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''Tip öğrencilerinde obsesif-kompulsif belirtiler ve ortoreksiya nervozayı araştıran web tabanli, kesitsel bir çalişma'

''Küçük hücreli dışı akciğer tümörlerinin değerlendirilmesinde tc-99m MIBI spect'in yeri',

''2010-2022 yılları arasında Batman'da ekinokokkoz olgularının dökümantasyonu'',

''Labiyal füzyona yaklaşımlar: Karadeniz bölgesinde bir eğitim ve araştırma hastanesinin 3 yıllık deneyimi'',

''İdiyopatik trombositopenik purpura nedeniyle takip ve tedavi edilen hastaların retrospektif değerlendirilmesi: 21 yıllık tek merkez deneyimi'',

''Tükrük bezi karsinomlarında HSPA2 ekspresyon profili ve prognostik parametreler ile ilişkisi'

değerli yazarlarımız tarafından etkili bir şekilde ele alınarak bilim dünyasına sunulmuştur.

"Akut bilinç kaybı ile tanı alan medulloblastom olgusu'nun ve 'izole kemik kitlesi: granülositik sarkom olabilir mi?' sorusu ile çocuklarda ekstramedüller kitle varlığında ayırıcı tanıya nadir bir durum olan granülositik sarkomun da alınması gerektiğini vurgulayan olgu sunumumuzun dikkatinizi çekeceğini umuyorum

Dergimiz 2 yıllık yayın süreci içerisinde uluslararası bir dergi statüsüne doğru ilerlemektedir. Uluslararası indekslere kabul konusunda ciddi adımlar atmaktayız. ULAKBİM/TR dizinleme yolunda da çalışmalara başlamış bulunuyoruz ve umut ediyorum ki yakında güzel haberleri sizlerle paylaşırız.

Değerli yazarlarımız ve etkin bir değerlendirme sürecini gerçekleştiren hakemlerimize ,yayın hayatımızın ilk gününden itibaren büyük bir özveri gösteren editör arkadaşlarım Doç. Dr. Erkan Cem Çelik ve Doç. Dr. Ali Ahıskalıoğlu başta omak üzere değerli editöryal kadromuza, yayın hayatımıza başlamamız için bizi yüreklendiren ve bu güne kadar ki süreçte desteklerini her zaman yanımızda hissettiğimiz, dekanımız Prof. Dr. Fatih Albayrak'a, kaliteli bir yayın hayatı geçirebilmemiz için bilgi ve deneyimi ile bizlere katkısı ve desteği büyük olan Prof. Dr. Sinan Aktaş'a destek ve katkıları için çok teşekkür ederim.

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Research Article/ Araştırma Makalesi

OBSESSIVE-COMPULSIVE SYMPTOMS AND ORTHOREXIA NERVOSA IN MEDICAL STUDENTS: A WEB-BASED, CROSS-SECTIONAL STUDY

TIP ÖĞRENCİLERİNDE OBSESİF-KOMPULSİF BELİRTİLER VE ORTOREKSİYA NERVOZA: WEB TABANLI, KESİTSEL BIR ÇALIŞMA

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Abstract / Özet

Aim: The aim of this study was to investigate medical students' tendencies towards orthorexia nervosa (ON) and its relationship with obsessive-compulsive symptoms. **Materials and methods**: This descriptive study was conducted with 822 medical students. The data were collected via an online survey. A sociodemographic information form, the ORTO-11 scale, and the Maudsley Obsessive Compulsive Symptom Inventory (MOCI) were used as data collection forms. **Results:** The mean age of the students was 20.5±2.1 years, and 50.7% (n=417) were female. Orthorexia tendency was detected as 19% (n=156). A significant negative relationship was found between the students' ORTO-11 and MOCI scores ($p<0.001$). There was no significant difference between ORTO-11 and MOCI scores according to sex and years of training. Participants who did not eat at night, did not consume packaged food, checked the expiration date and content of the food, and had regular meals had significantly lower ORTO-11 scores. There was no significant relationship between students' mean body mass index and their ORTO-11 and MOCI scores ($p>0.05$ for all). **Conclusion:** The study results show that the tendency to ON is high among medical students. ON is more common in students with obsessive-compulsive symptoms. Interventions to eliminate obsessive-compulsive symptoms should be added to the fight against ON. **Keywords:** Medical students, orthorexia, obsessive-compulsive symptoms

Amaç: Bu çalışmanın amacı tıp öğrencilerinin ortoreksiya nervoza (ON) eğilimlerini ve obsesif-kompulsif belirtiler ile ilişkisini araştırmaktır. **Materyal ve Metot:** Bu tanımlayıcı çalışma 822 tıp öğrencisi ile yürütülmüştür. Veriler çevrimiçi bir anket aracılığıyla toplanmıştır. Veri toplama formu olarak sosyodemografik bilgi formu, ORTO-11 ölçeği ve Maudsley Obsesif Kompulsif Belirti Envanteri (MOCI) kullanılmıştır. **Bulgular:** Öğrencilerin yaş ortalaması 20.5±2.1 yıl olup, %50.7'si (n=417) kadındır. Ortoreksiya eğilimi %19 (n=156) olarak tespit edilmiştir. Öğrencilerin ORTO-11 ve MOCI puanları arasında negatif yönde anlamlı bir ilişki bulunmuştur ($p<0.001$). Cinsiyet ve eğitim yılına göre ORTO-11 ve MOCI puanları arasında anlamlı bir fark bulunmamıştır ($p>0.05$). Gece yemek yemeyen, paketli gıda tüketmeyen, gıdaların son kullanma tarihini ve içeriğini kontrol eden ve düzenli öğün yapan katılımcıların ORTO-11 puanları anlamlı derecede düşüktü. Öğrencilerin ortalama vücut kitle indeksi ile ORTO-11 ve MOCI puanları arasında anlamlı bir ilişki bulunmamıştır (tümü için $p>0.05$). **Sonuç:** Çalışma sonuçları, tıp öğrencileri arasında ON eğiliminin yüksek olduğunu göstermektedir. Obsesif-kompulsif semptomları olan öğrencilerde ON daha yaygındır. ON ile mücadeleye obsesif-kompulsif belirtileri ortadan kaldırmaya yönelik müdahaleler de eklenmelidir. **Anahtar kelimeler:** Tıp öğrencisi, ortoreksiya, obsesif kompülsif belirtiler

1. INTRODUCTION

Orthorexia nervosa (ON) is a pathological obsession with consuming healthy foods (1). Although it is quite natural for an individual to eat healthily, the behavior toward healthy eating has become obsessive in ON. This situation adversely affects the individuals' health and quality of life (2, 3). Orthorexia nervosa is not a diagnostic criterion in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, but is considered an unidentified eating disorder (1).

Although ON has similar aspects to eating disorders such as anorexia nervosa and bulimia nervosa, orthorexic individuals are mainly concerned with the healthiness of food, not its calories (1, 2). Therefore, it is crucial for orthorexic individuals that the food is pure and has no additives. They control food exaggeratedly and are very strict about ingredients and expiration dates (3). They examine food packaging at length and check whether there are any hormones, additives, carcinogenic substances, or dyes. They spend most of their time researching the properties of the foods they will consume and preparing pure foods. This obsessive approach to healthy eating negatively affects the health of individuals with ON and may cause them to lose weight even though they do not calculate calories (3-6).

Orthorexic individuals often lead a life away from society because they do not eat food prepared by others. This situation limits their lives over time, negatively affects their social relationships, and reduces their quality of life (6). Sometimes efforts starting as just a healthy diet can turn into ON over time (7). The prevalence of ON in the population is between 6.9% and 57.6% (8-13).

The etiology of ON is complex, multidimensional, and their psychological factors are crucial. Although there are aspects similar to known eating disorders, the desire to consume pure and healthy food is more critical in ON than the desire to lose weight. This desire, which initially started as a healthy eating behavior, turns into an excessive mental and behavioral struggle over time. Thus, the desire to eat healthy food becomes obsessive and challenging. In these respects, it is similar to obsessive-compulsive disorder (OCD) (1, 8).

OCD is a disease that progresses with obsessions and compulsions and affects the individual's daily life. Obsessions are impulses, thoughts, or images that occur involuntarily, cause the individual to be agitated, alien to the self (ego-dystonic), and show repetitive features, whereas compulsions are actions that occur with these thoughts, and the person feels compelled to engage in these behaviors (9, 10).

Orthorexia nervosa has a pathological obsession, similar to obsessive-compulsive disorder, leading to strict rules for dietary practices and intense anxiety. When the adopted diet is violated, guilt and shame are seen (11). Therefore, obsessive-compulsive tendencies and perfectionism may be risk factors for orthorexia (8, 12).

It is predicted that people with ON disorder will gradually increase, and orthorexia will be a global public health problem. The university life is a period in which the eating habits of young individuals are reshaped. Orientation to fast-food, unbalanced eating or malnutrition can be seen in the adaptation to the new environment especially in students who move to another city (5). Therefore, determining the eating habits acquired during university that will likely last a lifetime is vital in preventing future problems (13).

Health and disease information may also affect orthorexic tendencies. Therefore, health professionals are a risk group for ON due to their increasing emphasis on healthy eating and the pressure to be role models in healthy living (14).

Medical students are also among the risk groups regarding ON (15). Hence, knowing the frequency of ON and the influential factors in students is essential to intervene early.

Understanding the relationship between orthorexic attitudes and obsessive-compulsive symptoms requires searching for and treating obsessive symptoms, especially in treatment-resistant ON cases. Studies evaluating the orthorexic attitudes of medical students are limited in Turkey (16). To the best of our knowledge, there has not been a study investigating the orthorexic attitudes of medical students in Turkey for the last 15 years. This study aimed to evaluate the orthorexia attitudes of medical students and the relationship of obsessive-compulsive symptoms.

2 MATERIALS AND METHODS

2.1 Ethical Approval

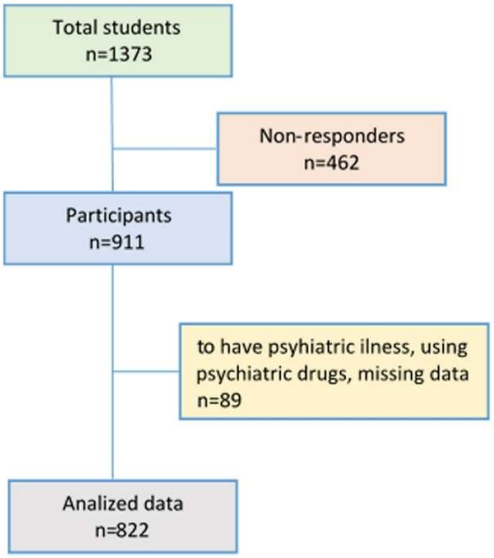
The ethical approval required for the study was obtained from the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (IRB Number: B.30.2.ATA.0.01.00/633, Number: 7/44, Date: 29.09.2022). The study was conducted following the principles of the Helsinki Declaration, and informed consent was obtained from the participants.

2.2 Study Setting and Participants

This cross-sectional study was carried out with students of Atatürk University Faculty of Medicine between October and November 2022. The data were collected through an online survey. First, students were informed about the purpose and scope of the study through class WhatsApp groups and emails. The survey was administered online through Google Forms. Information about the purpose of the study was included at the beginning of the survey. Participation in the study was voluntary. The

survey's first question was "I voluntarily agree to participate in the study," and the participants were asked to consent to this statement. Second question was about having a psychiatric illness and/or using psychiatric medications. Students who did not give their consent or having a psychiatric illness and/or using psychiatric medications could not answer the survey questions. The questionnaire was left open for answers for three weeks. During this time, three reminder messages were sent, once every week. At the end of the specified period, the survey was terminated. All students in grades 1-5 were invited to the study (n=1373). Nine hundred-eleven students responded to the survey, making a participation rate of 66%. Eighty-nine questionnaires excluded for various reasons. Data from a total of 822 students were analyzed (Figure 1).

Figure 1: Participant flowchart



2.3 Measures

The study questionnaire consisted of three sections: 1) sociodemographic characteristics and nutritional habits, 2) the ORTO-11 scale, and 3) the Maudsley Obsessive Compulsive Symptom Inventory (MOCI).

2.3.1 The sociodemographic information form

Items in this section were age, education year, height, weight, smoking and alcohol use, exercising status, weight perception, night eating (eating after 9 pm), regular eating, place of having lunch, number of meals a day, place of accommodation, regular eating behavior, fast food consumption, packaged food consumption, and eating at night. Body mass index (BMI) was calculated according to the self-reported height and weight values by dividing weight by height squared (weight (kg)/ height (m2) (17).

2.3.2 The ORTO-11 Scale

The ORTO-15 scale was first developed by Donnini et al. (3). During the adaptation of the scale to Turkish, four items with low internal reliability were removed from. When the items' statistical characteristics were considered, the scale was brought to the best possible operability level with its 11-item form, and it was named ORTO-11 (5). The items on the scale consist of expressions that investigate the obsessive behaviors of individuals in selecting, purchasing, preparing, and consuming foods that they consider healthy. Scale items are answered according to the Likert system of 4 and are scored as always (1 point), often (2 points), sometimes (3 points), and never (4 points). For each item, 1 point reflects orthorexic tendency, and 4 points reflect normal eating behavior tendency. The total score is obtained by summing the points of all items. The score that can be obtained from the scale ranges between 11 and 44. Low scores on the scale indicate orthorexic tendency. There is no recommended cut-off value. We pragmatically chose the cut-off 24 (25th percentile) and below as orthorexic tendency. The Cronbach's alpha value of the scale is reported as 0.62 (5). In our study, Cronbach's alpha was 0.61.

2.4 The Maudsley Obsessive Compulsive Symptom Inventory

MOCI is a self-assessment tool developed by Hodgson and Rachman (1977) to measure the type and prevalence of obsessive-compulsive symptoms. The original scale was developed with 30 items (18). The scale was adapted to Turkish by Erol and Savaşır (1988). Seven more items related to obsessional thinking were added to the Turkish version, and a scale of 37 items was obtained. The scale's Cronbach's alpha value is reported as 0.86 (19). Every item on the scale is answered as ‘yes’ or ‘no.’ Each ‘yes’ answer is given one point, and ‘no’ is scored zero points. High scores on the scale indicate the severity of obsessive-compulsive symptoms (OCS) (19). In our study, the scales Cronbach's alpha value was 0.87.

2.5 Statistical Analysis

Statistical analysis was performed with the SPSS 20 statistical package program (SPSS Inc., Chicago, IL, USA). Suitability of the data to normal distribution was assessed with the Kolmogorov–Smirnov test. Numerical variables were expressed as the mean and standard deviation, and categorical variables as numbers and percentages. The t-test for independent groups was used to evaluate two independent groups. The Mann–Whitney U test was used for skewed data. Depending on data distribution, the one-way ANOVA test or the Kruskal–Wallis test was used to compare more than two groups. Backward stepwise model logistic regression analysis was used to evaluate the factors affecting orthorexia nervosa and OCS. When looking at the relationship between two

quantitative variables, Pearson correlation analysis was used in those with normal distributions, and Spearman correlation analysis for skewed data. The reliability of the scales was tested with the Cronbach's alpha coefficient. The statistical significance level was accepted as $p< 0.05$.

3. RESULTS

The mean age of the students was 20.5±2.1 (range 18-32) years, and 50.7% (n=417) were female. Four hundred ninety-seven students (60.5%) described their body perception as normal. Of the students, 69.8% (n=574) stated that they ate at night (after 9 pm), and 92.6% (n=761) consumed packaged foods. Two hundred forty-one (29.3%) were engaged in regular sports, and 51.7% (n=425) consumed fast food more than once a week. Four hundred and fifty-seven 55.6% (n= 457) ate lunch in the school cafeteria. The students' sociodemographic characteristics, nutrition, and lifestyle habits are shown in Table 1. The mean ORTO-11 score of the participants was 27.2 ±4.2 (range 14-41), and the average MOCI score was 14.7±7.2 (range 1-36).

Table 1: Sociodemographic characteristics of students.

