an end-artery organ. Renal infarction is mostly seen in older ages, but it can be seen at any age. The etiology of RI due to thromboembolism includes hypercoagulation, atrial fibrillation, valvular heart diseases and atherosclerosis [3, 4]. Since it has no pathognomonic clinical finding, diagnosis can be difficult. Sudden-onset of oblique pain, nausea, vomiting and fever may be observed. It is often confused with renal colic. In cases with no stone detection on examination and imaging, RI is easily diagnosed with appearance of hypodense infarct areas on contrast-enhanced computed tomography (CT). Renal dysfunctions may be seen depending on the size of the infarction. In treatment, angiographic thrombolysis or embolectomy is not recommended for segmental artery occlusions. In the current study, our aim was to reveal the clinical and radiological findings of acute segmental RI and its effect on renal functions.

Material and methods

After obtaining ethical approval (no. 2020/04-10 dated 25.02.2020) from the non-interventional ethics committee of Kutahya University of Health Sciences, we included 8 patients who were followed up with the diagnosis of acute RI in our clinic between 2018 and December 2020. The files of the patients were examined, and their complaints, clinical findings, comorbidities, serum creatinine and leukocyte values and all contrast-enhanced abdominal tomography images were recorded. The treatments and examinations were noted. In the follow-up, the patients' prognosis and the problems encountered were recorded. The data were analyzed using the SPSS (Statistical Package for Social Sciences) for Windows 22.0. In the data analysis, descriptive statistical methods (frequency, percentage, mean, standard deviation) were used. The results were evaluated at 95% confidence interval and 5% significance level.

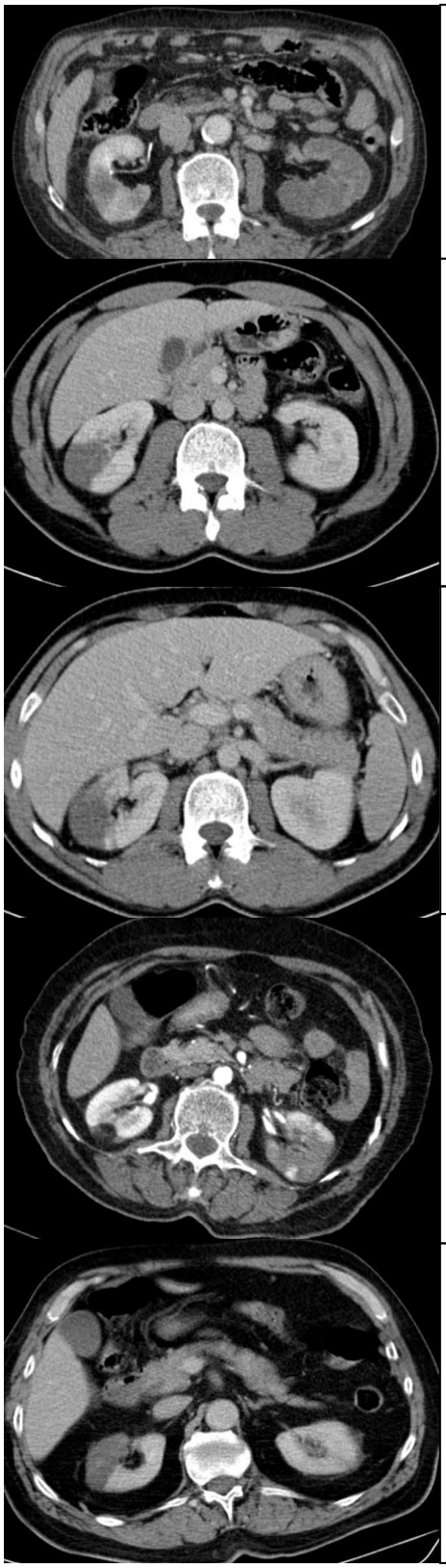
Results

Of the patients, 5 were male and 3 were female. The mean age was 55.13 (29-69) years (Table 1). All patients were admitted to the emergency room with the complaints of severe oblique and abdominal pain. Contrast-enhanced CT angiography revealed that 4 patients had RI on the right side, 3 had RI on the left side and 1 patient had bilateral RI (Figure 1). The infarction sizes varied between 4-10 cm. Renal functions prior to RI were observed to be normal. Interventional radiology was consulted for angiographic thrombolysis or embolectomy. However, no intervention was considered due to the presence of segmental embolism in all patients. In the initial diagnosis, elevated serum creatinine levels were detected in one patient. The mean serum creatinine level was 1.24 (0.7-3.2) mg/dl. Leukocytosis was present in all patients. The mean blood leukocyte level was 16925 (11000-26000) mcL (Table 2). As etiological factors, 3 patients had atrial fibrillation (AF), while 3 had a history of coronary artery disease and peripheral arterial disease. The two remaining patients had no history of comorbidity. All patients were hospitalized, and initiated on hydration, parenteral antibiotics and analgesic treatment. All patients were relieved of their pain complaints after 1-3 days. The length of stay was 4.6 (3-7) days. The patient with bilateral RI persisted to present with elevated serum creatinine levels, which did not require renal replacement therapy. The 2 patients with no etiological factors

Table 1. Demographic and clinical data

Gender	
Male	5
Female	3
Age (mean)(min-max)	55.13 (29-69)
Kidney with infarction	
Right	4
Left	3
Bilateral	1
Mean serum creatinine level , (min-max) mg/dl	1.24 (0.7-3.2)
Mean blood leukocyte level, (min-max) mcL	16925 (11000-26000)
Mean length of hospital stay, (min-max) days	4.6 (3-7)

Figure 1: CT angiography images



Patient 1. Bilateral RI, Diffuse infarction in the left kidney, infarction in the lower pole of the right kidney.

Patient 2. Infarction in the upper and middle poles of the right kidney.

Patient 3. Infarction in the middle and lower poles of the right kidney.

Patient 4. Diffuse infarction in the left kidney.

Patient 5. Diffuse infarction in the lateral half of the right kidney.

were examined in detail for hypercoagulopathy. However, no pathology was found. In the follow-up of one patient, pulmonary embolism developed with stroke secondary to cerebral embolism after 1 month on prophylaxis (Table 3).

Table 2. Demographic data and clinical and laboratory findings

Patients	Gender	Age	Affected kidney	Localization	S-Creatinine mg/dl	Leukocyte mcL
1	Male	63	Bilateral	Left: Diffuse Right: Lower pole 3 cm	3.2	19000
2	Female	29	Left	Upper and middle pole 4 cm	0.8	11000
3	Male	43	Right	Middle and lower pole 6 cm	0.8	13500
4	Female	57	Left	Diffuse	0.9	26000
5	Male	69	Right	Diffuse	0.9	13900
6	Male	58	Right	Upper and middle pole 5 cm	0.8	18000
7	Female	68	Right	Upper, middle and lower pole 9 cm	1.1	18000
8	Male	54	Left	Middle and lower pole 5 cm	1.0	16000

Table 3. Etiology, comorbidities and prognosis

Patients	Etiology	Comorbidities	Prognosis
1	AF	AF, ischemic heart disease, hypertension	Pulmonary embolism and stroke after 1 month
2	Idiopathic	No	Healthy
3	Idiopathic	No	Healthy
4	Atherosclerosis	Diabetes, ischemic heart disease, hypertension	Healthy
5	AF	AF, ischemic heart disease, hypertension	Healthy
6	AF	AF, ischemic heart disease, hypertension	Healthy
7	Atherosclerosis	Diabetes, ischemic heart disease, hypertension	Healthy
8	Atherosclerosis	Diabetes, ischemic heart disease, hypertension	Healthy

Discussion

Renal infarction is a rare health condition that may lead to serious morbidity and mortality. The literature shows that patients admitted to the emergency room have an incidence rate of 0.003-0.013% [3-5]. We found that patients admitted to the emergency room in the city of Kutahya had an RI incidence rate of 0.003%. The diagnosis of RI consists of nonspecific symptoms and laboratory findings such as abdominal pain, oblique pain, fever, nausea, vomiting, leukocytosis and high creatinine levels, and it can be quite difficult to diagnose [6]. Renal infarction patients considered to have renal colic, and in cases of no ureteral stone on non-enhanced abdominal CT, RI should be considered in the differential diagnosis. In these cases, CT should be repeated as contrast enhanced. Renal infarction can only be diagnosed by contrast-enhanced abdominal CT. On CT, the hypodense infarction separated from renal parenchyma by sharp borders is observed as an area with no blood supply [7]. While contrast-enhanced CT can show this hypodense infarction area, CT angiography is recommended to observe arterial anomalies and the embolism area [8].

The etiology of RI often includes pathologies such as AF, which causes cardiac thromosis, hypercoagulation and atherosclerosis, although it can also develop idiopathically [9, 10]. In the present study, similar to the literature, 3 patients were thought to have developed AF, 3 atherosclerosis and 2 idiopathic RI. In the follow-up of these patients, the risk of recurrent RI and thromboembolism in other organs is quite high [11]. For patients with etiological risk factors after RI, anticoagulant therapy is recommended. In the current study, anticoagulant therapy was initiated in 6 patients with AF and atherosclerosis. One patient with AF had cerebral embolism in addition to pulmonary embolism 1 month after RI, despite the anticoagulant therapy.