Variables		Count (n)	Percent (%)
Sex	Female	417	50.7
	Male	405	49.3
Education year	1	156	19.0
	2	165	20.1
	3	202	24.6
	4	185	22.5
	5	114	13.9
In your opinion, what is your body's perception?	Normal	497	60.5
	Slim	145	17.6
	Overweight	134	16.3
	Obese	46	5.6
Do you eat anything at night? (after 9 pm)	No	248	30.2
	Yes	574	69.8
Do you consume packaged foods?	No	61	7.4
	Yes	761	92.6
Do you usually look at the expiration date of food?	No	195	23.7
	Yes	627	76.3
Do you usually look at the content of food?	No	371	45.1
	Yes	451	54.9
Are your meals regular?	No	435	52.9
	Yes	387	47.1
Do you do sports regularly?	No	581	70.7
	Yes	241	29.3
Do you consume alcohol?	No	694	84.4
	Yes	128	15.6
Do you smoke?	No	651	79.2
	Yes	171	20.8
Do you think you are eating healthily?	No	462	56.2
	Yes	360	43.8
Where are you staying?	Dormitory	408	49.6
	Alone at home	52	6.3
	At home with my friends	70	8.5
	At home with my family	292	35.5
How many meals do you eat per day?	One	17	2.1
	Two	339	41.2
	Three	377	45.9
	More than three meals per day	89	10.8
Where do you eat your lunch?	I don't eat lunch	90	10.9
	In the school cafeteria	457	55.6
	Restaurant	49	6.0
	In the canteen	104	12.7
	At home	122	14.8
How often do you consume fast food?	Once a week	194	23.6
	Less than once a week	203	24.7
	More than once a week	425	51.7

3.1 Relationship between ORTO-11 and MOCI scores

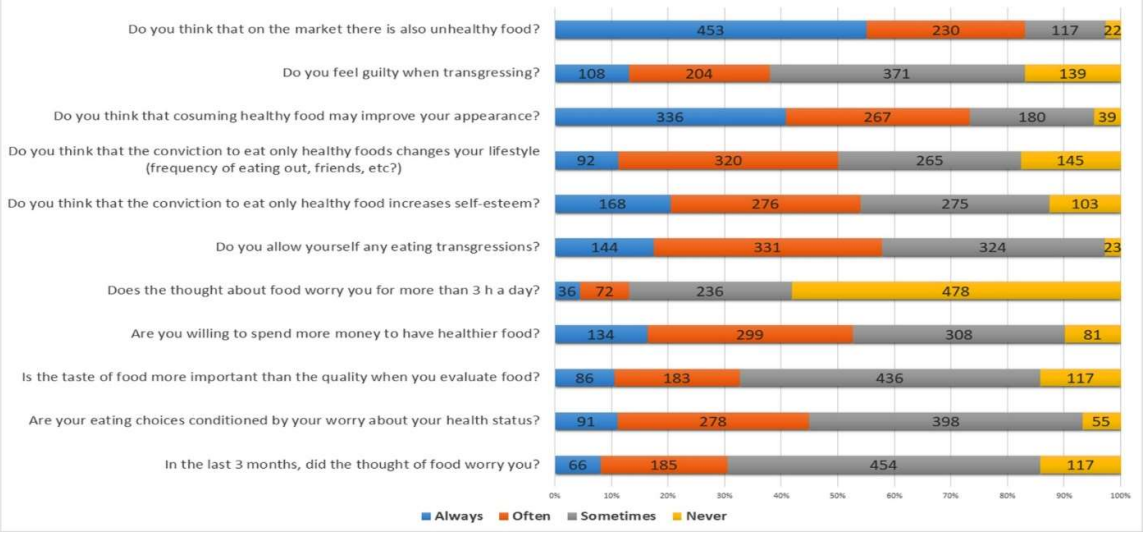
There was a significant negative relationship between students' scores on ORTO-11 and MOCI ($p<0.001$) (Spearman's $r=-0.253$, $p<0.001$).

3.2 The relationship of ORTO-11 and MOCI scores with sociodemographic variables

There was no significant difference between the students' ORTO-11 and MOCI scores according to sex and school year ($p>0.05$ for both, Table 2). Participants who did not eat at night (after 9 pm), did not consume packaged food, looked at the expiration date and content of the food, and had regular meals had significantly lower ORTO-11 scores ($p=0.02$, 0.02, 0.01, <0.001, <0.001, respectively). There was no significant difference between the ORTO-11 scores of students who smoked or consumed alcohol and those who did not ($p>0.05$). The ORTO-11 scores of the students who thought they were eating healthy were significantly lower than those of the students who did not think they were eating healthy ($p=0.02$).

The students' grade point average was 71.0±11.4 (range 25-98), their mean weight was 66.3±13.4 (range 42-124), and their mean BMI was 22.9±4.5 kg/m2. No significant correlation was found between grade point average and BMI, ORTO-11, or MOCI scores ($p>0.05$ for all). While there was no significant relationship between the students' perceptions of their bodies (slim, overweight, fat) and ORTO-11 scores, there was a significant relationship between them and their MOCI scores.

Figure 2: Students' responses to ORTO-11 scale items



According to logistic regression analysis, ORTO-11 scores were 2.4 times higher in those who did not consume packaged food than in those who did consume it, 0.5 times higher in those who controlled the content of the food than in those who did not, and 0.4 times higher in those who did regular exercise (Table 3).

4. DISCUSSION

Orthorexia nervosa (ON) is a new concept in the field of eating disorders. Studies to determine the prevalence of ON among medical students are limited (16). In this study, obsessive-compulsive symptoms and the role of gender on the tendency to ON in medical students were investigated. While gender did not significantly influence the tendency to ON, obsessive-compulsive symptoms had a significant predictive effect. Accordingly, as the OCS scores of the students increases, their tendency to ON also increases.

In the current study, 19% of medical students had a tendency to ON. Different study results are reported regarding the frequency of ON. The prevalence of orthorexia in the study conducted with medical students in Turkey was reported as 43.6% (16) and 45.5% in the study with assistant doctors (14). In the study by Donini et al. in Italy, the ON frequency was 6.9% (8). In two studies conducted in Italy, the prevalence of ON in athletes was 28% (20) and 12,6% in university students (21). In a study conducted in an athlete sample, the prevalence of ON was reported as 81%. These differences may depend on the characteristics of the group studied, the cultural characteristics, the measurement tools used, or the difference in accepted cut-off points.

In our study, the mean ORTO-11 score of the students was 27.2±4.2, and the mean MOCI score was 14.7±7.2. Students' ORTO-11 scores were similar to the results of a study with medical students in the same region in 2018 (16). Fidan et al. found a significant relationship between the age of the

students and their ORTO-11 scores (16). However, other studies did not find a significant relationship between age and orthorexia scores (5, 22-25). In a study conducted in an Italian sample, Donini et al. reported the average age of the orthorexic group being higher (8). In our study, there was no significant relationship between the students' ages and ON attitudes. The close age of the students who made up the study group may have impacted the results.

Table 2. The relationship of ORTO-11 and MOCI scores with sociodemographic variables

		ORTO-11 Score				MOCI Score			
		Mean±SD	Med	Min-max	*p*	Mean±SD	Med	Min-max	*p*
Education year	1	27.25±4.55	28	14-41	0.149	14.39±7.23	13	1-36	0.756
	2	27.73±4.01	28	14-38		14.76±6.96	15	1-35	
	3	26.97±4.21	27	14-38		14.80±6.79	15	1-36	
	4	26.68±4.21	27	15-38		15.15±7.63	14	2-36	
	5	27.71±4.39	28	16-41		14.23±7.99	13	1-36	
Sex	Female	27.36±4.05	28	14-41	0.573	14.73±7.30	14	1-36	0.963
	Male	27.06±4.49	28	14-41		14.70±7.23	14	1-36	
Do you eat something at night? (after 9 pm)	No	26.74±4.20	27	15-41	0.021	14.90±7.01	13	1-36	0.130
	Yes	27.41±4.29	28	14-41		15.00±7.35	15	1-36	
Do you consume packaged foods?	No	25.90±4.85	26	17-35	0.023	14.39±7.21	15	1-31	0.946
	Yes	27.32±4.21	28	14-41		14.74±7.27	14	1-36	
Do you usually look at the expiration date of food?	No	27.86±4.10	28	15-41	0.014	14.33±7.31	14	1-36	0.491
	Yes	27.01±4.31	27	14-41		14.83±7.25	14	1-36	
Do you usually look at the content of food?	No	28.16±3.88	29	15-41	0.000	14.45±6.73	14	1-35	0.656
	Yes	26.44±4.42	26	14-41		14.94±7.67	14	1-36	
Are your meals regular?	No	27.65±4.27	28	15-41	0.004	14.74±7.45	14	1-36	0.876
	Yes	27.42±4.22	27	14-36		14.69±7.05	14	1-36	
Do you exercise regularly?	No	27.66±4.06	28	15-41	0.000	14.66±7.20	14	1-36	0.957
	Yes	26.13±4.58	26	14-38		14.84±7.42	14	2-36	
Do you consume alcohol?	No	27.72±4.17	28	14-41	0.770	14.53±7.02	14	1-36	0.324
	Yes	26.87±4.78	28	14-36		15.70±8.41	14	2-36	
Do you smoke?	No	27.26±4.14	28	14-41	0.821	14.29±7.09	14	1-36	0.001
	Yes	27.01±4.76	28	14-41		16.33±7.70	17	2-36	
Do you think you are eating healthily?	No	27.55±4.16	28	15-41	0.025	14.84±7.22	15	1-36	0.412
	Yes	26.78±4.38	27	14-38		14.56±7.33	14	1-36	

Table 3. The probability of orthorexia nervosa according to different variables

					95% C.I. for OR	
	B	S.E.	*p*	OR	Lower	Upper
Sex	-0.17	0.19	0.36	0.83	0.57	1.23
Do you eat something at night? (after 9 pm)	-0.08	0.20	0.66	0.91	0.60	1.37
Do you consume packaged foods?	0.88	0.30	0.003	2.42	1.33	4.38
Do you usually look at the expiration date of food?	-0.16	0.24	0.50	0.85	0.53	1.36
Do you usually look at the content of food?	-0.56	0.21	0.008	0.56	0.37	0.86
Are your meals regular?	-0.29	0.22	0.19	0.74	0.47	1.16
Do you do sports regularly?	-0.71	0.20	0.001	0.48	0.32	0.73
Do you eat breakfast regularly?	-0.08	0.22	0.71	0.92	0.59	1.42
Do you think you are eating healthily?	0.05	0.23	0.80	1.05	0.67	1.66

Regarding the effects of sex on ON, different results are reported in the literature. In Fidan's study, the ON frequency in males was higher than in female students (16). In the studies of Sanlier et al. and Arusoğlu et al., higher rates were found in women. It was reported that gender had a strong predictive effect on orthorexic attitudes (5, 26). In another study conducted in Turkey, the frequency of diabetic patients and orthorexia was significantly higher in men (27). Also, in a study by Donini et al. in Italy, the tendency to ON was higher in men. This result was explained by men possibly entering the influence of "body culture" earlier in some societies (8). In addition to cultural and social differences, the different measurement tools used may have been effective in these variations. Our study did not find a significant difference between the sexes regarding ON attitudes.

Conflicting results regarding the relationship between education level and ON are observed. Some studies have observed a higher tendency to ON in individuals with lower education levels. In a study conducted by Korinth et al., the tendency to orthorexia decreased toward the last years of university education. In the studies of Aksoydan and Bosi, no significant relationship was found between orthorexic tendency and education level. In a recent study by Yeşilçayır et al. with individuals who exercised, the relationship between ON and education level was not determined. Our study did not find a relationship between education level and orthorexic attitudes. Additional studies are needed to reach definitive conclusions. The current study did not find a relationship between how students perceive their bodies and ON tendencies. However, students who felt fat and overweight were significantly more likely to have obsessive-compulsive symptoms than other students.

Body mass index is an important variable related to eating disorders. BMI did not have a significant effect on orthorexic tendencies. The information on this subject is contradictory. In addition to the studies reporting that BMI does not affect ON (5, 24, 27), there are also studies claiming that orthorexic tendency is higher in those with higher BMI (28, 29). This may be related to the need for healthy nutrition or weight control of individuals who are overweight. Another study determined that participants who frequently controlled their weight had high ON tendencies (14). In two studies conducted with medical doctors and medical students in Turkey, those with low BMI had a higher tendency to ON (14, 16). Similarly, in another study, orthorexic tendencies decreased as BMI increased (23).

There are many benefits of healthy eating for physical and mental health. However, this has become a very advanced obsession in individuals with ON. When this obsession exceeds a certain duration, it can become a disorder that concerns the dimensions of personality and behavior (6). In this respect, the relationship between ON and OCD is interesting. In the study of Arusoğlu et al. in Turkey, obsessive-compulsive symptoms were associated with the tendency to ON. It was understood that the group with high obsessive-compulsive symptoms showed more orthorexic tendencies. This finding was confirmed in our study. In the current study, we determined that students' tendency to ON had a significant association with obsessive-compulsive symptoms. As the students who participated in the study had obsessive-compulsive symptoms, the tendency to ON also increased.

Contrary to our findings, in the study conducted by Donini et al. in Italy, no relationship was found between orthorexic attitudes and OCS, which was explained by the difference in the measurement tools used (3). In addition to the deterioration of health in eating disorders, it has been reported that problems such as difficulty in learning and decreased intelligence averages occur due to unbalanced nutrition (30). Our study did not confirm this. We did not find a significant relationship between the average school grades of the students participating in our research and their ORTO-11 scores. More comprehensive and long-term follow-up studies may be helpful in this regard. In our study, there was no difference in the tendency toward orthorexia between the students who smoked or drank alcohol and those who did not. Similar results were obtained in a study of performance artists (31). Only one-third of the students who participated in our study exercised regularly. Strategies should be developed to encourage medical students to eat healthily and participate in sports. More than half of the students consumed fast food more than once a week, two-thirds perceived body weight as normal, and nine out of ten students consumed packaged food.

Students who did not eat at night (after 9 pm), did not consume packaged food, looked at the expiration date and content of food, had regular meals, thought they were eating healthily, and played sports had significantly more orthorexic attitudes than other students. In the study of Bossi et al., people examined label information when purchasing products (14). According to regression analysis, the tendency to ON was 2.4 times higher in those who did not consume packaged food, 0.5 times more in those who controlled the content of the food than in those who did not, and 0.4 times more in those who exercised regularly. These findings are consistent with orthorexic behaviors. The limited number of studies on orthorexia nervosa, a new concept, reveals the need for further investigation in high-risk groups. Medical students are at risk for eating disorders due to their age and health education. Considering medical students' public information and social roles, increasing their knowledge and awareness of the subject is crucial. Medical students who are physician candidates in the future should be aware of ON. Understanding the relationship between ON attitudes and obsessive-compulsive symptoms is

vital for prevention and intervention approaches. For this, more large-scale and diverse sampling studies on ON are needed.

Considering the peer education roles of medical students, it should also be seen as an opportunity for them to educate those around them with the right information. For this reason, it may be helpful to include courses on nutrition in the medical education curricula and motivate students to take responsibility in social sensitivity projects and to inform society. Cultural differences should be considered when planning individual and community training, and measures should be taken to prevent medical students from becoming obsessive while improving healthy nutrition awareness.

4.1 Strengths and limitations

There are some limitations of our study. First, it is a cross-sectional study with participants from a single medical school. This makes it difficult to generalize the results for medical students. Second, the obsessive-compulsive symptoms and orthorexic attitudes of the students were evaluated through scales. There were no face-to-face interviews or examinations. All data, including weight/height measurements and co-morbidities, were collected by self-reports. Third, the influence of time and training on the ON tendency was not assessed. Finally, medical students' attitudes could not be compared with those of students in different departments. Despite these limitations, the fact that it is one of the limited numbers of studies conducted in a large sample in the field and that there has been no other study evaluating orthorexic attitudes of medical students in our region for more than a decade makes our study strong.

5. CONCLUSION

In this study, the relationship between orthorexia nervosa and gender and obsessive-compulsive symptoms was investigated in a large sample, and obsessive-compulsive symptoms had a substantial predictive effect on orthorexic attitudes. Gender did not affect orthorexic attitudes. As tomorrow's doctors, students should be provided with knowledge and awareness about ON from the early stages, and obsessive-compulsive symptoms should be sought and treated in students with ON. Future studies should compare different groups of students.

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THE ROLE OF Tc-99m MIBI SPECT IN THE EVALUATION OF NON-SMALL CELL LUNG TUMORS

KÜÇÜK HÜCRELİ DIŞI AKCİĞER TÜMÖRLERİNİN DEĞERLENDİRİLMESİNDE Tc-99m MIBI SPECT'İN YERİ

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Abstract / Özet

Objective: In this study, it was aimed to investigate the role of Tc-99m MIBI scintigraphy in the diagnosis and evaluation of non-small cell lung cancers and also to evaluate the use of MIBI scintigraphy and MDP bone scintigraphy together in the detection of metastases. **Methods:** For this purpose, 30 patients with non-small cell lung cancer and 15 patients with benign lesions other than lung cancer (as a control group) were included in the study. By applying Tc-99m MIBI and Tc-99m MDP scintigraphy to whole patients with benign and malign lung lesions, anterior-posterior planar and SPECT MIBI images were obtained. Bone scintigraphy was performed as whole-body images. Scintigraphic findings were compared with the histopathological diagnosis of patients. Data were analyzed statistically. **Results:** According to the result of the findings, the sensitivity, specificity, positive, predictive value, negative predictive value, and accuracy rate of Tc-99m MIBI scintigraphy in the detection of non-small cell lung tumors were determined as 87%, 93.5%, 96%, 77.7%, and 88.8%, respectively. Scintigraphic findings were evaluated quantitatively and visually. While there was no statistically significant difference between the early uptake rates of non-small cell lung tumors and benign lesions in the quantitative evaluation using planar MIBI images, late Tc-99m MIBI uptake rates were significantly higher in lesions with non-small cell lung tumors than that of benign lesions. However, it was detected that both the early and late uptake ratios were significantly higher in malign lesions than in benign lesions in the quantitative evaluation of SPECT images. It was observed that MIBI washout in benign lesions was higher than in malignant lesions in visual washout analysis. Additionally, multiple bone metastases were observed in 14 patients on the visual evaluation of bone scan of the patients with non-small cell lung cancer. Tc-99m MDP uptake was not observed in the malignant lung lesion region or in the soft tissue except the lesion. **Conclusion:** In light of the findings, it was concluded that Tc-99m MIBI scintigraphy is a non-invasive method with high sensitivity and specificity that can be used to differentiate non-small cell lung tumors from benign lesions.

Key words: Non-small cell lung cancer, planar, SPECT, Tc-99m MIBI, Tc-99m MDP bone scintigraphy.

Amaç: Bu çalışmada, Tc-99m MIBI sintigrafisinin küçük hücreli dışı akciğer kanserlerinin tanısında ve değerlendirilmesindeki yerini araştırmak ve ayrıca metastazlarının tespitinde MIBI sintigrafisi ve MDP kemik sintigrafisinin birlikte kullanılabilirliğini değerlendirmek amaçlandı. **Materyal ve Metot:** Bu amaçla, 30 küçük hücreli dışı akciğer kanseri hastası ve 15 akciğer kanseri dışında benign lezyonu olan (kontrol grubu olarak) hasta çalışmaya dahil edildi. Benign ve malign akciğer lezyonu olan tüm hastalara Tc-99m MIBI ve Tc-99m MDP sintigrafisi uygulanarak ön-arka planar ve SPECT MIBI görüntüleri elde edildi. Kemik sintigrafisi tüm vücut görüntüleme şeklinde yapıldı. Sintigrafik bulgular hastaların histopatolojik tanıları ile karşılaştırıldı. Veriler istatistiksel olarak analiz edildi. **Bulgular:** Elde edilen bulgulara göre, Tc-99m MIBI sintigrafisinin küçük hücreli dışı akciğer tümörlerinin tespitindeki sensitivitesi %87, spesifisitesi %93,5, pozitif prediktif değeri %96, negatif prediktif değeri %77,7 ve doğruluk oranı %88,8 olarak belirlendi. Sintigrafik bulgular sayısal ve görsel olarak değerlendirildi. Planar MIBI görüntüleri kullanılarak yapılan sayısal değerlendirmede, küçük hücreli dışı akciğer tümörleri ile benign lezyonların erken tutulum oranları arasında istatistiksel olarak anlamlı bir fark bulunmazken, küçük hücreli dışı akciğer tümörlü lezyonlarda geç dönemdeTc-99m MIBI tutulum oranları iyi huylu lezyonlardan anlamlı derecede yüksekti. Bununla birlikte, SPECT görüntülerinin sayısal değerlendirmesinde hem erken hem de geç tutulum oranlarının malign lezyonlarda benign lezyonlara göre anlamlı derecede yüksek olduğu tespit edildi. Görsel washout analizlerinde ise, benign lezyonlardaki MIBI washoutunun malign lezyonlara göre yüksek düzeyde olduğu izlendi. Ayrıca, küçük hücreli dışı akciğer kanserli olan hastalarda kemik sintigrafileri görsel olarak değerlendirildiğinde; 14 hastada multipl kemik metastazı izlendi. Lezyon bölgesinde veya lezyon dışındaki yumuşak dokuda Tc-99m MDP tutulumu izlenmedi. **Sonuç:** Elde edilen bulguların ışığında, Tc-99m MIBI sintigrafisinin küçük hücreli dışı akciğer tümörlerinin benign lezyonlardan ayırımında kullanılabilecek, yüksek sensitivite ve spesifisiteye sahip non-invazif yöntem olduğu sonucuna varıldı. **Anahtar kelimeler:** Küçük hücreli dışı akciğer kanseri, planar, SPECT, Tc-99m MIBI, Tc-99m MDP kemik sintigrafisi.

1. INTRODUCTION

Lung cancer is the most common type of cancer globally; its incidence is increasing every year. Although environmental pollution and occupational conditions also play a certain role in the etiology, the main factor of the disease is smoking. Therefore, lung cancer is a largely preventable disease (Arseven, 2019, s. 156). Lung cancers are the most common type of cancer in men and women. However, it is 4-8 times more common in men than in women. This is due to the difference in smoking rates. Lung cancers have been seen more than prostate cancer in men, and breast cancer in women. Due to the increase in the smoking rate in women, lung cancer has surpassed breast cancer in some countries and has become the leading cause of death from cancer in women. It has most commonly seen between the ages of 50-70 (1,2).

Epidermoid cancer, adenocarcinoma, large cell cancer, and adenosquamous cancers except for small cell cancers, are called "non-small cell lung cancers" (1) and constitute approximately 75% of all lung cancers (3–5). Generally, resistant metastases have developed when the diagnosis was made, and the 5-year survey rate after surgical resection is less than 1%. They can be treated surgically highly if detected before metastasis (6,7). In this group of lung cancers, while the 5-year survey rate in the absence of nodal metastasis (Stage N0) is 46%, it is 33% in the presence of only hilar nodal metastasis (Stage Nl) and it is 8% in the presence of mediastinal nodal metastasis. The strongest prognostic factor in terms of the survey is whether there is a possibility of complete resection. If cancer can be detected before metastasis, there is potential for surgical treatment (8,9). Chest CT in patients with lung cancer is a standard examination in preoperative staging and diagnosis. In the detection of mediastinal lymph nodes, its sensitivity is reported as 46-91% and its specificity as 69-89% (5). It has been shown that scintigraphic imaging help to detect cancer in the early stage, to help in the differential diagnosis of active residual tumor or recurrent tumor after treatment in lung cancers (10). It has been found that 91% of patients with untreated non-small cell lung cancer have Tc-99m MIBI retention (high sensitivity) in recent studies (5,11,12).

1.1. Tc-99m MIBI scintigraphy

Technetium-99m 2-hexakis-methoxy-butyl-isonitrile (Tc-99m MIBI, MIBI, Tc-99m sestamibi) is a lipophilic monovalent cation primarily used in myocardial perfusion studies. The Tc-99m MIBI is preferred in all types of studies due to its superior physical properties (half-life of 6 hours, single gamma ray 140keV), easy, continuous, and cheap availability for use in imaging. But it is difficult to find pharmaceuticals that can be marked with Tc-99m for all types of applications. As a result of research, agents have been developed that can replace Tl-201, which is used to show myocardial perfusion. MIBI is one of them and is used as a myocardial perfusion agent in the basic sense. However, during clinical practice, it has been observed that Tc-99m MIBI is involved in some tumors and research has focused in this direction. Very precise information regarding the uptake mechanism of MIBI is not yet available. However, it was detected that it is perfusion-dependent and settled in mitochondria. Due to the negative and lipid structure of membrane potentials, it passes through the plasma membrane and mitochondrial membrane by passive diffusion and has a significant amount in the mitochondria in the cell. Therefore, it is more involved in tissues with good perfusion and a high number and activity of mitochondria in their cells. For this reason, it has been observed that many cancer tissues accumulate MIBI. Glioblastomas, head and neck tumors, lung cancers, breast cancers, and sarcomas are found among them (13–15).

The clinical contributions of MIBI imaging in this type of cancer are localization, metastasis, and post-treatment evaluation, however some studies in recent years have changed the way the work is done. For example, in the study conducted on breast cancers, it has been reported that the masses detected in the breast hold MIBI if they are malignant and not if they are benign and the sensitivity is over 90% (16). It has been also understood that uptake was altered according to the grade of the tumor tissue, with more MIBI uptake in more aggressive tumors (17). Another important improvement in MIBI studies is its association with MDR (Multiple Drug Resistancy). Another factor affecting the retention of MIBI in tumor cells is the multidrug resistance P glycoprotein (MDR l Pgp). According to some data, MDR receptors on the cancer cell surface are included in the localization mechanisms of MIBI. Thus, it is possible to determine whether there is MDR in cancer cases in vivo. This is undoubtedly an important development for oncology. In lesions with adequate perfusion and positive MDR1 Pgp function, as a result of active transport of Tc-99m-MIBI out of the cell by MDR1 Pgp, MIBI uptake may be undetectable or low or has a rapid washout. Similarly, in MDR l Pgp positive lesions, a decrease in retention in lipophilic and cationic cytotoxic drugs that have no chemical or functional similarity has been observed. However, with the administration of MDR inhibitors, washout of the agents in tumor cells is reduced and accumulation is observed. Thus, Tc-99mMIBI is one of the Tc-99m agents used in the in-vivo detection of MDR l Pgp function and inhibition. Tc-99m MIBI cannot be metabolized in-vivo and is excreted 27% urinary in 24 hours and 37% fecally excreted in 48 hours (18–20).

1.2. Tc-99m MIBI tumor scintigraphy indications

In nuclear oncology, Tc-99m MIBI is generally used for imaging primary and secondary tumors of the lungs, breasts, thyroids, parathyroids, brains, melanoma, lymphoma, bone, and soft tissues. In

tumors of the gastrointestinal tract and urogenital tract, radiopharmaceuticals are not widely used due to physiological involvement in the liver, biliary system, and splanchnic region (12,21,22).

Indications for Tc-99m MIBI tumor scintigraphy:

1. Differentiation of benign-malignant lesions
2. Staging of the disease
3. Distinguishing the necrotic and fibrotic tissue changes that occurred after treatment from recurrent or residual tumor tissue
4. Detection of early local recurrence or distant metastases
5. Evaluation of disease progression and lesions' response to chemotherapy, radiotherapy, or surgical treatment.
6. Determination of the presence, localization and viability of the tumor mass before biopsy or operation
7. Investigation of the primary tumor focus in cases with suspected tumors that cannot be detected despite being investigated by other examinations
8. Investigation of thyroid cancer metastases in patients with elevated serum thyroglobulin levels but having normal I-131 or I-123 whole-body scanning.
9. In the follow-up of cytologically high-risk thyroid nodules such as Hurtle Cell adenoma and follicular adenoma and hyperproliferative (fibrocystic) breast lesions
10. In functional thyroid cancer metastases, in the detection of suppressed thyroid tissue
11. It is used to evaluate the response of tumor tissue to chemotherapy.

As a result, MIBI applications have taken their clinical place, especially in breast and lung cancers. Even the name "sintimammography" for breast cancers has gained its terminological character. These tests can make significant contributions through whole-body scanning even in cancer cases where no primary is found, and it is of great importance for patients and physicians to include these tests, which can be easily performed in every nuclear medicine center (22–24).
In this study, we aimed to investigate the role of Tc-99mMIBI scintigraphy in the diagnosis of non-small cell lung tumors and the joint use of MIBI scintigraphy and MDP Bone scintigraphy in the detection of non-small cell lung cancers and their metastases.

2 MATERIALS AND METHODS

After receiving approval from the Clinical Research Ethics Committee of Atatürk University Faculty of Medicine, 30 patients with non-small cell lung cancer who applied to the Department of Radiation Oncology, Department of Chest Diseases, and Department of Internal Medicine-Oncology and 15 patients with lung disease other than lung cancer were included in our study. Informed consent was obtained from all patients included in the study.

2.1. Patient group

In the study, a total of 30 patients (mean: 60.9±10.88) with non-small cell lung cancer (27 men and 3 women aged between 42-83 years) and 15 patients (mean: 43.9±15.18) whit lung disease except lung cancer (11 men and 4 women aged between 25-72 years) were included (Table 1).

The patients included in the study were those diagnosed with non-small cell lung cancer by biopsies and/or sputum cytology. Control group patients who are shown to have lung disease other than lung cancer are; 6 were tuberculosis and 9 were pneumonia (Table 1).

2.2. Imaging method

Scintigraphic examinations of the patients were performed approximately 3-7 days before the start of chemotherapy and radiotherapy. 600 MBq (18 mCi) Tc 99m-MIBI was used for whole-body imaging and thorax-SPECT study. Fifteen control patients with lung disease except for lung cancer underwent whole-body imaging and thorax-SPECT studies with 600 MBq Tc 99m-MIBI.

MIBI whole body and SPECT images were taken 15 minutes after Tc 99m-MIBI injection (early) and 180 minutes later (late). In patients, anterior and posterior whole-body images, SPECT images of the thoracic region, as well as anterior and posterior planar thoracic images were taken. Tc 99m-MDP whole body bone scintigraphy images and thorax-SPECT images were obtained in the same patient group.

2.3. Evaluation of scintigraphic findings

Tc 99m-MIBI tumor screening and Tc 99m-MDP bone scintigraphy were evaluated visually and numerically.

2.3.1. Visual evaluation

The visual evaluation was performed by two different physicians. The degree of Tc 99m-MIBI retention of the lesions was evaluated in planar-anterior and posterior thorax images and thorax-SPECT images taken in early (15th min.) and late (180th min.) periods. The evaluation was made according to the degree of heart and ground retention of activity by comparing the images. The degree of retention was scored as follows:

0: Less than ground activity

1: At the ground activity level

2: More than ground activity, less than heart activity

3: Retention of activity at the heart level

4: Retention of activity in excess of the activity of the heart

In addition, the images of both isotopes taken at the 15th and 180th minutes were compared by viewing them on the same screen. The assessment was carried out by re-evaluating the degree of isotope involvement of the lesions without knowing whether they were early or late-period images.

Early and late images were compared with each other to examine whether there was a change in the retention of radiopharmaceuticals in tumor tissue or non-tumor pathologies over time. Changes in the form of increase or decrease in early and late images over time were examined in terms of malignant or benign pathologies.

The retention of Tc-99m-MIBI outside the primary lung tumor was investigated and the efficacy of MIBI in showing metastatic retention outside the primary focus was visually evaluated. Bone scintigraphy performed in patients with non-small cell lung cancer was visually evaluated and bone metastases in patients were investigated.

2.3.2. Numerical evaluation

When performing numerical evaluation; in each case, anterior, posterior planar thoracic images (static) and coronal sections obtained from thorax-SPECT images taken in early (15th min.) and late (180th min.) periods were used.

The numerical evaluation was performed in the lesions where radioactive material retention could be visualized most clearly in the early and late periods. Lesions in which substance retention was not seen in early images were evaluated together considering that they could be detected by decreasing ground activity in late-period images. In some lesions, the lesion that was observed in the early period could not be observed in the late period. While numerical evaluation was performed in the images where lesion involvement could not be detected in one of the early or late images, the localization compatible with the detected lesion in one of the images was selected. In lesions where substance retention was not observed in early or late images, numerical evaluation was not performed.

In the anterior, posterior planar thorax, and thorax SPECT images taken in the early and late period, mean counts per pixel were obtained by taking irregular areas of interest bordering the lesion site showing Tc 99m-MIBI at the pathological level. In the contralateral normal lung tissue, the dimensions of the irregular area of interest corresponding to the lesion site were arranged according to the normal lung tissue by means of a computer, without changing the number of pixels, and average counts per pixel were obtained. In one of the early or late periods, lesion involvement was observed and in the other, if the retention was at the ground activity level, the irregular interest area was drawn on normal ground activity. Average counts of the related areas that were drawn to the lesion site and normal lung tissue, were calculated.

2.3.3. Retention rates

In the differentiation of benign and malignant lesions, it is proposed to compare the ratio of lesions to normal tissues. In line with the times, the decrease in activity involvement in the normal lung tissue that constitutes the ground activity in the late-period images makes the difference in the lesion/ground activity rate evident. In the studies conducted, it has been observed that high rates were compatible with malignant and low rates were compatible with benign lesions. However, these ratios give an idea about the type of lesion but cannot lead to a definitive diagnosis.

In the anterior and posterior images taken in the early and late periods, the average counts obtained from the lesion site that fit the area of interest of each case were compared to the average counts in the area of normal lung tissue interest. Thus, lesion/normal lung tissue involvement rates were obtained. The lesion/normal lung tissue involvement rates of anterior and posterior images were averaged and thus the mean retention rate was calculated.

In addition, lesion/normal lung involvement rates obtained from SPECT images were calculated separately for early and late periods images.