Renal dysfunction with high morbidity can also be seen after RI. Renal dysfunction is associated with the size of the infarction area [12, 13]. Patients with renal dysfunction before RI, bilateral cases and unilateral global infarctions often present with impaired renal functions. In these patients, the contrast agent given during CT angiography is also a nephrotoxic agent. Contrast nephropathy can aggravate renal dysfunction in risky cases. In this study, one patient who developed bilateral RI developed kidney failure that did not require renal replacement therapy.

There is no curative treatment protocol after RI. Patients are recommended to receive anticoagulant therapy, hydration, antibiotherapy and symptomatic treatments such as analgesics and antiemetics. In cases of renal dysfunction, nephrotoxic medical agents should be avoided [14, 15]. In our study, all patients were hospitalized. Then, prophylactic antibiotherapy, hydration and symptomatic treatments were administered. No complication was observed in the follow-up, and the patients were discharged with no problems.

The main limitations of our study are its retrospective design, single-center nature, and limited number of patients. Despite that, our study can be a guide for prospective studies on RI.

Conclusion

Although rare, RI is an important disease that is difficult to diagnose, has no clear treatment, and can occasionally cause serious morbidity such as chronic renal failure. For patients with etiological risk factors such as AF and other pathologies that lead to cardiac thrombosis, atherosclerosis and hypercoagulation, anticoagulant therapy is the key to prevent the development of RI. In patients with RI, care should be taken along with preventive measures for renal dysfunction and recurrent thromboembolism.

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Bilirubin metabolism and its role in atherosclerosis

Bilirubin metabolizması ve aterosklerozdaki rolü

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Abstract

Hemoglobin is not an guiltless bystander of the pathophysiology in a number of atherosclerotic diseases. Heme, which is released from hemoglobin or other heme proteins, triggers various pathophysiological consequence, including heme stress as well as intracellular stress. Although heme serves key functions and is tightly controlled, high levels of free heme, which may occur in various pathophysiological conditions, are may hazardous via pro-oxidant, pro-inflammatory, and cytotoxic effects.

Heme oxygenases are heat shock protein enzymes that use heme as a substrate and function as an essential antioxidant adaptive response by all human cells. A major function of heme oxygenases is clearance of heme that accumulate in tissues due to erythrocyte turnover. The potentially toxic free heme is converted by heme oxygenases into carbon monoxide, iron, and biliverdin, the third of which is reduced to bilirubin. In literature the heme degradation pathway has been demonstrated to play a protective role against the development of atherosclerosis. Because growing evidence suggests that oxidative stress is involved in atherosclerosis.

This review documents the roles of bilurubin in atherosclerosis and focuses on the clinical significance as a potential therapeutic target in atherosclerotic diseases, such as coronary artery disease.

Keywords ; Bilirubin, Atherosclerosis, Heme oxygenases, Oxidative stress, Cardiovascular diseases.

Öz

Hemoglobin bir dizi aterosklerotik hastalığın patofizyolojisinde suçsuz bir seyirci değildir. Hemoglobinden veya diğer hem proteinlerinden salınan hem hücre içi stresin yanında hem stresi de dahil olmak üzere çeşitli patofizyolojik sonuçları tetikler. Hemin anahtar fonksiyonları olması ve sıkı bir şekilde kontrol edilmesine rağmen, çeşitli patofizyolojik koşullarda ortaya çıkabilen yüksek serbest heme seviyeleri, pro-oksidan, pro-enflamatuar ve sitotoksik etkiler nedeniyle tehlikeli olabilir.

Hem oksijenazlar, hemi bir substrat olarak kullanan ve tüm insan hücreleri tarafından gerekli bir antioksidan adaptif yanıt olarak işlev gören ısı şoku protein enzimleridir. Hem oksijenazların en önemli fonksiyonu eritrosit döngüsüne bağlı dokularda biriken hemin temizlenmesidir. Potansiyel toksik serbest hem hem oksijenazları tarafından karbon monoksit, demir ve biliverdine dönüştürülür, bunlardan üçüncüsü bilirubine indirgenir. Literatürde hem degradasyon yolunun ateroskleroz gelişimine karşı koruyucu bir rol oynadığı gösterilmiştir. Çünkü artan kanıtlar oksidatif stresin aterosklerozda rol oynadığını düşündürmektedir.

Bu derleme bilurubinin aterosklerozdaki rollerini belgelemekte ve koroner arter hastalığı gibi aterosklerotik hastalıklarda potansiyel bir terapötik hedef olarak klinik öneme odaklanmaktadır.

Anahtar Kelimeler; Bilirubin, Ateroskleroz, Hem oksijenaz, Oksidatif stres, Kardiyovasküler hastalıklar

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In this review we aimed to examine several experimental and clinical studies investigating the relationship between atherosclerotic diseases and bilirubin and the effects of bilirubin on the atherosclerotic process. It is known that oxidative stress is involve in atherosclerosis. Heme degradation pathway which bilirubin is synthesised has been demonstrated to play a protective role against the development of atherosclerosis. The protective properties of bilirubin are observed at every stage of the atherosclerosis process. This review documents the roles of bilurubin in atherosclerosis and focuses on the clinical significance as a potential therapeutic target in atherosclerotic diseases.

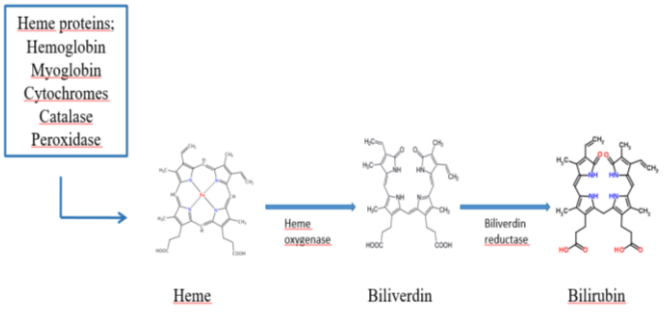
Bilirubin

Bilirubin become of four pyrrole rings, both connected by carbon bridges formed during its catabolism. From an evolutionary perspective, protoporphyrin ring is a exclusive metal chelator with outstanding properties. In contrast, for many years, bilirubin had been thought to be a toxic waste product, especially for the central nervous system [1]. Thus bilirubin often has been considered as a metabolic waste. However, recent evidence suggests that bilirubin may have many other beneficial effects, including anti-oxidant effects, anti-inflammatory effects, and direct effects on cell signaling [2]. Today many epidemiological data highlight that bilirubin may play a protective role against atherosclerosis [1].

Bilirubin Synthesis

The bulk of bilirubin is caused by the breakdown of red blood cells that fill its life. Approximately 85% of total bilirubin is originated from hemoglobin in mature red blood cells destroyed in reticuloendothelial cells. The remaining 15% consists of immature red blood cells that break down in the bone marrow and other molecules such as; myoglobin, cytochromes, catalase and peroxidase [3]. When both pathways reach the oxygenase enzyme system, iron is usually upgraded to ferric (Fe+3) form and Hemin is formed. Hemin is reduced to NADPH, switching to become iron ferro (Fe+2) form. Then porphyria with more oxygen is added to the alpha text bridge between the pyrrole rings, and ferro iron is oxidized again in the form of ferri. Finally with the addition of oxygen, iron is released, carbonmonoxide is formed, biliverdin is revealed. Biliverdin by reducing the text bridge between the pyrrole rings to the methylene group, it forms bilirubin, a yellow pigment [4]. Bilirubin formation pathways are shown in figure 1.

Figure 1. Bilirubin synthesis.



The first formed bilirubin is known as indirect bilirubin (free bilirubin, unkonjuge bilirubin). Indirect bilirubin is insoluble in water, does not pass through urine and is not excreted with bile. Unconjuge bilirubin is usually carried to the liver through circulation by binding to albumin [3]. Serum albumin-bound bilirubin comes to liver, leaving albumin in the hepatocyte sinusoidal membrane and passing through the membrane. Bilirubin entering the liver cell binds reversibl to soluble proteins known as Ligandins or Protein Y (glutathione-S-transferase gene family). Hepatocytes add glucuronic acid molecules to bilirubin, transforming it into a polar form conjuge bilirubine that can be easily excreted into bile. This process is called conjugation. The conjugation of bilirubin is catalysed by a specific glucuronosyltransferase in the endoplasmic reticulum, uses UDP-glucuronic acid as the glucronosyl transmitter, and is defined as bilirubin-UGT [3] (Figure 2).

Firstly bilirubin monoglucuronide is an intermediate and then decoded into diglucuronide. Most of bilirubin thrown into bile is in the form of bilirubin diglucuronide. However, when bilirubin conjugates are abnormally present in human plasma, they are mostly in the form of monoglucuronids. Conjugated bilirubinin secretion of bile is known as the rate-limiting step in bilirubin metabolism. This transport process takes place through the active transport mechanism via MRP-2 (multidrug resistance-like protein 2). When conjugated bilirubin reaches the terminal ileum and large intestine, glucronides with β-glucronidases are removed and urobilinogens, which are colorless tetrapyrol compounds, are formed [4].

Under physiological conditions, the dominant circulation form of bilirubin is the un-conjugated albumin-bound form but four forms of bilirubin have been isolated in the serum. Non conjugated-bilirubin (α-bilirubin) 27%, mono-conjugated bilirubin (β-bilirubin) 24%, conjugated bilirubin, Di bilirubin (γ-bilirubin) 13% protein, which is connected and 37% irreversible bilirubin (δ-bilirubin) in serum. Antioxidant activity and cardioprotective potential can be attributed to any of the bilirubin forms [5].

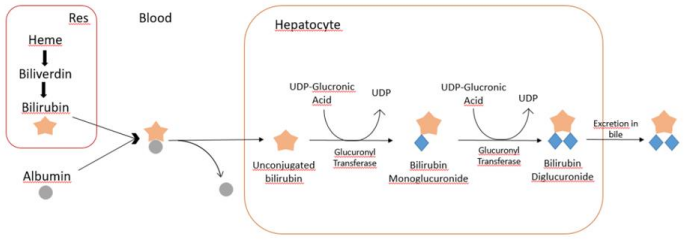
Endogenous Antioxidant Effects Of Bilirubin

Bilirubin was for many years considered a waste product of oxygenases. While much attention was not shown to the physiological roles of bilirubin until the 1987 year studies showing that bilirubin suppresses the oxidation of peroxyl radicals more than α-tocopherol [6]. Today, bilirubin's antioxidant potential has been confirmed by additional studies; it has been shown that bilirubin is 20 times more effective in preventing LDL oxidation than Trolox [7]. It has also been reported that non-conjugated bilirubin concentrations as low as 10 nmol/L protect neuronal cultures from oxidative stress [8]. Nowadays bilirubin is considered the most potent endogenous antioxidant due to its continuous improvement in the bilirubin / biliverdin redox cycle, resulting in both in vitro and in vivo protective lipid peroxidation. Besides this antioxidative effect, bilirubin also exerts immunosuppressive effects on antigen presenting cells and T cells, as well as on inhibition of adhesion molecule expression and immune cell migration. These concepts might form the basis of a new understanding of bilirubin metabolism, creating a new treatment approach for atherosclerosis, cancer, autoimmune diseases [9].

Bilirubin as an anti-atherogenic molecule

Undoubtedly atherosclerosis is a leading cause of death in developed and developing countries. Yet, well known labile free heme is one of the many known risk factors for atherosclerosis and contributes to the formation of this complex disease. Nowadays total bilirubin in circulation is known to be inversely and independently associated with the risk of future cardiovascular heart disease (CHD). A large number of clinical trials have strongly demonstrated the protective role of bilirubin against atherosclerotic heart diseases. Undoubtly higher total bilirubin contributes to lower CHD risk [10].

Figure 2. Bilirubin diglucuronide synthesis in hepatocytes.



Res: Reticulo-endothelial system, UDP: Uridine diphosphate

In 1994, Schwertner et al. they were the first researchers to report a negative relationship between lower serum bilirubin concentrations and CHD on as many as 900 men. The strength of this relationship was found to be similar to smoking, hypertension and dyslipidemia. In this pioneering study, a 50% decrease in total bilirubin was associated with a 47% increase in the likelihood of more severe coronary artery disease, which was proven by coronary angiography [11]. Later, Vitek et al. they started a retrospective study on cases with Gilbert Syndrome, known as benign hyperbilirubinemia and characterized by slightly increased unkonjuge hiperbilirubinemia. Although the cohort was small (n = 50), individuals with benign hyperbilirubinemia were found to have a lowest 2% prevalence rate for CHD compared with the general population. This study was continued prospectively and patients were followed up for 3 years. While there was a 3,1% incidence of CHD in control subjects during this period, no cases of were seen in patients with Gilbert Syndrome [12].

A year later, a meta-analysis involving 11 studies by Novotny and Vitek were reported strong negative correlation between serum bilirubin levels and atherosclerosis severity in men (p<0,0001). Also, nonparametric regression analyses have shown a negative relationship between serum bilirubin concentrations and atherosclerotic diseases. In a one study, it was found that every 1,0 µmol/L increase in serum bilirubin was associated with a 6,5% decrease in cardiovascular disease [13]. The same relationship was also demonstrated in a study on patients with cardiac X syndrome, which was followed up for 5 years. Patients with the lowest serum bilirubin levels were reported to have a higher incidence of hospitalization for non-fatal myocardial infarction, ischemic stroke, unstable angina [14]. Indeed lower serum bilirubin was able to independently estimate long-term mortality in coronary artery disease (CAD) (HR 0.34, 95% CI 0.16-0.70) and unstable angina (UAP) (HR 0.49, 95% CI 0.31-0.78) groups [15].

It has also been reported to be associated bilirubin with coronary artery calcification (CAC), which is a good indicator of the presence and amount of coronary atherosclerosis. Because in a cross-sectional study of 398 men and 239 women, serum bilirubin concentrations were found to be strongly associated with CAC scores and independent predictors of CAC in both men and women [16]. Similarly in a cross-sectional study conducted on 2682 non-CAD patients for bilirubin was found to be inversely related to total coronary plaque. In this prevalence of coronary atherosclerosis or >50% coronary artery stenosis was found to be lower in people with high serum bilirubin levels (>1,2 mg/dL) than those with normal serum bilirubin levels [17]. As a result; serum bilirubin, creates antioxidant-antilipoperoxidative effects in atherosclerotic plaques and appears to be negatively associated with the severity of atherosclerosis [18].

In addition to these studies, there are studies that suggest a relationship between serum bilirubin levels and general mortality [19]. Similarly, in 533 patients with acute coronary syndrome had followed in terms of revascularization and acute heart failure, and it had been concluded that bilirubin was might be associated with a mortality risk at the end of year 2,4. Also many experimental data obtained in animal models strongly supported the protective role of bilirubin [20]. However, clinical studies regarding the prognostic role of total bilirubin in patients with acute myocardial infarction (AMI) in short-term are conflicting. Marginally higher serum total bilirubin level may be a predictor of major cardiac events and cardiovascular death in patients with AMI. Whereas higher baseline bilirubin levels were significantly associated with an increased risk of short-term mortality hazard ratio (HR) 2.35, (95% confidence interval (CI) 1.15-4.77) in the AMI group [21]. When conflicting results were found in the literature, new studies are required.

Therefore in another one meta-analysis the effect of serum total bilirubin level on the risk of atherosclerotic heart diseases were evaluated. A total of 20 studies (323,891 cases) were included in the meta-analysis and identified as coronary artery disease, acute coronary syndrome, stable angina, coronary revascularization, atherosclerotic stroke or transient ischemic attack, and peripheral artery disease (PAD). This meta-analysis showed that bilirubin was significantly negatively associated with cardiovascular mortality, major adverse cardiac events, and AMI prognosis, bilirubin levels. According to this reported, it can be concluded that higher serum bilirubin showed significant negative relationship with cardiovascular disease (HR = 0.83 (95% CI 0.73-0.94) [22]. Later the relationship between serum bilirubin levels and PAD has also been extensively investigated. Increased serum total bilirubin levels were associated with decreased PAD prevalence. Even the combined analysis showed that lower bilirubin levels were significantly associated with PAD (OR = 0.91 (95% CI 0.85-0.98)) [22]. Also in 2008, Perlstein et al. published a retrospective study on more than 7000 adults from the National Health and Nutrition Examination Survey (NHANES). In this study, every 0,1 mg/dL (1,7 µmol/L) increase in serum bilirubin level after adjustment for possible confounding factors was associated with a 6% decrease in the incidence of PAD [23].

In addition to PAD research other studies have shown that bilirubin is associated with intracranial atherosclerosis (ICAS). In a population-based study to investigate the epidemiology and natural history of asymptomatic ICAS in middle age and older adults, after adjusting for all contradictions, bilirubin levels were found to be negatively associated with ICAS, especially in individuals over 60 years of age. This result showed that bilirubin can have a protective effect on ICAS, especially in older individuals [24]. Clinical trials of bilirubin and results are given in Table 1.

Bilirubin and metabolic disturbances leading to atherosclerosis

Considering the atheroprotective effects of bilirubin, it is not surprising that the same negative correlations exist for other diseases commonly associated with atherosclerosis. So there are numerous studies showing that bilirubin levels are associated with metabolic syndrome or diabetes. The first report published in this context was about the association of bilirubin with metabolic syndrome between children and adolescents. Furthermore, in diabetic rats, up-regulation of heme oxygenases1 increases serum bilirubin, reduces superoxide anion and endothelial sloughing induced by hyperglycemia [19].This graded relationship was also significantly preserved after the adjustment of other co-variables [25]. Another important study

Table 1:Clinical studies for bilirubin and atherosclerotic heart disases.