The retention index, which is calculated by the early and late retention rates of the lesions, reflects the isotope retention in the lesions. In our study, the retention of Tc-99m sestamibi in tumor tissue and non-tumor lung lesions was calculated using the following formula:

RI = 100 x (Late rate - Early rate)/ Male Ratio

2.3.4. Statistical evaluation

The sensitivity and specificities of Tc-99mMIBI scintigraphy were calculated by comparing lung lesions evaluated as benign or malignant in scintigraphy with their histopathological results. Early and late involvement rates calculated for malignant and benign lung lesions on Tc-99m MIBI scintigraphy were compared using "The Mann-Whitney U test". The change between early and late involvement rates calculated at the 15th and 180th minutes in malignant and benign lesions was evaluated by the "Wilcoxon paired two sample test" method. The retention index values of the malignant and benign groups were compared by using the "Mann-Whitney U test". $p<0.05$ value was accepted as significant.

3. RESULTS

3.1. Findings of visual evaluation

In our study, by taking images at two different times (15th and 180th min), it was investigated whether early and late imaging contributed to the diagnosis in

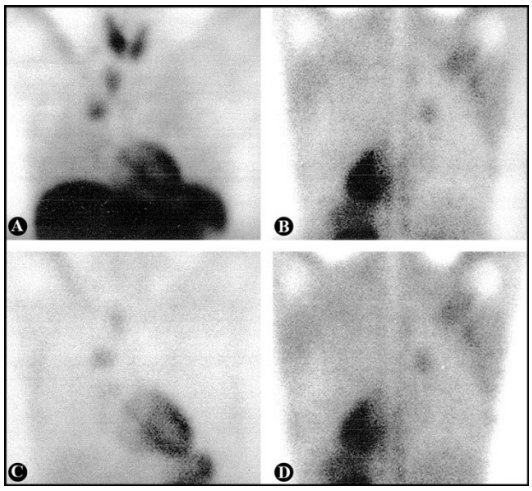
Table 1: .Demographic data and histopathological diagnosis of control group and non-small cell lung cancer cases

	Control	Non-Small Cell Lung Cancer
Number of patients	n=15	n=30
Age	43.9 ± 15.18	60.9 ± 10.88
Gender	Male=11 Female=4	Male=27 Female=3
Histopathological Diagnosis	Tuberculosis (n=6) Pneumonia (n=9)	Squamous cell (n=26) Bronchoalveolar (n=1) Adenocancer (n=1) Adenosquamous (n=2)

Table 2: Visual evaluation of Tc-99m MIBI involvement in malignant and benign lung lesions

	Tc-99m MIBI Retention			
	Malignant		Benign	
Patient No	15th Min.	180th min	15th Min.	180th min.
1.	2	2	1	1
2.	2	2	1	1
3.	2	2	1	1
4.	2	2	2	1
5.	1	2	1	1
6.	2	2	1	1
7.	1	1	2	1
8.	2	2	2	1
9.	2	2	2	1
10.	1	1	2	1
11.	2	2	1	1
12.	1	2	2	1
13.	2	2	2	2
14.	2	2	1	1
15.	2	2	2	1
16.	1	2		
17.	2	2		
18.	1	1		
19.	2	2		
20.	2	2		
21.	2	2		
22.	2	2		
23.	2	2		
24.	3	3		
25.	2	2		
26.	1	1		
27.	2	2		
28.	1	2		
29.	2	2		
30.	2	2		
Ort.±s.d	1.76±0.50	1.90±0.40	1.53±0.51	1.06±0.25

Figure 1: A. 15th minute anterior thoracic planar, B. 15th minute posterior thoracic planar, C. 180th minute anterior thoracic planar, and D. 180th minute posterior thoracic planar images of a patient with non-small cell lung cancer.



the differentiation of benign and malignant lung lesions (Figure 1).

Although there was no statistically significant difference between visually malignant and benign lung lesions (l.76±0.50, 1.53±0.516; >p.0.01) in early images of Tc-99m MIBI scintigraphy, there was a statistically significant difference in late images (l.90±0.40, 1.06±0.25; p<0.01) (Table 2). In our group of thirty patients with non-small cell lung cancer, early images showed 22 (73.5%) cases with pathological activity involvement and 8 (26.5%) cases that did not. Late imaging showed that 26 (87.5%) patients had pathological activity involvement and 4 (12.5%) patients did not. In the benign patient (control) group consisting of fifteen cases, it was observed that 7 (46.5%) cases did not show pathological activity involvement in early images, while 8 (53.5%) cases showed activity involvement. In the late images, it was seen that no involvement of pathological activity in 14 (93.5%) cases, and there was in 1 (6.5%) case.

When visual evaluations of the images of lung lesions taken in early and late periods are made, it is correct positive that a malignant lesion has scintigraphically malignancy criteria, and false negative if it is not; the presence of these criteria in a benign lesion as false positive and the absence as true negative with was evaluated.

When the visual evaluation results of the lesions are interpreted according to their histopathological diagnosis (Table 3); Tc-99m MIBI scintigraphy revealed that visual evaluations of early and late images were evaluated as true positive in 26 cases, true negative in 14 cases, false positive in 1 case and false negative in 4 cases.

The visual evaluation was performed using the diagnostic test criterion formulas given below:

Sensitivity	:	DP/(DP+YN)
Specificity	:	DN/(DN+YP)
Positive Predictive Value	:	DP/(DP+YP)
Negative Predictive Value	:	DN/(DN+YN)
Accuracy Rate	:	(DP+DN)/tüm olgular

As a result of these evaluations, the sensitivity of Tc-99m MIBI scintigraphy in the differentiation of benign-malignant lung lesions was determined as 87%, its specificity was 93.5%, its positive predictive value was 96%, its negative predictive value was 77.7%, and its accuracy rate was 88.8%.

When bone scintigraphy is visually evaluated in patients with non-small cell lung cancer; multiple bone metastases were observed in 14 patients. Tc-99m MDP involvement was not observed at the site of the lesion or in soft tissue outside the lesion (Figure 2).

Table 3: Interpretation of scintigraphic results according to histopathological diagnosis

Lesion	Malignancy criteria (Tc-99m MIBI retention)	Assessment
Malignant	+	True Positive (TP)
Malignant	-	False Negative (FN)
Benign	+	False Positive (FP)
Benign	-	True Negative (TN)

3.2. Numerical evaluation (retention rates) Findings

While there was no statistically significant difference between Tc-99m MIBI uptake rates for early images of malignant and benign lesions ($p>0.05$), late images showed that Tc-99m MIBI uptake rates were significantly higher in malignant lesions than in benign lesions ($p<0.05$) (Table 4).

In addition, when the change in the retention rates of malignant and benign lung lesions in early and late images over time was examined, it was found that the retention rates in both malignant lesions and benign lesions decreased in late images compared to early images. This decrease in the retention rates in malignant and benign lesions over time was statistically significant ($p<0.05$) (Table 5).

Table 4: Lesion/normal lung involvement rates in anterior and posterior planar images of Tc-99m MIBI scintigraphy in malignant and benign lung lesions.

	Lesion/normal lung Tc-99m MIBI involvement	
	15th Min.	180th min.
Malignant	1.569 ± 0.619	1.313 ± 0.155*
Benign	1.332 ± 0.242	1.167 ± 0.134*

*: $p<0.05$

Table 5: Lesion/normal lung involvement rates obtained from Tc-99m MIBI SPECT images taken in early and late periods in malignant and benign lung lesions

	Tc-99m MIBI SPECT lesion/normal lung involvement	
	15th Min.	180th min.
Malignant	1.639 ± 0.439*	1.823 ± 0.484*
Benign	1.388 ± 0.377*	1.424 ± 0.436*

*: $p<0.05$

Table 6: Retention index values of malignant and benign lesions

	Tc-99m MIBI retention	
	Malignant	Benign
Planar	-9.67 ± 20,58	-10.9 ± 12.3
SPECT	15.6 ± 30.8	3.8 ± 22.6

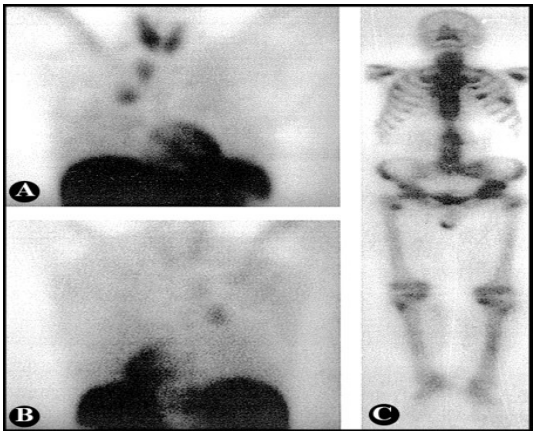
*: $p<0.05$

Early and late Tc-99m MIBI SPECT images of malignant lesions had significantly increased retention rates compared to benign lesions ($p<0.05$).

In addition, when the change in the involvement rates of benign and malignant lung lesions in early and late images over time was examined, it was observed that the involvement rates increased in both malignant lesions ($p<0.05$) and benign lesions ($p>0.05$) compared to early images in late images.

The retention index, which is calculated by the early and late retention rates of the lesions, reflects the isotope retention in the lesions. When the retention indices obtained from planar and SPECT images were compared in terms of malignant and benign lesions, there was no statistically significant difference ($p>0.05$) (Table 6)

Figure 2. A case with non-small cell lung cancer. 15 minSPECT, B. 180 min. SPECT, C. anterior whole body bone scan images (multiple metastatic foci are seen).



4. DISCUSSION

Although the diagnosis of malignant lung lesions is important, the diagnostic methods applied in the clinic are based on the principle that benign lesions can be diagnosed correctly and benign lesions are not considered malignant. The main purpose here is to reduce the number of thoracotomies performed in suspicious benign lesions or malignant lesions that do not require surgical treatment. In clinical trials, in the accumulation of knowledge formed by the use of two or more imaging methods; nuclear medicine methods allow us to visually and numerically evaluate the anatomical localization of the lesions and the functional activities of the tissues within these determined anatomical localization limits.

With the introduction of Thallium-201, which is used as a myocardial perfusion agent in Nuclear Medicine, to imaging benign or malignant lung lesions, much research has been carried out on the imaging of benign or malignant lung lesions (11). Thallium, a monovalence cationic radioisotope, is similar to potassium in terms of its biological properties. The involvement of thallium-201 in tumor tissue is mainly related to blood flow. Mechanism of intracellular involvement; is the exit of the sodium ion out of the cell and the potassium ion enters into the cell with the effect of the ATPase enzyme in the cell membrane. However, the intracellular involvement of potassium and thallium is not the same. Thallium binds to two places in the enzyme system, while potassium binds to one place. This may explain the clearance of thallium that lasts longer than the myocardium relative to potassium (25).

In the studies conducted to investigate the biological distribution of Thallium-201 in tumoral and inflammatory lesions by Müller et al. (26); it has been reported that activity decreased over time in inflammatory lesions with Tl-201 involvement, but following the delay of Tl-201 washout Tl-201 was mainly retained by living tumor tissue in malignant lesions. it has been reported that activity decreased over time in inflammatory lesions with Tl-201 involvement, but following the delay of Tl-201 washout Tl-201 was mainly retained by living tumor tissue in malignant lesions. In addition, it has been found that Tl-201 was kept to a lesser extent in connective tissue containing inflammatory cells and not in necrosis tissue. The absence of Tl-201 involvement in necrosis tissue is due to the nonfunctional ATPase activity in the cell membrane, hence the lack of active transport of Tl-201 to necrotic tumor cells.

In a study of 30 patients with suspected lung cancer, Tonami et al. (27), have reported that late tumor/ground activity rate and retention index may be parameters that can be used in the benign-malignant differentiation of tumors and in the evaluation of histological types. However, the same group later studied a group of 170 patients (147 malignant, 23 benign patients) to evaluate pulmonary nodules larger than 20 mm in diameter. And they found that the late tumor/ground activity ratio on Tl-201 SPECT images at the 15th to 180th minute did not differ in the differentiation of malignant histological groups and benign-malignant lesions except for adenocarcinoma and large cell lung cancer. These researchers found that the retention index of benign lesions was 6%±24% and that malignant lesions were 25%±24%, and suggested that this index could be used to distinguish between benign and malignant lung lesions, but was not useful in the histological typing of lung cancers (28).

Suga et al. (29), in the study conducted by taking images at early (15.dk.) and late (180th min.) periods in a group of patients with thoracic lesions larger than 20 mm in size (58 benign and 48 malignant), reported that tumor/ground activity rates could not help distinguish benign-malignant lesions, but retention index values were important. In the study of this group, retention index values have been found -4.3% ± 13.6% for benign lesions, and 23.3% ± 18.9% for malignant lesions. They have determined that benign lesions were not detected in late images or that their retention index was negative as benign criteria and reported the accuracy rate in identifying benign lesions as 81.1% and positive predictive value as 95.2%.

Sehweil et al. (30), in the study they conducted for diagnosing and staging lung cancer, breast cancer,

and malignant lymphomas in a group of 188 patients, visually evaluated the static images obtained 20 min later from the iv-injection of Tl-201. In addition, 10 patients with benign lung lesions were included in the study group. They reported that Tl-201 had a high sensitivity in detecting primary tumors (87.5% in lung cancer, 100% in breast cancer, 85% in lymphomas), but low sensitivity in the detection of mediastinal lymph nodes, and Tl-201 involvement in two cases of tuberculosis and one sarcoidosis from the benign lesion group. In conclusion, they reported that the specificity of Tl-201 was low (70%) in the differentiation of benign-malignant lung lesions. However, the fact that they did not take late period images of Tl-201 stands out as a deficiency of the study.

Duman et al. (31), in their SPECT study for benign-malignant differentiation of solitary lung lesions using Tl-201 and post-radiotherapy follow-up of primary lung cancer, in semiquantitative evaluation, have found that the sensitivity of Tl-201 in the differentiation of benign-malignant lesions was 56%, its specificity was 71%, and its accuracy value was 58%. Also, according to the results of quantitative analysis, they have detected the sensitivity as 88.8%, the specificity as 100%, and the accuracy value as 92%. They also reported a retention index of 2.9±1.3 for primary lung cancers, 2.78 ± 0.9 for benign lesions, and -2.3±1.5% for metastatic pulmonary lesions. However, they concluded that Tl-201 scintigraphy is a sensitive method for the differentiation of benign-malignant lung lesions, but has limited value in the differentiation of metastatic lesions and benign lesions and in the histological classification of primary lung cancers. They also observed compatibility between clinical follow-up of patients after radiotherapy and lesion involvement on Tl-201 scintigraphy.

In lung lesions, benign lesions (tuberculosis, silicosis, radiation pneumonia, atypical mycobacterial pneumonia, pneumonia, inflammatory pseudotumor, aspergilloma, granulomas, breast adenomas, sarcoidosis, abscess, sternotomy, atelectasis, cardioversion) with Tl-201 involvement have been reported without using late images or retention indices (32). However, there are few studies in which numerical evaluations are applied for these lesions.

As mentioned above, Tl-201, which is frequently used in tumor imaging, has a number of disadvantages such as its resolution not being good enough due to its low gamma energy (69-83 keV) and limiting the amount of activity applied due to its long half-life (73 h.). These disadvantages led researchers to investigate tumor imaging methods with radiopharmaceuticals with properties more suitable for Nuclear Medicine examinations.

The characteristics of an ideal radiopharmaceutical used in nuclear medicine methods should be as below (33):

It should be easily obtained in a hospital setting.

Its preparation should be simple and inexpensive.

Its effective half-life (the amount of radiation absorbed by the tissue) should not be longer than the time required to complete the study.

It should not emit gamma rays, should not form particle scatters (alpha or beta). The interest/ground activity ratio should not be high.

In in-vivo conditions, it should not be metabolized before its accumulation in the target organ.

Radiopharmaceuticals labeled with technetium-99m have almost all of the properties listed above. Therefore, approximately 80% of the radiopharmaceuticals used in nuclear medicine are radiopharmaceuticals labeled with Tc-99m. The superiority of Tc-99m in clinical use is due to its physical and radiation-related properties. Although the amount of activity applied to the patient is greater than Tl-201, the physical half-life is shorter (6.02 hours) and the fact that it emits fewer electrons causes the patient to receive fewer doses of radiation and the image quality to improve due to the increase in the number of counts obtained from the patient. In addition, gamma cameras have photon (140 keV) energy that is best suited for imaging, which doubles the image resolution. Tc-99m-labeled radiopharmaceuticals can be prepared by labeling commercially available kits with Tc-99m pertechnetate obtained from sterile, pyrogen-free, and carrier-free Mo-99-Tc-99m generators in radiopharmaceutical laboratories.

Because of these superior properties, Tc-99m-labeled radiopharmaceuticals are widely used today in the imaging of many soft tissue and bone tumors.