Studies	Participants of study	n	Change of parameters	Results
Schwertner H et al. 1994	Coronary artery disease (CAD)	900	%50 decreases in Total bilirubin	%47 increases in CAD severty
Vitek L et al. 2002	With Gilbert Syndrome	50	Increase serum bilirubin	%2 decrease of CAD prevalence
Novotny L and Vitek L. 2003 (meta-analysis)	With Gilbert Syndrome		1.0 µmol/L increases in serum bilirubin	%6.5 decreases in cardiovascular diseases (CVD)
Huang ss et al. 2010	Cardiac X syndrome	108	Lowest serum bilirubin	Higher myocardial infarction(MI), ischemic stroke, unstable angına (UAP)
Huang FY et al. 2017	CAD	3013	Serum bilirubin	Pozitif correlation with short-term mortality in AMI Negatif correlation with long-term mortality in CAD and UAP
Tanak M et al. 2009	Cardiovasculer Heart disease (CHD)	637	Serum bilirubin	Associated with coronary artery calcification (CAC) score
Kang Sj et al. 2013	Non-CAD	2682	Higher Serum bilirubin (>1.2mg/dL)	Lower prevalence >%50 stenotic coronary plaque
Xu C et al. 2019	Acute coronary syndrome	533	Serum bilirubin	Association with revascularization, acute heart failure and mortaliy
Yang L et al. 2019 (meta-analysis)	Atherosclerotik cardiovasculer disease (ASCVD)	323,891	Serum total bilirubin Lower serum total bilirubin	Negative association with cardiovasculer mortality, major advers cardiac events and prognosis of AMI Corelation with peripheral artery disease(PAD)
Perlstein TS et al. 2008	NHANES	7000	0.1 mg/dL increases in serum bilirubin	%6 decrease in incidence of PAD
Zhong k et al. 2020	Asymptomatic intracranial atherosclerosis (aICAS)		Serum bilirubin	Negative association wtih aICAS
Lin LY et al. 2009	Methabolic syndrome(MS)	7177	Lower serum bilirubin	Higher prevalence of MS
Cheriyath P et al. 2010	NHANES	15,867	Increases in total bilirubin	% 26 decrease in diabetes risk
Fu YY et al. 2010	Hyperbilirubinemic Gunn rats		Pretreatment with 0.1 mg/dL bilirubin	Decrease cell death and apoptosis in the cell line of rat insulinoma
Jıraskova A et l. 2011	Type 2 diabetes	700	0.1µmol/L increase in serum bilirubin	Reduce the likelihood of developing diabetes
Vitek et al. 2002	Gilbert syndrome		Increased serum bilirubin	Increased total antioxidant capacity (TAS)
Hwang Hj et al. 2011	Healty people	2307	Total and direct bilirubin	Negative association with serum CRP
Seung JK et al. 2013	CAD	2862	Higher serum bilirubin (>1.2 mg/dL)	Lower serum CRP

reported a strong relationship between bilirubin and diabetes. In the study of 15,876 participants from NHANES between 1999 and 2006, total bilirubin increase after age adjustment was associated with a 26% decrease in diabetes risk (or 0.74, 95% CI 0.64 - 0.88) [26].

This relationship has also been supported by studies on animals. Korean researchers reported that hyperbilirubinemic Gunn rats showed significant resistance to developing diabetes after exposure to intraperitoneal streptozosine compared to their normobililubinemic offspring. It has also been found that pretreatment with bilirubin (0.1 mg / dL) in the cell line of a rat insulinoma reduces cell death and apoptosis caused by streptosis and suppresses H_2O_2 production [27]. A study published in 2011 covered more than 500 patients with type 2 diabetes mellitus and 200 healthy controls. The findings showed that serum bilirubin levels were low and that the probability of developing diabetes increased every 1,0 µmol/L [28].

Recently reported that higher serum concentrations of bilirubin are associated with a decreased risk of developing CAD and all-cause death in diabetic patients. So serum bilirubin improves the may be risk predictions of cardiovascular and total death in diabetic patients [29]. In conclusion, low serum total bilirubin levels were associated with a significant increase in the risk of diabetes in patients with impaired fasting glucose [27]. In observational studies being included in metabolic syndrome and diabetes, including meta-analyses involving participants almost one million, the negative relationship between serum bilirubin levels and metabolic syndrome with diabetes has been shown once more [30]. Finally, a meta-analysis showing the relationship between bilirubin and atherosclerosis was published. According to the findings obtained in this meta-analysis, higher bilirubin significantly has improved the good prognosis of atherosclerotic cardiovascular diseases [22].

Gilbert Syndrome and Bilirubin

Last two decades to investigate the link between bilirubin and reduced risk of cardiovascular disease, the relationship between oxidative stress, inflammation, and markers of vascular dysfunction and bilirubin has been clinically investigated [5]. After all, many beneficial advised linked to moderate elevations of serum bilirubin have been recognized. Thus, Gilbert Syndrome provides invaluable evidence for investigating the anti atherosclerotic effects of bilirubin.

Also the effects of hyperbilirubinemia on decreasing plasma levels of advanced glycosation end products (AGE) that contribute to atherosclerosis have been investigated [31]. As it is known, increased AGE formation in the collagen in the artery wall contributes to the Atherosclerosis process by increasing the rigidity in the vessel structure. In addition, AGE-bound collagen found in the vascular structure accelerates the formation of plaque by binding to LDL. In one of the clinical trials related to Gilbert Syndrome, serum levels AGE were significantly lower than the in these hyperbilirubinemic individuals [31]. In another study involving subjects with Gilbert Syndrome, with kidney diseases were significantly lower compared with the control group [32].

The relationship between bilirubin and total antioxidant capacity (TAS) has been reported in some studies. While, Vitek et al published in 2002 in a study involving Gilbert cases, and the control group. They found that TAS differed significantly between these groups. TAS was significantly higher in patients with Gilbert Syndrome compared with control cases. As showed in the other in vitro experiment, serum levels of TAS was might be associated with increased bilirubin concentration [12].

Chronic inflammation and Bilurubin

The elevation of bilirubin concentration in plasma is well known as a marker of hemolytic conditions, liver damage or bile-duct impairment. Endothelial activation and recruitment of inflammatory cells are two pivotal steps in the development of atherosclerotic lesions [2,3]. Especially, also the production of bilirubin in peripheral tissues has been proposed to be protective the anti-inflammatory effect of bilirubin was already observed in hyperbilirubinemic rats. Also in vitro studies demonstrated that bilirubin prevents TNFα-induced leukocyte adhesion to endothelial cells by reducing the expression of pro inflammatory molecules [2-4].

There are also studies focusing on the relationship between C-reactive protein (CRP) and bilirubin, a marker that reflects chronic vascular inflammation. For example a cross-sectional study of 2307 healthy Korean adults found that total and direct bilirubin elevations were associated with low serum CRP levels. After adjusting age, body mass index, hypertension, diabetes, hypercholesterolemia, cardiovascular disease, aspirin, smoking, alcohol and regular exercise, the negative association of CRP with both total and direct bilirubin was maintained. Thus it is hypothesized that low serum CRP levels may be due to the antioxidant and antiinflammatory effects of bilirubin metabolism [33]. In another study (n=2862), those with a high serum bilirubin level (>1,2 mg/dL) had a lower CRP level than those with a low serum bilirubin level (<1,2 mg/dL) (34). Slight increases in plasma total bilirubin concentrations (1.53 ± 0.48 mg/dl) have been reported to preserve flowmediated vasodilation compared to subjects with low levels of plasma bilirubin (0.40 ± 0.08 mg/dl(10,35). Also recently repoted that the serum total bilirubin level was found to be 0.41 ± 0.21 ng/dL in the severe erectile dysfunction, 0.43 ± 0.19 ng/dL in the moderate erectile dysfunction, and 0.48 ± 0.11 ng/dL in the mild erectile dysfunction groups. Also the prevalence of multiple sclerosis was 6.6 ± 1.2% in the group with the lowest bilirubin concentration, while bilirubin concentration was 2.1 ± 1.9% in the highest bilirubin concentration group [36].

Bilirubin is able to protect against atherosclerotic diseases by means of different metabolic pathways? We can only answer this question by looking at studies related to Hem metabolism.

Heme and Atherosclerosis

Heme, an amphipathic iron-protoporphyrin complex, is one of the most important prosthetic groups on Earth, which serves as an oxygen transporter and participates in various oxido/reductive processes in aerobic and anaerobic cell metabolism. However, free heme released from the safe sanctuary area of heme proteins triggers a number of adverse events. In last two decades, several reports revealed the detrimental role of heme in neuronal damage and the potential role of heme in health and disease. Heme, due to its amphipathic nature, shows high affinity towards biological membranes, sensitizing them towards reactive oxygen species and leading to the oxidative damage of membrane lipids, cell lysis, genomic, and mitochondrial DNA damage [34]. For these reason recently administration of FDA-approved hexyl 5-aminolevulinate hydrochloride has begun to be used in clinical trials to produce anti-inflammatory carbon monoxide and bilirubin in atherosclerosis [37].