Lung malignancies are one of the most common uses of Tc-99m MIBI, and researchers have worked to develop many qualitative and quantitative methods for the differentiation of malignant and benign lung tumors (34).

Physiological changes such as plasma and mitochondrial membrane potentials, mitochondrion quantity, perfusion, and cell metabolism are reported to promote the involvement of Tc-99m MIBI by tumor tissue (5). Caner et al. (35) have reported in their studies with Tc-99m MIBI in benign-malignant bone lesions that isotope involvement of the lesions was related to blood flow, necrotic changes, metabolic function, and mitochondrial activity rather than the benign or malignant lesion. Furthermore, it has recently been reported that the involvement of Tc-99m MIBI in tumor tissue is related to the P-gp (P glycoprotein) levels of the tissues and that the

involvement of Tc-99m MIBI in tumor tissues with high P-gp levels is low.

Hassan et al. (36), in their study investigating the involvement and kinetics of Tc-99m MIBI in benign and malignant lung lesions, detected localized increased Tc-99m MIBI involvement in 10 patients with untreated malignant lung lesions; however, they were unable to detect Tc-99m MIBI involvement in an untreated undifferentiated epidermoid cancer, two lung cancers responding to radiation therapy, and four benign lung lesions. They have also observed a diffuse increase in lung involvement in two patients diagnosed with fibrosing alveolitis. In this first study for the imaging of lung lesions with Tc-99m MIBI, it has been reported that malignant lesions showed increased levels of Tc-99m MIBI involvement, unlike benign lesions.

In another study to evaluate the clinical significance of Tc-99m MIBI in the differential diagnosis of solitary-solid lung lesions; In a group of 54 patients, SPECT images have been taken 10 minutes after intravenous injection of Tc-99m MIBI. 75% (6/8) of benign lesions and 65% (30/46) of malignant lesions have been visualized and it has been detected that the sensitivity of Tc-99m MIBI in the differential diagnosis of solitary-solid lung lesions was 65%, specificity was 57%, and accuracy rate was70%. In this study, it has been reported that the use of Tc-99m MIBI scintigraphy in the differential diagnosis of lung lesions was limited.

Mueller et al. (23), comparing the SPECT study in bronchial cancers with Tc-99m MIBI and Tl-201 involvement, reported that both isotopes gave similar scintigraphic results and that the SPECT method was more sensitive in detecting lesions than static images.

In a study conducted by Aktolun et al. (37), they have compared Tc-99m MIBI and Tl-201 scintigraphy in various malignant tumors including lung cancers and reported the sensitivity of Tc-99m MIBI as 82.5% and the sensitivity of Tl-201 as 76.4%. They have also evaluated chest X-rays and computed tomography images of patients they included in their tumor imaging research programs with Tc-99m MIBI. And they have detected increased levels of Tc-99m MIBI involvement in pulmonary actinomycosis, which appeared to be a mass resembling a mediastinal tumor, and giant lymph node hyperplasia of the mediastinum (Castleman's disease), and also in seven cases of pulmonary sarcoidosis (38,39).

Lebouthillier et al. (40) have emphasized that Tc-99m MIBI is a sensitive agent in the evaluation of hilar and mediastinal lymph node involvement in the detection of primary lung cancer, and that SPECT or static scintigraphy with Tc-99m MIBI are noninvasive methods that can be applied before the operation.

In our study, we visually and numerically evaluated the Tc-99m MIBI images taken for the differentiation of malignant and benign lung lesions.

In the visual evaluation method, we apply to distinguish malignant pathologies (non-small cell lung cancers) from benign pathologies (control group patients); we interpreted the criteria such as no activity involvement of the lesion or decreasing of the activity of the lesion over time which initially showed activity involvement, in the direction of "benignity". We interpreted the increase or unchanged or slight decrease of the initial activity over time in favor of "malignancy".

In our study, scintigraphic findings were carrying malignant lesions in 26 out of 30 patients diagnosed with non-small cell lung cancer in their biopsies and/or sputum cytology. The lesion activity involvements of these lesions thought to be malignant were above-the-ground activity both in early images (score: 2, 3) and in late images. However, on scintigraphy with Tc-99m MIBI, we not observed monitor activity involvement in early and late images in 4 patients with non-small cell lung cancer. Histopathological diagnosis of these cases was: squamous cancer (7th, 10th, 18th, and 26th cases). These cases were evaluated as false negative results. In addition, Tc-99m MIBI scintigraphy revealed late involvement in 4 non-small cell lung cancer cases (score: 2), although no activity involvement was detected in the early period (score: 1). The histopathological diagnoses of these cases are; squamous cancer (cases 5, 16 and 28) and adenosquamous cancers (case 12).

We also obtained retention index values in our study. We calculated the retention index value in malignant lesions as -9.6 ±20.58 and the value in benign lesions as -10.9 ± 12.3 in anterior and posterior planar images. In SPECT images, we measured the retention index value in malignant lesions as 15.6 ±30.8 and the value in benign lesions as 3.8 ± 22.6.

While there was no statistically significant difference between the Tc-99m MIBI uptake rates of early planar images of benign and malignant lesions, we found that the late Tc-99m MIBI uptake rates of malignant lesions were significantly higher than benign lesions. In addition, on Tc-99m MIBI scintigraphy, we found that the retention rates in late images of malignant lung lesions remained the same or decreased slightly compared to early images, while in benign lesions they decreased significantly or the involvement disappeared completely. This situation has shown us that in order to make the correct distinction between malignant and benign lesions, it is absolutely necessary to take images in the late period.

In early and late Tc-99m MIBI SPECT images of malignant lesions, the retention rates significantly increased compared to benign lesions. In addition, when the change in the retention rates of benign and

malignant lung lesions in early and late images over time was examined, it was observed that the retention rates increased in both malignant lesions and late images in benign lesions compared to early images.

When we compared the retention indices obtained from planar and SPECT images in terms of malignant and benign lesions, we did not find a statistically significant difference.

Tc-99m MDP scintigraphy was also applied to all patients with non-small cell lung cancer. Tc-99m MDP scintigraphy revealed no involvement in lung tissue or soft tissues other than lung tissue in any case with non-small cell lung cancer. In addition, in the Tc-99m MDP whole-body scan scintigraphy from all patients, it was revealed metastatic bone pathologies in the thoracic, lumbar, and cervical vertebrae, ribs, pelvis, femoral head-acetabular regions in 14 cases.

5. CONCLUSION

In conclusion, we have shown that Tc-99m MIBI scintigraphy is an easy-to-apply, successfully used, reliable, noninvasive method with high sensitivity and specificity in the differentiation of non-small cell lung tumors from benign lesions. We also concluded that Tc-99m MDP scintigraphy, as mentioned above, is very successful, especially in terms of detecting the presence of metastases, and is useful in guiding the clinician.

In addition to the visual evaluation of scintigraphic results, we have seen that the use of numerical evaluation methods increases the superiority of these methods. We have shown that early and late involvement rates, which we consider numerical evaluation methods, can be used to distinguish between malignant and benign lesions. We found that in malignant lesions, while late-term involvement rates increased or remained the same, these rates decreased significantly in benign lesions. As a result of these findings, we have once again shown the importance of taking late images as well as early images in the differentiation of malignant and benign lesions.

If Tc-99m MIBI scintigraphy can be made widely available in the clinic to distinguish between malignant and benign lung lesions, we think it may be useful in reducing unnecessary invasive interventions, especially in benign lesions.

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A DOCUMENTATION OF ECHINOCOCCOSIS CASES IN BATMAN BETWEEN 2010-2022

2010-2022 YILLARI ARASINDA BATMAN'DA EKİNOKOKKOZ OLGULARININ DÖKÜMANTASYONU

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Abstract / Özet

Objective: Echinococcosis is characterized by cystic structures formed by Echinococcus parasites in various organs, particularly the liver, lung, and spleen. Our aim is to document echinococcosis cases detected in Batman province in Turkey. **Materials and Methods:** Clinicopathological data of all echinococcosis cases with histopathological diagnosis in Batman province between 2010-2022 were retrospectively recorded. Descriptive analyses of the data were made using the IBM SPSS 22.0 package program. **Results:** A total of 55 echinococcosis cases, 23 male (41.8%) and 32 female (58.2%) were identified. The average age is 30 (3-77). Of 33 cases with known clinical complaints, 22 (66.7%) had abdominal pain, two (6.1%) had chest pain, two (6.1%) had cough, and seven (21.2%) had other complaints. One case was diagnosed incidentally in the post-traumatic examination. The mean diameter was 8.5 cm (2.8-25 cm) in 43 lesions of known diameter. The localization was liver in 36 (65.5%) cases, lung in 10 (18.2%) cases, and spleen in three (5.5%) cases. In three cases (5.5%), there was more than one organ involvement. In addition, echinococcosis was detected in the brain, kidney, and arm in three cases (5.5%). Of 45 cases with known data, 32 (71.1%) were unifocal and 13 (28.9%) were multifocal. Excision was performed in 34 (61.8%) cases, resection in 20 (36.4%), and aspiration in one (1.8%) case. **Conclusion:** Echinococcosis can be seen in all age groups and presents with a variety of findings depending on the organ involvement. It should be kept in mind in the differential diagnosis of cystic lesions in Turkey, which is among the endemic countries.
Keywords: echinococcosis, hydatid cyst, Batman, pathology

Amaç: Ekinokokkoz, özellikle karaciğer, akciğer ve dalak gibi çeşitli organlarda Echinococcus parazitleri tarafından oluşturulan kistik yapılarla karakterizedir. Amacımız, Türkiye'nin Batman ilinde tespit edilen ekinokokkoz olgularını belgelemektir. **Materyal ve Metot:** Batman ilinde 2010-2022 yılları arasında histopatolojik tanısı konmuş tüm ekinokokkoz olgularının klinikopatolojik verileri retrospektif olarak kaydedildi. Verilerin tanımlayıcı analizleri IBM SPSS 22.0 paket programı kullanılarak yapıldı. **Bulgular:** Toplam 55 ekinokokkoz olgusu, 23'ü erkek (%41,8) ve 32'si kadın (%58,2), tespit edildi. Ortalama yaş 30 (3-77) idi. Bilinen klinik şikayeti olan 33 olgudan 22'si (%66,7) karın ağrısı, ikisi (%6,1) göğüs ağrısı, ikisi (%6,1) öksürük ve yedisi (%21,2) diğer şikayetlere sahipti. Bir olguda travma sonrası yapılan muayene sırasında tesadüfen teşhis konuldu. Çapı bilinen 43 lezyonda ortalama çap 8,5 cm (2,8-25 cm) idi. Lokalizasyon, 36 olguda (%65,5) karaciğer, 10 olguda (%18,2) akciğer ve üç olguda (%5,5) dalak idi. Üç olguda (%5,5) birden fazla organ tutulumu mevcuttu. Ayrıca, üç olguda (%5,5%) beyinde, böbrekte ve kolda ekinokokkoz tespit edildi. Mevcut verilere göre 45 olgudan 32'si (%71,1) unifokal, 13'ü (%28,9) multifokaldi. Otuz dört olguda (%61,8) eksizyon, 20 olguda (%36,4) rezeksiyon ve bir olguda (%1,8) aspirasyon uygulandı. **Sonuç:** Ekinokokkoz tüm yaş gruplarında görülebilir ve organ tutulumuna bağlı olarak çeşitli bulgularla kendini gösterebilir. Endemik ülkeler arasında yer alan Türkiye'de kistik lezyonların ayırıcı tanısında akılda bulundurulmalıdır.
Anahtar kelimeler: Ekinokokkoz, kist hidatik, Batman, patoloji.

1. INTRODUCTION

Echinococcosis is a parasitic disease caused by species belonging to the genus Echinococcus (E.) in humans and manifested by cystic structures in various organs, especially the liver (1–3). Currently, there are five putative species belonging to the Echinococcus genus: E. granulosus, E. multilocularis, E. oligarthrus, E. vogeli, and E. shiquicus (4–6). Echinococcus species are 2-8 mm long on average and consist of three parts: head, neck, and tail. There are four suckers in the head parts called scolex and a variable number of hook structures in their rostellum. The number of proglottids (segments) in the parasite's body part (strobila) is usually three but varies from two to seven segments. In intermediate hosts, cystic echinococcosis (CE) is the disease caused by E. granulosus larvae, alveolar echinococcosis by Echinococcus multilocularis larvae, polycystic echinococcosis by Echinococcus vogeli or Echinococcus oligarthrus larvae (2,7,8). Most cases are seen in unilocular form caused by E. granulosus (9,10).

All E. species have similar life cycles. They complete their biological development in two different mammalian hosts. The larval form of E. granulosus, the most common species in Turkey, inhabits herbivorous animals such as sheep, cattle, and humans. Dogs, which are the definitive hosts, play the most important role in transmission. Humans are the random intermediate host of the cycle between dogs and herbivorous animals. The parasite is transmitted through dog feces, infected foods, and close contact with the dog. The embryo that emerges from the egg taken orally disperses through the blood and forms a cyst when it finds a suitable implantation area. Cysts formed by larvae settle in various organs and tissues, especially in the liver. The inside of the cyst is filled with a colorless, odorless, clear liquid, in which millions of tiny larvae, called protoscolex, swim (3,8).

In Turkey, the prevalence of CE was reported as 50-400/100.000 and the incidence was 3,4/100.000 till 2019 (11). Within the scope of the "Cystic Echinococcosis Action Plan (2019-2023)" of the Ministry of Health of the Republic of Turkey, epidemiological studies conducted between 2009 and 2019 were compiled and the disease incidence rate was found as 8.7/100.000 between 2015-2019. The provinces reported with the highest incidence rate of CE were Van, Agri, Igdir, and Kirsehir (6). In the HERACLES Project, 53 of the 8,618 people (0.6%; 1/163) screened in six provinces of Turkey (Ankara, Aksaray, Balikesir, Bitlis, Edirne, Sanliurfa) were found to be infected with CE (12). These results indicate that CE is an important health problem in Turkey.

In our study, we aimed to retrospectively evaluate the cases that were histopathologically diagnosed as echinococcosis over 12 years in Batman.

2. MATERIALS AND METHODS

This study was approved by the Non-Invasive Clinical Research Ethics Committee of the Hospital with the decision number 293 on 12 January 2022. All patients gave informed consent at the time of surgical intervention.

We retrospectively recorded the clinical data of all echinococcosis cases with pathological diagnosis in Batman province between 2010-2022 using the hospital information system. We performed descriptive analyses of the data with the IBM SPSS 22.0 package program.

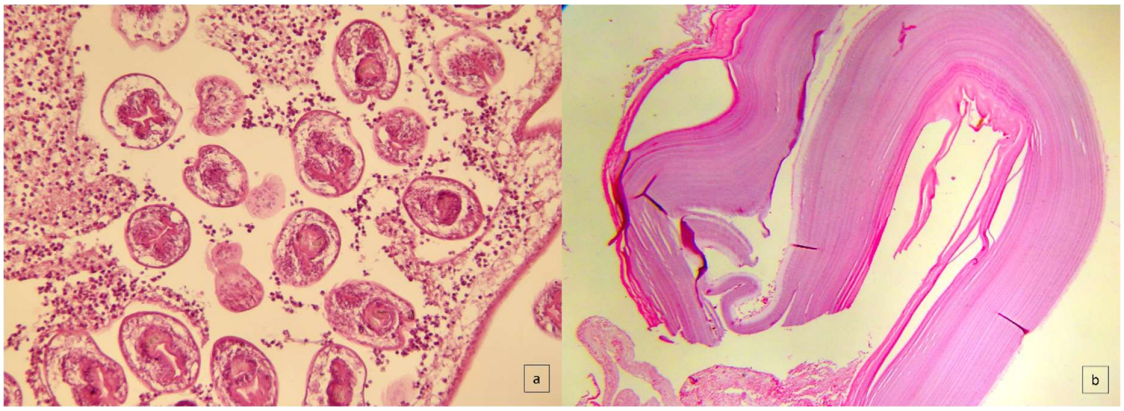
3. RESULTS

A total of 55 echinococcosis cases with histopathological diagnosis were identified including 23 males (41.8%) and 32 females (58.2%) (Figure). The average age was 30 (3-77). Of 33 cases with known clinical complaints, 22 (66.7%) had abdominal pain, two (6.1%) had chest pain, two (6.1%) had a cough, and seven (21.2%) had other complaints (ruptured cystic particles from the mouth, shortness of breath, headache, swelling in the abdomen, swelling in the arm). In addition, one case was diagnosed incidentally in the post-traumatic examination. The mean diameter was 8.5 cm (2.8-25 cm) in 43 lesions of known diameter. Echinococcosis was detected in the liver in 36 (65.5%) cases, lung in 10 (18.2%) cases, and spleen in three (5.5%) cases. Other localizations were the brain, kidney, and arm in three cases (5.5%). In addition, three cases (5.5%) had more than one organ involvement. Of 45 cases with known data, 32 (71.1%) were unifocal and 13 (28.9%) were multifocal. Excision was performed in 34 (61.8%) cases, resection in 20 (36.4%), and aspiration in one (1.8%) case.

4. DISCUSSION

Echinococcosis is one of the most important and overlooked public health problems in Turkey due to its prevalence, difficulty in treatment, and fatal course (13). It is more commonly reported in Southeast Anatolia, East Anatolia, and Central Anatolia regions where animal husbandry is prevalent (10). The number of surgeries performed for CE in Turkey is estimated to be 0.87-6.6/100.000. As a result of regional differences, the incidence of CE varies between 0.8-2.0/100.000 or 0.3%-0.087% according to some researchers. In the data of the Ministry of Health in 2017 for the province of Batman, which is located in the Southeastern Anatolia region, the incidence of CE cases is 1.5/100.000 (6). In our study, we identified 55 echinococcosis cases that were operated on in the province of Batman with an average population of 576.192 between 2010 and 2022. It was noted that CE can be encountered in almost any organ, causing quite a variety of complaints, diagnostic confusion, and treatment approaches depending on where it is located (14).

Figure 1: Parts of Echinococcus. a- Numerous scolices (H&E, 400X) b- Cuticular (laminated) layer (H&E, 100X).



Echinococcosis can be seen in all age groups. Although most of the hospitalized patients in some endemic regions are between the ages of 21 and 40; morbidity was found to be higher in younger individuals (6-20 years old) (15,16). The cases in our study were between 3-77 years of age and the mean age was 30 years. Most of the cysts (50-70%) formed by E. granulosus are located in the liver, 10-30% in the lung, and 10% in other organs or tissues of the body (17). In our study, in accordance with the literature, the most frequently involved organs were the liver, lung, and spleen, respectively. It has been reported that in 85-90% of cases, only one organ is involved, and in 70% of cases, a single cyst is found. In this study, most cases (%71.1) were also unifocal. CE may involve multiple organs or have atypical locations (18–20). In our series, there was more than one organ involved in three cases. In addition, three cases had atypical locations including the brain, kidney, and arm.

Cases with echinococcosis may present with various signs and symptoms, as a benign or severe disease, chronic, subacute, or sometimes with an acute course that requires emergency treatment (11). Patients may have systemic findings such as anaphylactic reaction, rash, and eosinophilia due to cyst rupture, or may present with local symptoms depending on organ location. For example, abdominal pain is common in a case with liver involvement, while a lesion located in the bone may cause a fracture. Some cases may not show any symptoms or may be diagnosed incidentally (21). For instance, one of our cases was diagnosed in the post-traumatic examination. Occasionally, as in one of our cases, cyst fluid and membrane expectoration can be seen as a result of the opening of the cyst into the bronchial system (22).

Today, noninvasive imaging methods and serological tests are very helpful in the diagnosis of echinococcosis. The definitive diagnosis is made by demonstrating protoscolices or parasites in samples obtained by surgery or puncture (21). In the pathological examination, grossly, E. granulosus cysts are unilocular or multivesicular (in the form of a main cyst and daughter cysts outside) with a fibrous wall. It may contain multiple daughter cysts and may reach 30 cm in diameter or more. Microscopically, the cystic echinococcal structure has an outer eosinophilic, anucleated, acellular cuticular (laminated) layer, and an inner germinative layer. The outermost layer is the fibrous layer formed by the host. Brood capsules and protoscolices are attached to the germinal layer or floating in the cyst. In some cases, a part of these findings may go undetected. Inflammatory response, including granulomatous inflammation, to the cyst may develop (23,24). E. multilocularis, on the other hand, consists of multilocular and necrotic cystic cavities, the largest of which is 1 cm in diameter, containing thick pasty material, and does not contain a fibrous wall (adventitia). Although E. vogeli and E. oligarthrus are morphologically similar to other species, the larvae are polycystic with small chambers (8).

There is no gold standard treatment for echinococcal cysts. The treatment aims to eliminate the disease and its complications, and reduce mortality, morbidity rates, and recurrences. Treatment options include surgery, "puncture, aspiration, injection and reaspiration (PAIR)", chemotherapy, and "wait and see" approaches. The treatment approach is determined according to factors such as the localization, type, number, size, presence of recurrence, the general condition of the patient, the training of the surgeon, and whether the surgeon works in an endemic region (25). Patients with calcified lesions can be followed up without the need for treatment. In some patients, there may be active cysts that cause complaints and require intervention. In the last decade, the PAIR method has become widespread. With the developments in interventional radiology, percutaneous treatment and drainage can be performed with the help of ultrasonography and computed tomography. This method is more safely used in the liver and abdominal cysts and is successful in non-complicated patients (25). If surgery is contraindicated, mebendazole and albendazole drugs can be used. This treatment option

is more effective in young patients than in elderly patients (26).

Although this study was carried out in a single center, it reflects the results of Batman province since all echinococcosis cases operated throughout the province were collected in this center. The types of species of the Echinococcus genus were not determined in our cases. Since only the operated cases were reported in this study, the data for other cases that were diagnosed clinically, serologically, or without a histological examination were not available. In addition, postoperative follow-up data of the patients were unavailable

5. CONCLUSION

Echinococcosis is a parasitic cystic disease that is one of the important public health problems seen endemic in Turkey. The most common species are E. granulosus (the causative agent of cystic echinococcosis) and E. multilocularis (the causative agent of alveolar echinococcosis). Although it is most seen in the liver, lung, and spleen, it can also be localized in other organs of the body and may cause diagnostic difficulties. The treatment approach is determined according to the involved organ, type, number, and size of the cyst, overall condition of the patient, and surgical factors. Success in disease control depends on the development of a national strategy, sufficient funding, and education of risk groups. In addition, it is critical to limit the number of dogs that play an important role in transmission, to keep them from becoming infected and transmitting parasites, and to treat them with antiparasitic drugs (6).

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ATATÜRK UNIVERSITY FACULTY OF MEDICINE JOURNAL OF SURGICAL MEDICAL SCIENCES

APPROACHES TO LABIAL FUSION: 3 YEARS EXPERIENCE OF A TRAINING AND RESEARCH HOSPITAL IN THE BLACK SEA REGION

LABİYAL FÜZYONA YAKLAŞIMLAR: KARADENİZ BÖLGESİNDE BİR EĞİTİM VE ARAŞTIRMA HASTANESİNİN 3 YILLIK DENEYİMİ

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Abstract / Özet

Objective: Labial fusion is a prevalent pediatric gynecological condition. This study aimed to conduct a retrospective analysis of patients diagnosed with labial fusion and treated in the Pediatric Surgery department of a tertiary hospital. The primary focus was on evaluating the topical and interventional modalities employed in the treatment of labial fusion and assessing the rates of recurrence. **Materials and Methods:** A retrospective evaluation was conducted on 520 patients treated for labial fusion at the Pediatric Surgery Clinic of Samsun Training and Research Hospital between January 1, 2020, and January 1, 2023. The investigation encompassed an analysis of patients' ages at the time of diagnosis, presenting symptoms, the application of topical, surgical, and combined therapeutic strategies, and the post-treatment recurrence rates of labial fusion. **Results:** Labial fusion was diagnosed in 520 patients, with ages ranging from 1 to 148 months and a mean age of 17.05±19.56 months. While a considerable proportion of patients were asymptomatic, symptomatic cases manifested urinary and vaginal symptoms. Initial treatment involved the application of topical agents to all patients. Notably, many cases referred to pediatric surgery clinics had previously undergone unsuccessful topical treatments administered by pediatricians at different medical institutions, prompting subsequent referral for manual separation. Success was achieved in 128 patients with topical treatment (98 estrogen, 30 betamethasone). Interventional procedures were performed on 392 patients, with an additional two weeks of topical treatment following the intervention for all relevant groups. Among the 95 patients undergoing manual separation, 1-5 recurrences were observed, while no recurrences were noted with repeated combined treatment. Statistically, higher labial fusion recurrence rates were identified in older age groups. **Conclusion:** In the management of labial fusion, we advocate for the importance of employing topical estrogen or betamethasone as non-invasive and secure treatment modalities. Considering the potential risks associated with prolonged topical therapy, manual or surgical separation is contemplated for patients exhibiting inadequate response to a two-week treatment course. Furthermore, we underscore the imperative for additional research to assess the long-term success of pre-pubertal labial adhesions and highlight the efficacy of post-surgical topical treatment as a prophylactic measure. **Keywords:** Labial fusion, topical estrogen, topical betamethasone, manual separation

Amaç : Labial füzyon çocukluk çağında sık görülen bir jinekolojik sorundur. Bu araştırmada üçüncü basamak bir hastanenin Çocuk Cerrahisi bölümünde labial füzyon tanısı ile takip ve tedavisi yapılmış olan hastaların retrospektif olarak incelenmesi, labial füzyon tedavisinde topikal ve girişimsel yaklaşımlarımızın ve nüks sayılarımızın değerlendirilmesi amaçlandı. **Materyal ve Metot :** Samsun Eğitim ve Araştırma Hastanesi Çocuk Cerrahisi Polikliniğinde 1 Ocak 2020-1 Ocak 2023 tarihleri arasında labial füzyon tanısı ile tedavi edilen toplam 520 hasta retrospektif olarak değerlendirildi. Hastaların tanı anındaki yaşları, şikayetleri, uygulanan topikal, cerrahi ve kombine tedavi yöntemleri, tedavi sonrası labial füzyon nüks oranları incelendi. **Bulgular:** Labial füzyon 520 hastada tespit edildi. Hastaların yaşı 1-148 ay olup ortalama 17,05±19,56 ay bulundu. Hastalar sıklıkla asemptomatikti, semptomatik olanlarda üriner ve vajinal semptomlarla karşılaşıldı. Tüm hastalara ilk olarak topikal tedavi uygulandı. Çocuk cerrahisi polikliniklerine başvuran labial füzyonlu olguların çoğunluğu, çeşitli hastanelerdeki çocuk hastalıkları uzmanlarınca topical tedavi denenmiş ve başarısız bulunması nedeniyle manuel seperasyon için yönlendirilmiş olgulardı. Topikal tedavi ile 128 hastada başarı sağlandı (98 östrojen, 30 betametazon). Girişimsel müdahale 392 hastaya yapıldı. Girişimsel tedavi uygulanan tüm gruplara, müdahalenin peşine 2 hafta topikal tedavi eklendi. Manuel seperasyon uygulanan 95 hastada 1-5 kez nüks görülürken, tekrarlanan kombine tedavi ile nüks gözlenmedi. İstatistiksel olarak labial füzyon nüks oranlarımız, ileri yaşlarda daha yüksek bulundu. **Sonuç:** Labial yapışıklığın tedavisinde, non-invaziv ve güvenli bir tercih olarak topikal östrojen veya betametazon uygulamasının önemine inanıyoruz. Uzun süreli topikal tedavi kullanımının potansiyel risklere işaret etmesi nedeniyle, 2 haftalık tedaviye yanıt vermeyen hastalarda manuel veya cerrahi ayrımı düşünüyoruz. Pre-pubertal labial yapışıklıkların uzun vadeli başarısının değerlendirilmesi için daha fazla araştırmaya ihtiyaç olduğunu düşünüyoruz ve cerrahi ayrım sonrasında topikal tedavinin profilaksi olarak etkili olduğunu vurguluyoruz. **Anahtar kelimeler:** Labial füzyon, topikal östrojen, topikal betametazon, manuel seperasyon

1. INTRODUCTION

Labial fusion represents a prevalent and acquired gynecological issue in the pediatric population, characterized by either partial or complete adhesion of the labia minora. Alternate terminologies for this condition encompass vulvae fusion, atresia of the vulva, synechia of the vulva, occlusion of the vestibule, atresia vulvae superficialis, adhesion of the labia minora, and agglutination of the labia minora. The incidence of this condition in prepubertal girls ranges from 0.6% to 3%, with the most frequently affected age group falling within 13-23 months.

The precise etiology of labial fusion remains elusive. In the neonatal period, there is a swift decline in estrogen levels shortly after birth, concomitant with the cessation of maternal circulation. The enduring effects of estrogen on vulvar tissues are postulated to persist, particularly until the age of three. It is hypothesized that the normal labial anatomy may undergo adhesion during the period of maternal estrogen withdrawal (1,2,3).

Labial fusion generally manifests without symptoms. However, symptomatic cases may present with chronic irritation, urinary or vaginal infections, urinary retention, perivaginal itching and inflammation, urine dribbling, or incontinence. The primary treatment modality for labial fusion typically entails the application of estrogen creams, administered twice daily. An alternative topical intervention includes betamethasone. In instances where topical treatments prove ineffective, manual separation or surgical intervention under local or general anesthesia is implemented (3,4).

The objective of this study was to scrutinize the topical and surgical methodologies employed in patients diagnosed with labial fusion and evaluate the recurrence rates.

2. MATERIALS AND METHODS

This study was conducted with the approval of the Samsun University Clinical Research Ethics Committee (Protocol no: SÜKAEK-2023 8/6, decision date: 26/4/2023), adhering to ethical principles and the guidelines outlined in the Helsinki Declaration.

A retrospective evaluation was carried out on a cohort of 520 patients diagnosed with labial fusion and treated at the of Samsun Training and Research Hospital Hospital Pediatric Surgery Clinic between January 1, 2020, and January 1, 2023. The analysis included an examination of patients' age at the time of diagnosis, presenting complaints, employed topical, surgical, and combined treatment modalities, and the post-treatment recurrence rates of labial fusion.

Throughout this process, patients underwent the following protocol steps. Parents were apprised of the chosen treatment method. Initial intervention involved the application of topical treatment. In cases where topical measures proved ineffective, manual separation was instituted, and for cases with robust adhesions, surgical separation was performed. Separation procedures were conducted under local anesthesia with EMLA cream, although in specific adhesion types, operating room conditions and sedation anesthesia were preferred. Subsequent to the operation, during the follow-up period, gentle traction and warm baths, accompanied by the application of topical estrogen or betamethasone cream twice a day, were recommended for two weeks.

Statistical analyses were executed utilizing SPSS 17.0. Descriptive statistics were employed, expressing numeric variables such as age as mean±standard deviation, while categorical variables were articulated as percentages (%). The Shapiro-Wilk test determined the normal distribution of numeric variables. For variables exhibiting a normal distribution, the ANOVA test analyzed mean values. The distribution of age among groups was assessed through frequency analysis. The Chi-square test was applied to evaluate age distribution among groups. The correlation between recurrences and age was assessed utilizing the Pearson correlation test.

3. RESULTS

Over the course of our three-year study, we conducted a retrospective examination of a cohort consisting of 520 patients diagnosed with labial fusion. The age spectrum within the patient population ranged from the youngest at 1 month to the oldest at 148 months, with an average age of 17.05±19.56 months. Predominantly, urinary symptoms were observed, while additional symptoms such as vaginal itching and discomfort were also documented. Initial therapeutic measures involved the application of topical treatment to all patients. Successful outcomes with topical treatment were realized in 128 patients, utilizing either estrogen (98 cases) or betamethasone (30 cases). Interventional procedures were undertaken in 392 patients, performed under local anesthesia with Emla cream; however, in 6 cases, sedation anesthesia was required under operating room conditions.

Following the separation procedures, all groups received topical treatment for a duration of two weeks, and combined treatment was administered to those undergoing interventional procedures. Among the 95 patients subjected to manual separation, recurrences were observed 1-5 times, while no recurrences were noted with repeated combined treatment. In the subset of four patients where separation was conducted under operating room conditions, recurrences occurred, and successful outcomes were achieved through postoperative combined treatment.

Table 1: Ages and topical treatment groups are shown below.

Treatment Groups	N	Mean ± Std. Deviation*	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
				Lower Bound	Upper Bound		
Estradiol	98	6,3878 ± 5,04543	,50967	5,3762	7,3993	1,00	26,00
Betametazon	30	7,0667 ± 5,44523	,99416	5,0334	9,1000	1,00	21,00
Separation	392	20,4847 ± 21,25571	1,07358	18,3740	22,5954	1,00	148,00

*Values expressed as a month

Table 2: The distribution of treatment groups according to age range are illustrated in table B.

		Group			Total
		Estradiol	Betametazon	Separation	
Age range	**0-1**	88[a]	25[a]	189[b]	302
	1-5	10[a]	5[a]	186[b]	201
	>5	0[a]	0[a]	17[a]	17
Total		98	30	392	520

The Pearson Correlation test revealed a statistically significant association, indicating a higher recurrence rate of labial fusion in older cases (p=0.021<0.05). The correlation between recurrences and age is further elucidated in Table C.