Bilirubin and Heme Oxygenases

Heme oxygenase is the first, rate-limiting enzyme in heme degradation pathway, with two major isoforms of heme oxygenase identified. First Heme oxygenase-1 is inducible whereas, expressed only under oxidative stress or when heme oxygenase-2 [38,39].

There are several experimental conditions where hem oxygenases-1 provides defense for cells and tissues. Heme oxygenases-1 catalyzes the opening of the prothoporphyrinic ring of heme, generating biliverdin, free iron and carbon monooxide (CO) (Figure 3). Moreover, biliverdin is considered to be an endogenous antioxidant in several clinical conditions [37]. CO has anti-apoptotic and antiinflammatory activities. While CO is an anti-inflammatory and anti-apoptotic gas molecule. The scientific importance of CO is increasing, since quite a lot of work proves its anti-inflammatory effects. Considering the protective effect of Heme oxygenases, it is a logical explanation that end-products of heme degradation, bilirubin, biliverdin, and CO are responsible for the beneficial action. The generation of free iron is potentially highly toxic but, under physiological conditions, a parallel induction of the heavy chain of ferritin, and the activation of membrane Fe-ATPase transporters occur. To eliminate the redox active free iron, cells rapidly express ferritin. The antioxidant character of ferritin depends on its ferroxidase activity and iron sequestering capability [39]. The possible mechanisms of underlying the relationship between high bilirubin and decreased atherosclerosis as monitored: bilirubin could effectively block the generation of cellular reactive oxygen species and intercellular adhesion molecule. High serum bilirubin levels resists for myeloperoxidase-induced oxidation and to prevent the formation of atherosclerosis; and higher bilirubin also has related for an anti-inflammatory effect on atherosclerotic process [37] (Figure 4). It has clearly been shown that unconjugated bilirubin mimics the hypolipidemic activity of fenofibrate. These data show that, in the vessel wall, the activity of bilirubin on lipid metabolism is complex and merits further investigation. As recently reviewed, bilirubin prevent platelets aggregation due its ability to interfere with the surface expression of adhesion molecules and its antioxidant activity, thereby supporting a role played in the prevention of hypercoagulability and thrombosis [39].

Figure 3: Heme oxygenase and products.

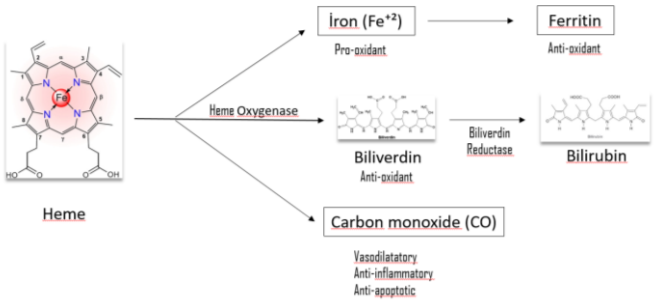
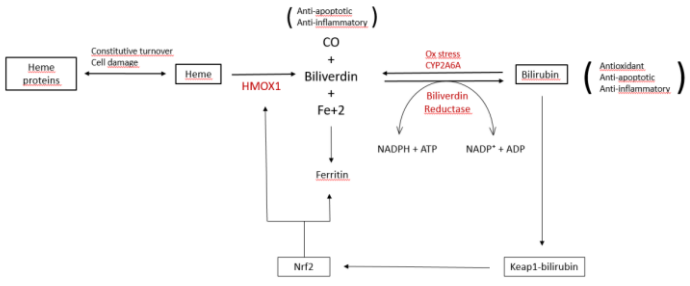


Figure 4: Enzymatic reactions of bilirubin generation and cytoprotection



HMOX1:Heme oxygenases1, CO:Carbon monoxide, Nrf2:Nuclear factor erythroid-2 related factor, Keap1:Kelch ECH-associating protein 1.

Heme oxygenases1 catalyzes the degradation of heme groups to CO, Fe2+ and biliverdin, the latter subsequently converted to bilirubin by biliverdin reductase. By reaction with oxidant species, bilirubin is oxidized back to biliverdin, amplifying the antioxidant effect. Bilirubin and CO exert anti-apoptotic and anti-inflammatory activity. Fe2+ is quenched by the heavy chain of ferritin, and further released to form heme. A positive feedback of cytoprotection can be generated by the ability of bilirubin to bind nucleophiles such as thiol reactive cysteines on Keap1, favoring Nrf2-dependent HMOX1 gene transcription.

Conclusions

In this review, several experimental and clinical studies investigating the relationship between atherosclerotic diseases and bilirubin and the effects of bilirubin on the atherosclerotic process were examined. Although different results are obtained in some studies, the protective properties of bilirubin are observed at every stage of the Atherosclerosis process. Clinical studies examining the relationship between Bilirubin and atherosclerotic diseases have suggested that low serum bilirubin concentrations are associated with increased risk of.

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Olfactory groove meningioma presenting with major depressive disorder symptoms: A case report

Majör depresif bozukluk belirtileri ile başvuran olfaktör oluk menenjiyomu: Bir olgu sunumu

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Abstract

Brain tumors without giving neurological symptoms yet; it can also occur with a wide range of psychiatric symptoms such as anxiety, panic attacks, depression, eating disorders, personality change, vision hallucinations and mania. Unfortunately, the diagnosis of brain tumor might be delayed in patients whose clinical symptoms are like these. Brain imaging techniques should be performed especially in patients who don't respond to psychiatric drug treatment and have no neurological symptoms. In this article, a female patient who presented to our psychiatry outpatient clinic with symptoms of depression, accompanied by psychosis symptoms in later periods, and whose mass was detected as a result of magnetic resonance imaging, is discussed in the light of literature studies. Here, we aimed to emphasize the importance of neurological examination and brain imaging methods in patients who come to psychiatry especially with atypical symptoms.

Key Words: Depression, psychosis symptoms, brain tumors, neuro-imaging.

Öz

Beyin tümörleri henüz nörolojik semptomlar vermeden; anksiyete, panik atak, depresyon, yeme bozuklukları, kişilik değişikliği, görme halüsinasyonları ve mani gibi çok çeşitli psikiyatrik semptomlarla da ortaya çıkabilir. Ne yazık ki, klinik semptomları böyle olan hastalarda beyin tümörü tanısı gecikebilmektedir. Beyin görüntüleme teknikleri özellikle, psikiyatrik ilaç tedavisine cevap vermeyen ve nörolojik semptomları olmayan hastalarda mutlaka yapılmalıdır. Bu yazınımızda psikiyatri polikliniğimize depresyon belirtileri ile başvuran, ileri dönemlerde psikoz belirtilerinin de eşlik ettiği, çekilen kontrastlı beyin manyetik rezonans görüntüleme sonucunda kitle tespit edilen kadın hasta, literatür araştırmaları ışığında tartışılmaktadır. Biz burada özellikle atipik semptomları olan psikiyatri hastalarında nörolojik muayene ve beyin görüntüleme yöntemlerinin önemini vurgulamayı amaçladık.

Anahtar Kelimeler: Depresyon, psikoz belirtileri, beyin tümörleri, nöro-görüntüleme

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Introduction

Brain tumors are manifested by headache, epileptic seizure, focal neurological deficit, cognitive or behavioral disorder. It is also accompanied by various symptoms such as forgetfulness, slowing speech speed, difficulty in maintaining mental functions, loss of interest in daily activities, personality changes, inability to hear high-frequency sounds [1, 2].

The localization of tumor, its edema and mass effect cause the dysfunction of neuronal foci and therefore psychiatric symptoms occur [3]. While a tumor in the dorsolateral prefrontal region may lead to deficiencies in executive function, a tumor in the orbitofrontal region may lead to disinhibition, medial-frontal region tumor may lead apathy and amotivation and temporal limbic tumors may lead to psychosis [4]. Approximately 90% of brain tumors that cause psychiatric symptoms are located in the frontal lobe. However, these symptoms may occur as a result of the affection of the temporal lobe, thalamocortical structures, cerebral white matter, long fiber systems and corpus callosum. Therefore, patients may be misdiagnosed with many psychiatric disorders, mood disorders, anxiety disorders, or psychotic disorders, during the first examination [5].

Psychiatric symptoms rarely accompany the clinical picture before the diagnosis of brain tumor [6]. Depression, anxiety disorder, mania, psychosis, personality changes and eating disorders are usually observed among psychiatric diagnostic symptoms [2]. Depressive disorder has been reported in % 2.5-15.4 of primary brain tumors [7]. Depression is seen 44% of patients who has primary and metastatic whole brain tumors and it is accompanied by functional impairment, cognitive dysfunction, and poor quality of life according to Mainio et al. [8, 9]. Depression symptoms can be seen at all stages of brain tumors (before, during or after diagnosis / treatment). It has been reported that depression is more common in frontal lobe tumors. More specifically, left frontal lobe tumors were more associated with depression [3, 7].

Meningioma is the most common primary central nervous system tumor responsible for almost 37% of all cases [10]. Meningioma frequently is seen in middle-aged or elder people and compared to men, women have a 2-fold risk of meningioma. It usually grows slowly and is asymptomatic. The diagnosis is usually made by neuroimaging tecniques or autopsy [10-12]. Total surgical resection is recommended in its treatment, but this may be difficult for deeply located skull base tumors [13]. Depression is the most common psychiatric symptom in these patients with meningioma and affects more than 20% of patients [14].

In this paper, we aimed to emphasize that the importance of using brain imaging methods in patients with atypical depression or treatment-resistant depression because of the underlying organic causes such as meningioma.

Case report

From a 55-year-old female patient who received written consent for a case report, it was learned that she was a primary school graduate and a housewife, lived alone, and that his wife died 7 years ago. There were symptoms of depression approximately for 3 months, such as inability to do household chores, lethargy, stagnation, retreat, malaise, unwillingness, irritability, feeling worthless, slow and less speech, and not leaving home. She did not have any additional illness, and she had been treated with antidepressant treatment for 8 months after she lost her husband 7 years ago. There was no family history of psychiatric illness. Routine blood tests were requested and it was observed that hemogram, serum iron, vitamin B12, folic acid, thyroid hormone results were at a normal level. The Hamilton depression scale (HDS) score was 25. As a result of the mental examination of the patient, major depressive disorder of melancholic type was considered according to Diagnostic and Statistical Manual of Mental Disorders-5 diagnostic criteria and treatment was started with 75 mg venlafaxine. It was observed that the patient was resistant to antidepressants as a result of regular monthly mood assessment. Although the dose of venlafaxine was increased to 225 mg in the 5th month of treatment, 30 mg of mirtazapine and 5 mg of aripiprazole were added; there was no regression in her complaints. Besides she had urinary incontinence 3 to 4 times in the last month and did not care about this situation, she sat with her wet clothes for hours. She also had symptoms like hearing difficulties, visional hallucinations, washing clothes in the kitchen sink, forgetting the faucet open, mixing the names of children. In the mental state examination, her thoughts were purposeful, but association of her ideas were slow and prone to disintegration, she was speaking unreasonably, she had disorganized behaviors, delusions of persecution and vision hallucinations, and deterioration in the place-time orientation. The positive and negative syndrome scale (PANSS) was 87. In addition, she had ataxic gait, dementia-like cognitive symptoms and her mini mental test result (MMT) was 12. Therefore, a contrast-enhanced MRI examination was requested to analyze organic etiology. In neuroimaging there was a giant mass on olfactory groove, extra axial location, that extending up to the vertex level in the superior, filling the anterior cranial fossa, pushing falx cerebri to left, pressing lateral ventricles, genu segment of corpus callosum and adjacent brain parenchyma. The size of mass measured 70x57x64 mm, it had homogeneous contrast enhancement after contrast injection. There were intense vasogenic edema around the mass in the brain parenchyma. It was considered an olfactory groove meningioma (Figure 1).

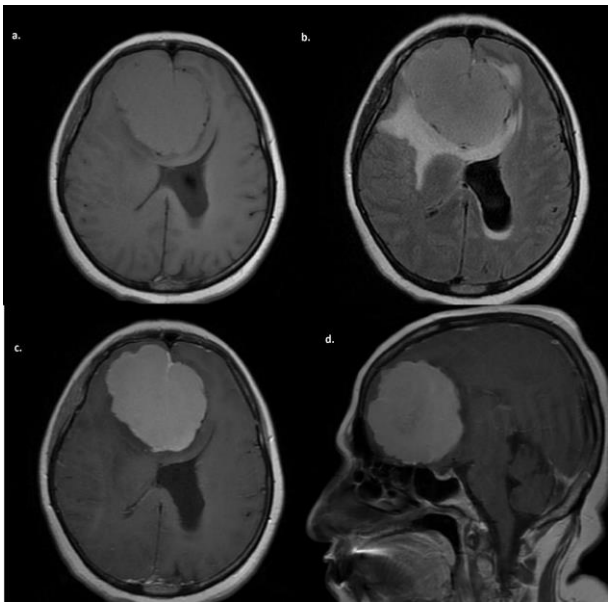

Figure 1: Preoperative brain MRI examination: The images without contrast are axial T1-weighted (a) and axial T2-FLAIR-weighted (b) MRI scans. There is compression of the lateral ventricle and genu segments of corpus callosum. There is intense vasogenic edema around the mass in the axial T2 FLAIR-weighted MRI scan. It shows intense homogeneous enhancement in contrast-enhanced axial T1-weighted (c) and sagittal T1-weighted (d) MRI scans.

The patient was consulted to neurosurgery, and the operation was planned one day later, and her psychiatric treatment was terminated immediately. Post-operative CT image is shown in figure 2. The biopsy taken from the surgical material revealed that the tumor was meningioma. The patient's symptoms regressed immediately after surgery; It was observed that her gait improved, her communication improved and her psychotic symptoms disappeared. One week after surgery, HDS score was 6, MMT result was 22, and PANSS score was 42 (Figure 2).

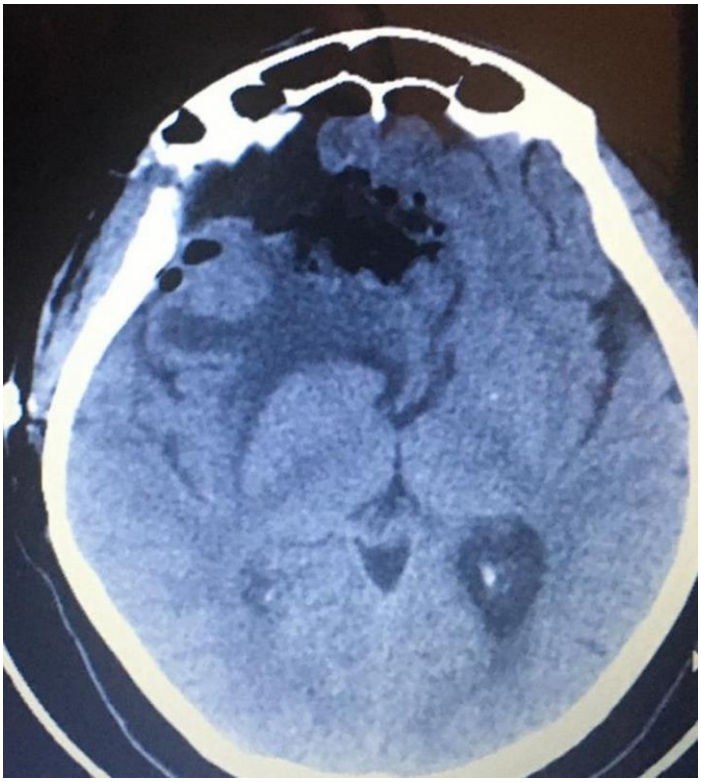

Figure 2: In the post-operative CT image, there is postoperative air density and a hypodense vasogenic edema.

Discussion

Olfactory groove meningiomas are benign, slow growing tumors originating from dura mater covering the surface of lamina cribrosa. Slowly growing mass begins to compress both frontal lobes over time and reveals clinical symptoms. Sometimes the tumor may reach large sizes without clinical symptoms. The first clinical sign is usually anosmia. Mostly, visual impairment and dementia may be developed on patients after a few years. As the mass grows, ipsilateral anosmia which the patient often does not realize, optic atrophy, optic disc edema due to contralateral eye stasis, visual impairment due to posteriorly located tumors pressing the optic nerve, urinary incontinence, epileptic seizure and mood changes can also be observed [15].

The effect of tumor localization on the emergence of psychiatric symptoms is demonstrated by studies conducted. Some common psychiatric symptoms are seen more often in certain brain area tumors. For example, It can be symptoms such as disinhibition in orbitofrontal region tumors, apathy, mania or psychosis in medial frontal tumors, psychosis in the tumors which affects third ventricle and surrounding structures [4]. In diencephalon and pituitary gland tumors, vegetative symptoms can be seen as a variant of depressive disorders [16].

In the 1980s, Owens et al. [17] did a cross-sectional study of 118 patients with schizophrenia, they found that one patient a meningioma in the left frontal lobe. The patient was reported to have hearing hallucinations and no other focal neurological findings. This means that the meningioma clinic can be asymptomatic and sometimes psychotic symptoms can be part of tumor symptoms. In a study in which 57 patients with supratentorial meningioma were prospectively studied, psychiatric symptoms were more common in temporal tumors than frontal tumors [14]. It was found that patients with frontal meningioma had depression symptoms, patients with base of frontal lobe and sphenoid wing meningioma had mania or depressive symptoms, patients with suprasellar and temporal convex meningioma had symptoms of delusional disorder symptoms. In accordance with these datas, in our case, meningioma itself was asymptomatic, and the clinical picture was completely based on depressive symptoms. In the following weeks, psychotic symptoms were added first and then neurological deficits appeared.

In a study conducted; it was found that apathy symptoms were more common in individuals with frontal lobe involvement, and apathy was significantly reduced after surgical resection [18]. This situation is an evidence proves that the localization of the tumor and psychiatric symptoms are related. Similarly; in our case, it was observed that both depressive and psychotic symptoms improved spontaneously after resection of the tumor.