Table 3. The correlation of recurrences with age is shown in table C.

		Recurrences	Age
Recurrences	**Pearson Correlation**	1	0,101*
	Sig. (2-tailed)		0,021
	N	520	520
Age	**Pearson Correlation**	0,101*	1
	Sig. (2-tailed)	0,021	
	N	520	520

Table A details the patient ages and topical treatment groups, whereas Table B illustrates the distribution of treatment groups categorized by age range

4. DISCUSSION

Labial fusion is a prevalent pediatric gynecological disorder, and the literature presents various approaches to its treatment. The prevailing belief is that the increased estrogen levels at the onset of adolescence lead to the spontaneous resolution of labial fusion. Consequently, some studies propose a watchful waiting approach in asymptomatic cases. However, in our study, an examination of recurrence rates following intervention revealed a higher recurrence in older cases, suggesting a more resilient recovery process. Consequently, we contend that solely associating labial fusion with estrogen levels may be inadequate. Other studies in the literature advocate for treatment, as labial fusion may induce symptoms and complications such as dysuria, local inflammation in the labial region, urinary tract infection, and obstruction (4). Our clinical protocol involves treating every case of labial fusion presenting to our clinic. The initial treatment typically commences with estrogen (traditionally) or betamethasone creams, administered twice daily with gentle traction. Success rates with estrogen cream application range between 50% and 88% in the literature (3). Most patients continue using estrogen creams until complete resolution of adhesions. In addition to physician recommendations, we frequently encounter parents who, at their discretion, apply creams such as care cream in our clinics. In cases referred to pediatric surgery clinics due to the ineffectiveness of treatments received at various pediatric clinics, irregular and repeated use of estrogen cream is more prevalent. This circumstance has resulted in a higher number of patients undergoing manual separation in our study. As our study is retrospective, the limited knowledge about the use of estrogen or other topical creams before referral is a study limitation. Extended exposure to estrogen poses potential dangers due to insufficient knowledge of potential adverse effects during this process. There is no consensus on the duration of treatment with topical estrogen therapy. Öztorun et al., with 16 years of experience, applied treatment for 15 days in 889 patients (5). Sanfilippo reported that one week of treatment was effective in more than 90% of cases (6). Opipari suggested a treatment duration of 4 to 12 weeks with topical estrogen (7). While topical estrogen is generally considered a safe treatment for labial fusion, long-term use can lead to undesirable side effects such as breast bud, labial growth, hyperpigmentation, and early puberty (8). To mitigate unwanted side effects associated with estrogen creams, betamethasone can be employed as an alternative topical treatment (3). In a retrospective comparative study by Mayoglou et al., comparing topical estrogen and betamethasone treatment, it was suggested that betamethasone might expedite the separation of labial fusion compared to topical estrogen treatment, resulting in fewer recurrences and fewer side effects (9). However, no significant difference was determined between the estrogen and betamethasone treatment groups in this study. In a study by Eroğlu et al., which examined 131 children with labial fusion, it was found that topical estrogen and betamethasone creams had similar success rates, yielding limited satisfactory results. Although combined treatment is considered slightly more effective than single

treatments, it did not reach statistical significance (11). Future studies with larger patient cohorts will significantly contribute to refining the treatment protocol.

Long-term risks associated with topical estrogen or betamethasone treatment, such as adrenal suppression and cancer, remain unknown (9). In instances where we completed the recognized safe treatment duration of a 2-week topical regimen without achieving regression, we opted for manual separation. Soyer et al. advocated the use of topical estrogens as prophylaxis to prevent recurrences following manual separation in cases of labial adhesions, achieving a 100% success rate with this approach (12). Following manual separation in our clinic, a 2-week topical cream prophylaxis was introduced to mitigate recurrences, coupled with combined treatment. Consequently, complete remission was attained in all patients with labial fusion.

A meticulous examination of the vulva is imperative for diagnosing labial fusion. The fused labial area may manifest as a thin, transparent tissue film at the center or encompass thick, resilient, fibrous adhesions. In 90% of cases, labial adhesions extend the full length of the labia minora (13). Among 392 patients, six presented with notably tight, fibrous adhesions. Recurrences were observed in four of these cases, prompting separation under operating room conditions. While not all contributing factors are known, literature suggests that factors associated with recurrence may encompass poor hygiene, diaper rash, trauma, recurrent infections, or dermatological disorders (10). Thus, we underscore the significance of prophylactic topical treatment post-intervention and integrate it into our clinical practice.

5. CONCLUSION

Our conviction persists in favoring the initial application of topical estrogen or betamethasone as a non-invasive and secure method in the treatment of labial fusion. Underlining the potential adverse effects associated with prolonged use, we emphasize that topical treatments may entail precarious circumstances. Furthermore, we draw attention to the consideration of manual separation or surgical intervention for patients with labial fusion who show no response to a 2-week topical treatment. We contend that further investigation is imperative to assess the long-term efficacy of pre-pubertal labial adhesions. Additionally, we stress that labial fusion, post-surgical separation, can be effectively addressed by incorporating topical treatment prophylaxis.

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RETROSPECTIVE EVALUATION OF PATIENTS FOLLOWED-UP AND TREATED FOR IDIOPATHIC THROMBOCYTOPENIC PURPURA: A 21-YEAR SINGLE-CENTER EXPERIENCE

İDİYOPATİK TROMBOSİTOPENİK PURPURA NEDENİYLE TAKİP VE TEDAVİ EDİLEN HASTALARIN RETROSPEKTİF DEĞERLENDİRİLMESİ: 21 YILLIK TEK MERKEZ DENEYİMİ

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Abstract / Özet

Objectives: Primary immune thrombocytopenia (ITP) is an autoimmune disorder that is distinguished by a low platelet count (<100×109/L) without any other underlying causes. The aim of this study is to determine the factors affecting chronicity by retrospectively evaluating the demographic characteristics, examination findings, laboratory results, treatment regimens and treatment responses of patients followed-up for idiopathic thrombocytopenic purpura in our clinic. **Materials and methods:** This study retrospectively reviewed the medical records of patients diagnosed with idiopathic thrombocytopenic purpura and admitted to the Department of Paediatrics at the Faculty of Medicine from January 1, 1997, to December 31, 2018. **Results:** A total of 447 patients diagnosed with idiopathic thrombocytopenic purpura (ITP) between January 1997-December 2018 were identified. Four hundred twenty-eight patients were included in the study. The mean age of diagnosis in chronic ITP was higher than that of acute ITP (p=0.000). Platelet count at admission was lower in acute ITP patients than that of chronic patients (p=0.035). ANA positivity was much higher among chronic patients than in other groups (p=0.014). The difference between the platelet count at the time of diagnosis and on the 3rd day was much higher in patients on steroid and IVIG therapy than that of the patients under combined therapy (p<0.001). The 3rd and 7th-day platelet counts of patients with remission was higher than that of the patients without remission (p<0.001). Age of diagnosis, mean follow-up period, and platelet count at day 7 were identified as the risk factors for chronicity. **Conclusion:** It was found that older age of diagnosis, absence of upper respiratory tract infections (URTI) history, high platelet count were the factors affecting chronicity in children with ITP. **Keywords:** Thrombocytopenia, childood, purpura, chronic

Giriş: Primer immün trombositopeni (ITP), altta yatan başka bir neden olmaksızın düşük trombosit sayısı (<100×109/L) ile ayırt edilen otoimmün bir hastalıktır. Bu çalışmanın amacı kliniğimizde idiyopatik trombositopenik purpura nedeniyle takip edilen hastaların demografik özelliklerini, muayene bulgularını, laboratuvar sonuçlarını, tedavi rejimlerini ve tedaviye yanıtlarını retrospektif olarak değerlendirerek kronikleşmeyi etkileyen faktörleri belirlemektir. **Materyal ve metot:** Bu çalışmada, 1 Ocak 1997 ile 31 Aralık 2018 tarihleri arasında Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları Anabilim Dalı'na başvuran ve idiyopatik trombositopenik purpura tanısı alan hastaların tıbbi kayıtları retrospektif olarak incelendi. **Bulgular:** Ocak 1997-Aralık 2018 tarihleri arasında idiyopatik trombositopenik purpura (İTP) tanısı alan toplam 447 hasta belirlendi. Dört yüz yirmi sekiz hasta çalışmaya dahil edildi. Kronik İTP'de ortalama tanı yaşı akut İTP'ye göre daha yüksekti (p=0.000). Başvuru sırasındaki trombosit sayısı akut İTP hastalarında kronik İTP hastalarına göre daha düşüktü (p=0,035). ANA pozitifliği kronik hastalarda diğer gruplara göre çok daha yüksekti (p=0.014). Tanı anındaki ve 3. gündeki trombosit sayısı arasındaki fark, steroid ve IVIG tedavisi gören hastalarda kombine tedavi gören hastalara göre çok daha yüksekti (p<0.001). Remisyona giren hastaların 3. ve 7. gün trombosit sayıları remisyona girmeyen hastalarınkinden daha yüksekti (p<0.001). Tanı yaşı, ortalama takip süresi ve 7. gün trombosit sayısı kronikleşme için risk faktörleri olarak belirlendi. **Sonuç:** İleri tanı yaşı, üst solunum yolu enfeksiyonu öyküsünün olmaması ve yüksek trombosit sayısının İTP'li çocuklarda kronikleşmeyi etkileyen faktörler olduğu bulunmuştur. **Anahtar Kelimeler:** Trombositopenik, çocukluk çağı, purpura, kronik

1. INTRODUCTION

Primary immune thrombocytopenia (ITP) is an autoimmune disorder that is distinguished by a low platelet count (<100×109/L) without any other underlying causes (1). ITP is a frequently occurring condition in children, with a prevalence rate ranging from 1.9 to 6.5 cases per 100,000 individuals (2). The disease is caused by the increased breakdown of platelets and suboptimal platelet production in the bone marrow due to humoral or cellular immunity mechanisms. In children, it is essentially common between ages 2-7 and usually there is a history of respiratory or gastrointestinal system infection 2-4 weeks prior. ITP is a disease that is generally characterized by petechiae, purpura, gingival bleeding, mucosal bleeding, thrombocytopenia, plasma anti-platelet antibodies and increased megakaryocytes (3). The classification of ITP duration has been revised based on the duration of platelet count below the threshold level of 100×109/L after the initial diagnosis. It is now categorised as acute (0-3 months), persistent (3-12 months), and chronic (>12 months) (4). Around 20-40% of newly diagnosed ITPs may progress to chronic ITP. Primary therapies for paediatric ITP encompass patient surveillance, corticosteroids, intravenous immunoglobulin (IVIG), and intravenous anti-D. Secondary therapy options including rituximab, thrombopoietin receptor agonists, other immunosuppressive medications, and splenectomy (5).

This study aimed to retrospectively analyse the demographic features, examination findings, laboratory data, treatment regimens, and treatment responses of patients with ITP in our clinic in order to discover the factors that contribute to chronicity.

2. MATERIALS AND METHODS

For this study, the files of patients younger than 18 years of age who were diagnosed with idiopathic thrombocytopenic purpura and admitted to Faculty of Medicine, Department of Pediatrics, Department of Pediatric Hematology-Oncology, between January 1, 1997 and December 31, 2018 were evaluated retrospectively. In the diagnosis of ITP, normal physical examination findings other than bleeding findings, absence of organomegaly and lymphadenopathy, normal erythrocyte and white blood cell counts in the complete blood count, peripheral smear, and complete blood count being compatible with thrombocytopenia (platelet count <100000/mm3), absence of a disease that causes thrombocytopenia, increased or normal megakaryocytes in bone marrow examination, were used. Patients who had lymphadenopathy or organomegaly, a history of splenectomy or thrombocytopenia due to other diseases, with no available data, ongoing treatment in another center, and did not give their consent to treatment were excluded from the study.

Demographic data, admission times (seasonal), admission complaints (skin findings, mucosal bleeding, other systemic bleeding findings) of all subjects included in the study were recorded from their files. In order to find the etiological causes in all subjects, the infections they had in the last month, their vaccination history, and the drugs they used were identified. In our clinic, complete blood count, peripheral smear, biochemical workup, viral serology, hepatic markers, direct Coombs test, Antinuclear antibody (ANA), Anti dsDNA, Helicobacter Pylori (H. Pylori) serological test data and treatments applied to the patients were obtained from the patient files. If the platelet count was below the threshold level of 100×109/L for 0-3 months after the initial diagnosis, this was defined as acute ITP; if it was below the threshold level for 3-12 months this was defined as persistent ITP; if it was below the threshold level for 12 months or longer this was defined as chronic ITP. Remission was defined as platelet count above 100,000/mm3 at the end of follow-up.

2.1 Statistical Analysis

Analyses were conducted with IBM SPSS 20 software for statistical analysis. The data were presented using descriptive statistics, including the mean, standard deviation, median, minimum, maximum, percentage, and quantity. For the comparison of continuous variables among several independent groups, the ANOVA test was employed when the normal distribution assumption was satisfied, while the Kruskal-Wallis test was utilised when this assumption was not met. The Backward Stepwise (Likelihood Ratio) method of logistic regression analysis was employed to analyse predictive risk factors between groups in multivariate analysis. The probable risk factors identified in earlier analyses were used in this research. A p value less than 0.05 was deemed to be statistically significant.

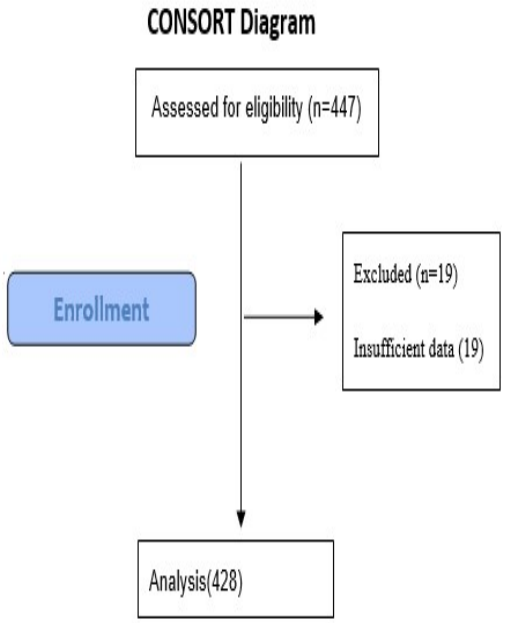
3. RESULTS

A total of 447 patients diagnosed with ITP between January 1997-December 2018 were identified. A total of nineteen patients were eliminated from the study due to the unavailability of their patient data, receiving ongoing therapy at another medical facility, being lost to follow-up, or withholding consent for treatment.

Of 428 patients, 208 (48.6%) were female and 220 (51.4%) was male. The age of the patients at the time of diagnosis was 73.6±47.9 months. The most common complaints at admission were bruising, epistaxis, gingival bleeding, and hypermenorrhea. The most common examination findings were petechiae and ecchymosis.

Of our patients, 291 (68%) were diagnosed with acute ITP, 29 (6.8%) with persistent ITP, and 108 (25.2%) with chronic ITP. The characteristics of the cases by ITP types are given in Table 1.

Figure 1: Consort Flow Diagram



The mean age at diagnosis in chronic ITP patients was found to be significantly higher than in acute ITP patients (p=0.000). Of the 428 patients included in the study, 166 (38.7%) had a history of infection 1-4 weeks before the admission date. It was found that patients with a history of infection became less chronic (p=0.04) (Table 2). Anti-nuclear antibody (ANA) was tested in 283 patients, and 42 (14.8%) patients were found to be ANA-positive. ANA positivity was statistically higher in chronic patients than in other groups (p=0.014). H. pylori seropositivity was found to have no effect on disease course.

There was no difference in terms of gender between the patients who entered remission. The rate of remission was significantly higher in ANA-negative patients (p=0.009). Remission was observed in 350 of the 428 patients included in the study. The remission rate was found to be significantly higher in patients with acute ITP compared to persistent and chronic ITP (p<0.001). When the platelet counts of the patients were examined based on their remission status, the 3rd and 7th-day platelet counts of the patients with remission were significantly higher than the platelet counts of the patients without remission (p<0.001). Table 3 presents the characteristics of the patients who went into remission.

A model was established with the variables that we consider as clinical risk factors between the groups in acute and chronic ITP. According to the results of the model, age at diagnosis, mean follow-up period, and 7th-day platelet count were found to be risk factors for chronicity (Table 4).