Researches on clinical and cost-effectiveness of depression, mood disorders, especially in first-episode psychosis patients, does not recommend routine brain imaging techniques [19]. However, this neuroimaging techniques may cause skipping of many underlying organic causes. Thus, a cranial mass was detected in 27 of the autopsies of 200 patients who died in a psychiatric hospital in South Africa between 1970 and 1973 [20]. This indicates that intracranial lesions are mostly undiagnosed in patients treated mainly for psychiatric symptoms. In a study by Keschner et al. Reported that 78% of 530 patients diagnosed with brain tumors had psychiatric symptoms and 18% admitted to the hospital with psychiatric symptoms before the diagnosis of brain tumor [21]. Similarly, in our case the patient was admitted with psychiatric symptoms later meningioma was detected.

In conclusion, tumors like meningioma may initially come with psychiatric symptoms to the outpatient clinics. Therefore, medical doctors should approach more carefully patients who have atypical clinical features of depressive disorder like personality changes and who do not respond to the usual treatment. A detailed history, medical examination and selection of appropriate brain imaging techniques are important for early diagnosis. Because treatment will be shaped according to the tumor and its complications like psychiatric symptoms. Psychiatric symptoms vary according to the localization and lateralization of tumors. Along with technological advances, correlation studies between anatomical location and psychiatric symptoms can provide associations that were not previously available. This will help better categorize and better understand of psychiatric symptoms, disorders and symptom structures caused by other brain tumors, including meningioma.

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Rare occurrence of coexistent squamous cell carcinoma and basal cell carcinoma in a case of Xeroderma Pigmentosum

Kseroderma Pigmentosum ile birlikte görülen Skuamöz Hücre Karsinomu ve Bazal Hücre Karsinomu: Nadir bir vaka sunumu

Suguna B.V [1], Aparna Muralidhar [2], Hemalata M [1], Sadaf Ahmad [3]

Abstract

Xeroderma Pigmentosum is an inherited disorder of DNA repair characterised by defective nucleotide excision repair, which is involved in repairing ultraviolet rays induced cross linking of pyramidine residues. Affected individuals are at increased risk of development of mucocutaneous cancers at a much earlier age than normal. This genodermatosis affects both sexes and all races. The incidence in India is still unknown. We report one such case of a nine year old boy with co-existent squamous cell carcinoma and basal cell carcinoma of the face.

Key words: Xeroderma Pigmentosum, DNA repair, ultraviolet rays.

Öz

Kseroderma Pigmentosum, ultraviyole ışın kaynaklı piramidin kalıntılarının çapraz bağlanmasının tamirinde rol oynayan nükleotid eksizyon tamiri aşamasındaki defekt ile karakterize kalıtsal bir DNA onarım bozukluğudur. Etkilenen bireyler normalden çok daha erken yaşta mukokutanöz kanser gelişme riski altındadır. Bu genodermatoza, tüm ırklarda ve her iki cinsiyette rastlamak mümkündür. Xeroderma Pigmentosum'un Hindistan'da görülme sıklığı hala bilinmemektedir. Bu çalışmada dokuz yaşında erkek hasta birlikte skuamöz hücreli karsinom ve yüz bazal hücreli karsinomu olan bir olguyu sunduk.

Anahtar kelimeler: Xeroderma Pigmentosum, DNA onarımı, ultraviyole ışınları

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Introduction

Xeroderma Pigmentosum is a rare, autosomal recessive genodermatosis characterized by deficient DNA repair. It involves both sexes and all races with an incidence of 1:2,50,000 and a gene frequency of 1:200. A high incidence of consanguinity between parents has been noted. There is genetic heterogeneity with at least nine different groups recognized by somatic cell fusion studies – so-called 'complementation groups'. These include types A-G and Xeroderma Pigmentosum variant.

Clinically, it is characterised by photophobia, severe solar sensitivity, cutaneous pigmentary changes, xerosis and early development of mucocutaneous and ocular cancers, particularly in sun exposed areas. Neurological abnormalities are present in up to 20% cases.[1]

We present a rare case of co-existent squamous cell carcinoma and basal cell carcinoma in a boy with Xeroderma Pigmentosum..

Case report

A nine year old boy presented to the dermatology department of our hospital with complaints of photosensitivity, reduced visual acuity and pigmentation on sun exposed areas of the body since one year. He had a nodular growth on the dorsum of nose since three months. The child was born to a first degree consanguineous marriage. The parents were clinically normal.

Clinical examination revealed an ulceroproliferative growth on the dorsum of the nose measuring 1.2x0.8x0.3 cm. A pigmented macule measuring 0.3x0.2 cm was noted in the left preauricular region. Variably sized pigmented macules were seen on the sun exposed regions (Figure 1).

The histopathology of lesion from the dorsum of the nose showed an infiltrating malignant neoplasm with islands and nests of polygonal tumor cells with moderate eosinophilic cytoplasm, vesicular to hyperchromatic nuclei with prominent nucleoli and keratin pearls. A diagnosis of well differentiated squamous cell carcinoma (SCC) was made (Figure 2).

Biopsy from the lesion in the preauricular region showed nests of basaloid cells with peripheral palisading and clefting at the tumor – stroma interface; suggestive of basal cell carcinoma (BCC) (Figure 3).

Based on the above presentation, a clinical diagnosis of Xeroderma Pigmentosum was made. The patient was referred to an appropriate oncology centre for further management.

The patient's consent was obtained for this case study.

Discussion

Xeroderma Pigmentosum was first reported in 1874 by dermatologist Moriz Kaposi.[2] The term 'xeroderma pigmentosum', means pigmented dry skin. It occurs with a frequency of approximately 1 in 250 000 in Europe and the USA . In Japan, the frequency has been reported to be higher (1 in 40 000).[3]

Its incidence in India is not known. However, many cases have been reported from South India, especially Karnataka.[4] The disease has a marked hereditary tendency and is transmitted as an autosomal recessive disorder. It is frequent following consanguineous marriage.

Xeroderma Pigmentosum is characterised by mutation in genes involved in nucleotide excision repair. Mutations in DNA-repair genes themselves are not oncogenic, but their abnormalities greatly enhance the occurrence of mutations in other genes during the process of normal cell division. [5]

Figure 1- Clinical photograph showing growth on dorsum of nose and pigmented macules on sun exposed regions of the body.

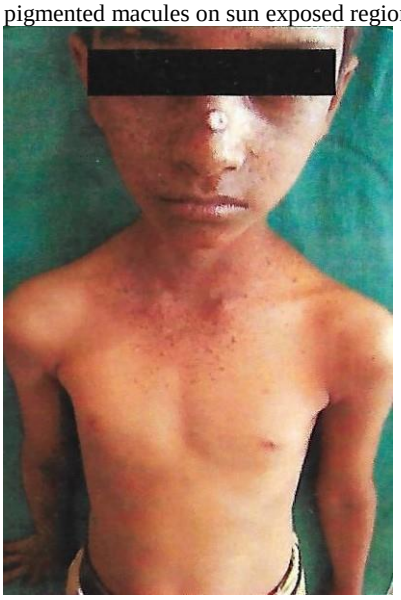


Figure 2 – Photomicrograph of squamous cell carcinoma, H&E, 100x. Arrow shows a keratin pearl.

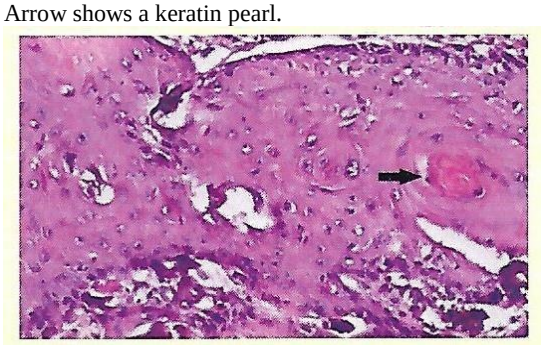
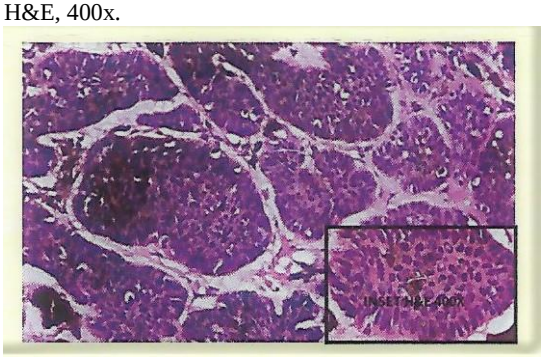


Figure 3 – Photomicrograph of basal cell carcinoma, H&E, 100x. Inset – H&E, 400x.



A review by DiGiovanna et al.[6] summarised the process of ultraviolet radiation induced DNA damage, according to which exposure of DNA to ultraviolet radiation produces multiple nucleic acid based photoproducts. These serve as substrates for DNA repair via the nucleotide excision repair. The damaged DNA is recognized by the transcription-coupled repair (TCR) pathway and global genome repair (GGR) pathway. Mutations in any of these proteins from either the TCR, GGR or nucleotide excision repair pathways lead to abnormalities in DNA repair.[2]

The earliest changes usually develop before the age of 2 years with a severe sunburn reaction. There is development of multiple freckles with variable melanin pigmentation and interspersed hypopigmented macules. Later, dry, scaly skin (xerosis) with poikilodermatous features are seen. Solar keratoses, cutaneous horns, keratoacanthomas, squamous and basal cell carcinomas, atypical fibroxanthoma, malignant melanomas and angiomas, may develop in late childhood.[1]

The first malignant tumours may develop as early as third or fourth year of life, with a median age of onset of eight years.

Patients also experience a variety of ophthalmologic and central nervous system involvement as well. Neurodegeneration occurs in about 24 % patients.[2]

Among the cutaneous malignancies, basal cell carcinoma, squamous cell carcinoma and melanomas are common.[3]

A similar case of squamous and basal cell carcinomas in the face in a 14 year old male has been reported in Maharashtra.[7] However, our patient presented much earlier. Halkud et al [8] reported 11 cases of Xeroderma Pigmentosum, of which most had facial SCC and BCC by 8 – 9 years of age, similar to our study.

Prophylactic measures such as avoidance of sunlight, minimizing ultraviolet rays exposure with the use of protective clothing, application of sunscreens, sunglasses with side shield play a significant role. Early and adequate excision of all tumors is essential to reduce the morbidity to a certain level. Chemoprohylaxis with systemic retinoids, topical T4 endonuclease V, 5 Fluorouracil and imiquimod significantly reduce the rate of new cutaneous malignancies in Xeroderma Pigmentosum. [9,10,11] Dermabrasion is another effective modality, as reported by König A et al. [12]

Awareness about this rare condition and prevention of ultraviolet rays induced skin damage should be propagated. Genetic counselling with emphasis on implications of consanguineous marriage plays a key role in its prevention. As the incidence of Xeroderma Pigmentosum in India is still unknown, [13] reporting every case may help in determining the incidence and prevalence of this genodermatosis in our country.

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Russel body gastritis associated with gastric adenocarcinoma: A rare case report

Mide adenokarsinomu ile ilişkili Russel body gastriti : Nadir bir olgu sunumu

Ayşe Nur Uğur Kılınç [1], Betül Duygu Şener [1]

Abstract

Russel body gastritis is a rare entity, the exact etiology of which is unknown. Approximately 50 cases have been reported in the literature so far. In the literature, especially Helicobacter pylori infection, HIV, and multiple myeloma have been associated with diseases, such as gastric adenocarcinoma and with alcohol use. Russel body gastritis has rarely been reported to be associated with gastric adenocarcinoma. We will present the determination of Russell body gastritis in the control biopsy of a 60-year-old female patient diagnosed with stomach adenocarcinoma six months ago. This case report presents this rare condition and etiology in light of the literature review.
Key words: Russel body, gastritis, gastric adenocarcinoma

Öz

Russel Body Gastriti (RBG), etiyolojisi kesin olarak bilinmeyen nadir görülen bir gastrit çeşididir. Literatürde günümüze kadar yaklaşık 50 vaka bildirilmiş olup Helicobacter pylori enfeksiyonu, HIV, multipl miyelom, gastrik adenokarsinom gibi hastalıklar ve alkol kullanımı ile ilişkili olabileceği bildirilmiştir. Russell body gastriti 'nin nadiren gastrik adenokarsinom ile ilişkili olduğu bildirilmiştir. Biz altı ay önce mide parsiyel rezeksiyonu sonrası mide adenokarsinomu tanısı alan 60 yaşında kadın hastanın; mide kontrol endoskopik biyopsisinde Russell body gastriti tanısını sunacağız. Bu olgu sunumu nadir görülen bu durumu ve etyolojiyi literatür eşliğinde sunmayı amaçlamıştır.
Anahtar kelimeler: Russel Body, Gastrit, Adenokarsinom

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Introduction

Russel Body Gastritis (RBG) is a rare entity with an unknown etiology. About 50 cases have been reported in the literature so far [1]. In the literature, especially Helicobacter pylori infection, HIV and multiple myeloma have been associated with diseases, such as gastric adenocarcinoma and with alcohol use [1-5]. This study aimed to present this rare etiology and condition with a literature review.

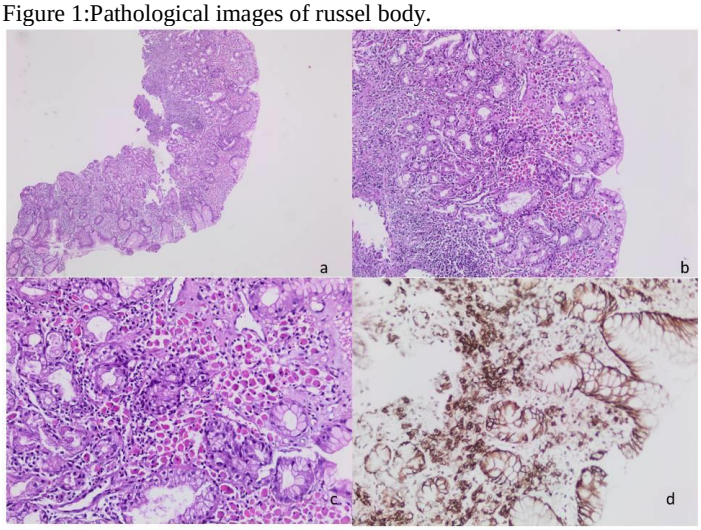
Case report

In our case, a 60-year-old female patient underwent subtotal gastrectomy for gastric adenocarcinoma five months ago. She was diagnosed with grade-2 adenocarcinoma, and no metastasis was detected in the lymph nodes. After six months of adjuvant chemo-radiotherapy, control endoscopy showed a clean anastomosis line, and a biopsy was taken from the ulcerated area proximal to the anastomosis line. Histopathological examination of the specimens revealed moderate gastritis in Giemsa staining and plasma cell deposition with many cytoplasmic Russell Bodies widespread in the lamina propria and chronic gastritis findings (Figure 1 a, b, c). Immunohistochemical staining applied to the large cytoplasm plasmacytoid cells showed positive expressions of CD 138, CD 79A, and kappa lambda (Figure 1d). In the serological analysis of our patient, HIV and Hepatitis C were negative, and Hepatitis B antigen was positive.

We eliminated the granular cell tumor with the S100 negativity and lymphoplasmacytic lymphomas by polyclonal staining of kappa lambda.

The patient's consent was obtained for this case study.

Figure 1:Pathological images of russel body.



a) Russel Body Gastritis H&E images 40X b)Russel Body Gastritis H&E images 100X c) Russel Body Gastritis H&E images 400X d)Plasma cells in the gastric mucosa CD 138 stain 200X

Discussion

RBG is a type of chronic gastritis characterized by the accumulation of plasma cells containing eosinophilic cytoplasmic inclusion, which is located in gastric lamina propria. In 1998, Tazawa and Tsutsami described intense RB-containing plasma cell infiltration in the gastric mucosa as RBG [6].

Russell bodies are the accumulation of condensed immunoglobulins in the perinuclear cistern of the flat endoplasmic reticulum and caused by intense stimulation of plasma cells. Plasma cells consisting of a large number of Russell bodies in the cytoplasm are called Mott cells. They may be localized in the gastrointestinal tract, usually in the antrum [1].

Tazawa has associated RBG with chronic inflammation, and it has been associated with Helicobacter pylori infection in later cases: four cases with adenocarcinoma, three cases with multiple myeloma, three cases with HIV infection, and 1 case with alcohol use [1-4, 6].

In a study conducted by Johansen et al., when the ratio of Russell body in peritumoral mucosa in tumor-free endoscopic biopsy materials in adenocarcinomas was compared, Russell body was significantly higher in peritumoral tissue compared to others [7].

In the literature, four cases associated with the tumor have been reported as in our case [1-3, 6]. However, when the cases in the literature were examined, other lesions were detected simultaneously with the tumor and in our case, the lesion was found after tumor treatment. In our case, the cause of plasmocyte stimulation can also be interpreted in response to the immunosuppressive effect of Helicobacter Pylori infection or chemotherapy treatment because the Mott cells were not observed when the gastric tissue sections of the tumor were examined during the initial diagnosis of our patient.

When diagnosing Russell body gastritis, several diagnoses need to be distinguished. Cytokeratin negation excludes carcinoma, while kappa and lambda polyclonal immunoreactive patterns exclude lymphoplasmacytic lymphoma and plasmacytoma. Cytological atypia can be distinguished from mucosa-associated lymphoid tissue (MALT) lymphoma by lymphoepithelial lesions, absence of centrocyte-like cells and monocytoid cells, and excessive plasmacytic differentiation [8]. Finally, there is no criterion for the prevalence of Russell body to define Russell body gastritis [1]. However, our personal view is that the Russell bodies should be aborted in the gastric mucosa.

Russell Body Gastritis is a rare entity that can be encountered, especially in endoscopic biopsy materials. Although it is usually associated with Helicobacter Pylori, it can be associated with various diseases. As in our case, it should be kept in mind that biopsy materials may be encountered in control adenocarcinoma cases.

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