Table 1: Comparison of Cases by ITP Types

	Acute ITP(n=291)	Persistent ITP(n=29)	Chronic ITP(n=108)	p
Gender	**n(%)**	**n(%)**	**n(%)**	
Male	154 (%70)	14 (%6,4)	52 (%23,6)	0,615[a]
Female	137 (%65,9)	15 (%7,2)	56 (%26,9)	
Mean age at diagnosis (months) mean±SD Median(min-max)	65,3±45,4 56(1.5-204)	79,9±48,9 84(5-158)	94,1±48,1 84(3-199)	**0,000[b]**
Platelet count (mm3) mean±SD Median(min-max)	10606±11115 7000(400-68000)	13878±14706 10000(1300-72000)	13408±12433 9000(1000-75000)	**0,035[b]**
Infection	n(%)	n(%)	n(%)	
Positive	111(%78,2)	8 (%5,6)	23 (%16,2)	**0.040[a]**
Negative	179 (%62,8)	21 (%7,4)	85 (%29,8)	
ANA	n(%)	n(%)	n(%)	
Positive	20 (%47,6)	3 (%7,1)	19 (%45,2)	**0,014[a]**
Negative	163 (%67,6)	23 (%9,5)	55 (%22,8)	
H.pylori	n(%)	n(%)	n(%)	
Positive	58 (%58,0)	8 (%8,0)	34 (%34,0)	0,150[a]
Negative	119 (%68,0)	16 (%9,10)	40 (%22,9)	
Treatment	n(%)	n(%)	n(%)	
Steroid	156 (%68,4)	18 (%7,9)	54 (%23,7)	0,229[a]
IVIG	76 (%73,8)	4 (%3,9)	23 (%22,3)	
Combined	26 (%56,5)	4 (%8,7)	16 (%34,8)	

Values are mean ± standard deviation (SD), n(%)

[a] Pearson's *chi-squared* test

[b] Kruskal-Wallis Test

Table 2. The Effect of Upper Respiratory Tract Infection History on the Course of the Disease

	URTI		p
	Yes	No	
Acute	111(%78,2)	179 (%62,8)	**0.040**[a]
Persistent	8 (%5,6)	21 (%7,4)	
Chronic	23 (%16,2)	85 (%29,8)	

Table 3. Characteristics of the Patients In Remission

		Remission		
		Positivie n(%)	Negative n(%)	p
Gender	**Male**	183 (%52,3)	39 (%50,0)	0,715[a]
	Female	167 (%47,7)	39 (%50,0)	
ANA	**Positive**	27 (%12,2)	15 (%25,9)	**0,009**[a]
	Negative	195 (%87,8)	43 (%74,1)	
Disease Process	**Acute ITP**	276 (%94,8)	15 (%5,2)	**<0,001**[a]
	Persistent ITP	24 (%82,8)	5 (%17,2)	
	Chronic ITP	50 (%46,3)	58 (%53,7)	
Platelet count at diagnosis mean±SD Median(min-max)		11678±12187 7000(400-75000)	11004±9750 7500(1000-41000)	0,586[b]
3rd day platelet count mean±SD Median(min-max)		78500±71202 64000(2000-531000)	54095±60312 37000(1000-313000)	**<0,001**[b]
7th day platelet count mean±SD Median(min-max)		190361±146454 150500(2000-934000)	86296±80646 62000(2000-376000)	**<0,001**[b]

[a] Pearson's chi-squared test
[b] Mann Whitney U Test

Table 4. Analysis of Factors Affecting Chronicity

	p	OR	OR for %95 GA
Diagnosis Age	,001	1,015	1,006-1,023*
Tracking Time	,000	1,080	1,051-1,110*
7th day platelet count	,012	1,000	1,000-1,000*

*Logistic regression (Method=Bacward Stepwise (Likelihood Ratio))

4. DISCUSSION

ITP is a haematological disorder marked by a reduced number of platelets caused by the destruction of platelets due to the immune system and inadequate platelet synthesis.

In the study by Güngör et al., (6) which covered a 4-year follow-up period; 49.3% of the patients were male and 50.7% female. In a retrospective study of 409 patients (7), the mean age of the patients was found to be 4.72 years. ITP occurs with equal frequency in both sexes and is most common in children aged 2-6 years (8). In this study, 212 patients presented with purpuric rash and ecchymosis; mucosal bleeding was observed in 78 patients, epistaxis in 37 patients, GIS bleeding in 11 patients, and menorrhagia with hematuria in 5 patients. Our findings were in accordance with many studies evaluating the demographic characteristics, age, and first admission complaints of the patients. Factors such as an early age upon diagnosis, a recent viral infection or immunisation, a lower platelet count, the appearance of wet purpura, and being male are associated with a higher probability of a more severe disease progression. (9).

In the multicenter study by Zeller et al. (10), it was found that 25.1% of the patients became chronic. In another study, (11) it was found that the incidence of chronic ITP was higher in girls than boys. In addition, the median age of patients with chronic ITP was found to be higher than patients with persistent ITP. In a study in which the natural course and remission rates of ITP were screened retrospectively (12), no difference was found between patients diagnosed with persistent ITP and patients with chronic ITP in terms of sex and platelet counts at the time of diagnosis, however, patients with chronic ITP found to be older at the time of diagnosis than the patients with acute ITP. In our study, chronicity was detected in 108 (25.2%) patients. While 51.8% of our chronic patients were female, 48.2% were male. The mean age at diagnosis was found to be higher in chronic patients than in acute patients. These findings were found to be in accordance with the literature. Platelet count at the time of diagnosis

was found to be lower in acute ITP patients than in chronic ones.

In the study of Roganovic et al. (13), a history of prior infection was found in 73% of patients diagnosed with acute ITP and 16% of the patients diagnosed with chronic ITP, and it was shown that the absence of a prior viral infection was associated with the development of chronic ITP. In another study (14), history of prior infection and vaccination were found to be predictive factors for acute ITP. Viral infections are thought to cause thrombocytopenia by triggering the formation of autoantibodies against platelets (15). Our study confirmed the findings of previous research, showing a significant decrease in chronicity among those with a prior infection. Factors such as early onset of diagnosis, recent viral infection or immunisation, decreased platelet count, presence of wet purpura, and male gender contribute to a higher probability of a more severe illness progression.

Immune thrombocytopenia in children is more common in winter and autumn when viral infections and infectious and environmental agents such as vaccination can trigger the immune system to produce autoantibodies against platelets. It is assumed that the seasonal differences in the distribution of ITP result from the difference in the incidence of viral infections according to the climate in different countries (16, 17). In a study by Hafiz et al. (18), the incidence was found to be high in summer months, but low in winter. In the study by Zeller et al. (10), the highest incidence was observed in the winter months, while an increased incidence was found in the summer months in another study (19). It was found that our patients were admitted mostly in the summer season, but this was not statistically significant. The harsh winter season in our region causes disruptions in transportation; this situation leads to less hospital admissions in winter. We think that due to school holidays and easier transportation in the summer, the number of admissions increase and more patients are diagnosed.

In their study, Altıntaş et al.(20) discovered a statistically significant disparity in ANA positivity between paediatric acute and chronic ITP patients. The study involved 365 children and 108 adult patients. In another study (21), no statistically significant difference was found between ANA-positive and ANA-negative groups in terms of chronic ITP development. In the study by Bensouda et al. (22), no relationship was found between ANA positivity and disease chronicity.

The decision to treat patients is contingent upon the extent of thrombocytopenia, the gravity of bleeding, and the existence of additional bleeding risk factors. The American Society of Hematology's evidence-based treatment guidelines advise that children who do not have bleeding or only have minimal bleeding (such as bruises or petechiae) should be managed with observation alone, irrespective of their platelet count. Therapeutic intervention should be administered to promptly elevate the number of platelets, sustain a consistent platelet count, or attain prolonged remission of the condition. (23, 24). In their study, Glanz et al. (25) found that 80% of patients diagnosed with ITP received at least one treatment. Of the patients who received treatment, 67% were treated with intravenous immunoglobulin, 42% with corticosteroids, and 15% with both drugs. In another study (14), the rate of patients receiving intravenous immunoglobulin (IVIG) and/or steroids were found to be more common in chronic ITP. Tamminga et al. (26) discovered that administering IVIG as the first treatment resulted in a slight yet significant enhancement in the long-term increase of platelet count after 6 months. This effect was observed regardless of other established risk factors. A meta-analysis (27) compared the efficacy of glucocorticoids and IVIG in pediatric acute ITP and showed that IVIG was more effective in raising the platelet count above 20000/mm3 in 48 hours. It was found that 25% of patients treated with corticosteroids and 18% of patients treated with IVIG progressed to chronic ITP. Bruin et al. (28) found that the risk of progression to chronic ITP in patients treated with IVIG was lower than in patients receiving corticosteroids.

The unresolved topic is whether IVIG treatment provides protection against chronic disease, or if corticosteroid treatment raises the likelihood of chronic disease. The rapid recovery of platelets in ITP patients may be attributed to two well-documented therapeutic effects of IVIG: the inhibition of FcɣR-dependent reticuloendothelial system (RES) function and the neutralisation of anti-idiotypic interactions. Therapeutic intervention should be administered to promptly elevate the number of platelets, sustain a consistent platelet count, or attain prolonged remission of the condition. (28). In their study in which they compared IVIG, steroid and Anti-D Ig treatments, Çelik et al. found that the 3rd and 7th-day platelet counts in the IVIG group were higher than the patients who were given steroids, and they found a significant difference in terms of the 7th-day platelet counts. As side effects of steroids they just observed weight gain, facial fat accumulation, and increased appetite (29). In our clinic, the majority of patients received steroids, others received IVIG or combined therapy. About 11% of these patients recovered without treatment. A relationship could not be determined between these treatments and the course of the disease (acute-chronic). In our study, the difference between the platelet count on the 3rd day and at the time of diagnosis was found to be higher in the IVIG group compared to the steroid group ($p<0.001$).

In the study by Kim et al. (12), IVIG, steroid, Rho (D) immunoglobulin, and observation were provided to the patients as the first treatment. No significant

difference was found between the patients who received treatment in terms of their treatment response rates. Glanz et al. (25) showed that the provided treatments protected from the complications of ITP, but no evidence was found that indicates they prevented the chronicity of ITP. Tamminga et al. (26) found that the rate of chronic ITP was 18% after IVIG treatment and 25% after steroid treatment, and it was found that children who were initially treated with IVIG had a higher chance of having normal platelet count 6 months after diagnosis compared to children who did not receive IVIG. In our study, when the disease course of the patients was evaluated by the type of treatment they received, it was observed that the treatments were not superior to each other and no statistically significant difference was found. Again, it was found that the treatment option had no predictive value in chronicity.

In a prospective study to further investigate the factors predicting remission in children, Bennet et al. (30) evaluated the remission rates at 12 and 24 months in a total of 1088 patients. Data such as demographic information, platelet count at diagnosis, initial treatment, bleeding sites, and bleeding severity were collected using the Bolton-Maggs and Moon scale. The predominant pharmacological interventions included the administration of intravenous immunoglobulin (IVIG) as a standalone treatment (25%), the use of corticosteroids as a standalone treatment (26%), and the combination therapy of IVIG and corticosteroids (13%). The utilisation of Anti-D immune globulin was infrequent, accounting for only 3% of cases. Remission was attained in 419 (59%) patients during a span of 12 months, and in 211 (55%) patients within a span of 24 months. Remission at both 12 months and 24 months was positively correlated with a younger age. The study revealed a substantial correlation between the initial pharmacological treatment administered at the time of diagnosis and remission rates at both the 12 and 24-month marks. The IVIG and corticosteroid treatment group exhibited the most elevated rates of remission, with percentages of 76% and 77% respectively. There was no discernible correlation between gender and platelet count at diagnosis, as well as the rates of remission from ITP after 12 or 24 months.

In our study, remission was observed in 350 out of 428 patients. Of the patients with remission, 52.3% were male and 47.7% were female. ANA-negative patients had high remission rates and this was statistically significant. In patients with acute ITP, the remission rate was higher than in persistent and chronic ITP, and the difference was statistically significant. While no relationship was found between the platelet count at the time of diagnosis and remission, the 3rd and 7th-day platelet counts of the patients who entered remission were higher than the platelet counts of the patients who did not enter remission and the difference was statistically significant. In addition, the relapse rates of patients who received IVIG treatment alone were found to be significantly lower than those who received steroids or steroid + IVIG.

Thrombocytopenia is a frequently seen issue during the perioperative period. Although numerous patient and procedure-related factors affect global haemostasis, accurately predicting the impact of thrombocytopenia on bleeding risk is challenging due to the lack of a linear correlation between platelet count and the probability of bleeding. The likelihood of bleeding is also influenced by the cause of thrombocytopenia. Patients with immune thrombocytopenia (ITP) experience bleeding less frequently compared to other patients with similarly low platelet counts. This is likely due to the larger size and enhanced functionality of their platelets (31).

Since the patient files were analyzed retrospectively, the lack of access to some data was our limitation.

In conclusion, our study demonstrated that low platelet count, younger patient age, the presence of a recent history of infection, and ANA negativity increased the likelihood of an acute disease course. In addition, in our study; age at diagnosis, mean follow-up period, and platelet count at day 7 were found to be risk factors for chronicity.

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Author Contributions: The study's design, sample collection, data collecting and/or processing, and preparation of the original manuscript were conducted by GD and ZKS.

Ethical Approval: The ethical approval for our study was obtained in the Atatürk University Clinical Research Ethics Evaluation Committee's Clinical Research Meeting No:5, Resolution No:10, dated 27.06.2019.

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TÜKRÜK BEZİ KARSİNOMLARINDA HSPA2 EKSPRESYON PROFİLİ VE PROGNOSTİK PARAMETRELER İLE İLİŞKİSİ

HSPA2 EXPRESSION PROFILE IN SALIVARY GLAND CARCINOMAS AND ITS RELATIONSHIP WITH PROGNOSTIC PARAMETERS

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Abstract / Özet

Amaç: İnsan sağlığı açısından önemli morbitidite ve mortalite sabebi olan tükrük bezi karsinomlarında (TBK) birçok histopatolojik alt tipi bulunmaktadır ve ayrımları zordur. Farklı alt tipler, tanının karmaşıklığına ek olarak farklı klinik özellikler sergilemektedir. Klinikopatolojik çeşitlilik nedeniyle doğru teşhis ve prognostik belirteçlerin belirlenmesi önemlidir. Heat shock 70 kDa protein 2 (HSPA2) farklı malignitelerde anormal seviyelerde eksprese edildiği belirtilen potansiyel kanseri teşvik eden protein olarak tanımlanmaktadır. TBK'de HSPA2 ekspresyonunu araştıran yeterli çalışma bulunmamaktadır. Bu nedenle çalışmamızda TBK'de HSPA2 ekspresyonununun varlığını ve bunun prognostik önemini belirlemeyi amaçladık. **Materyal Metot:** Çalışmamıza anabilim dalımızda Ocak 2012-2022 tarihleri arasında TBK tanısı konmuş 44 olgu dahil edildi. Tümöral ve non tümöral alanlarda HSPA2 ekspresyonu derecesi ve bu ekspresyonun prognostik parametreler ile ilişkisi immünhistokimyasal yöntem kullanılarak araştırıldı. **Bulgular:** Çalışmamızda 44 olgunun tamamında HSPA2 ile boyanma izlendi. Tümörlü ve tümörsüz alanların histoskor değerleri karşılaştırıldığında istatiksel olarak anlamlı bir şekilde tümörlü alanlarda boyanma daha kuvvetliydi (p<0,05). Ayrıca artmış HSPA2 ekspresyonu izlenen hastalarda ölüm oranı belirgin derecede yüksekti (p:0,026). HSPA2 ekspresyonu ile hastaların yaşı, cinsiyeti, makroskopik tümör boyutu, patolojik evre, histolojik alt tip, lenfovasküler invazyon, perinöral invazyon, nüks ve metastaz arasında anlamlı bir ilişki yoktu (tümü p>0.05). **Sonuç:** Çalışmamızın sonuçları TBK'lerde HSPA2 ekspresyonunun tümör gelişiminde rol oynayabileceğini akla getirmektedir. Ayrıca her ne kadar çoğu prognostik parametre ile anlamlı ilişki tespit edilmese de sağ kalım ile artmış HSPA2 ekspresyonu arasında anlamlı ilişki bulunması TBK'da yüksek HSPA2 ekspresyonunun prognostik belirteç olarak kullanılabileceğini düşündürmektedir. **Anahtar Kelimeler :** Tükrük bezi karsinomları, HSPA2, prognostik belirteçler

Objective: There are many histopathological subtypes in salivary gland carcinomas (SGC), which cause important morbidity and mortality in terms of human health, and their distinction is difficult. Different subtypes exhibit different clinical features, adding to the complexity of diagnosis. Due to clinicopathological diversity, accurate diagnosis and determination of prognostic markers are important. Heat shock 70 kDa protein 2 (HSPA2) is defined as a potential cancer-promoting protein that is expressed at abnormal levels in different malignancies. Thereare not enough studies investigating HSPA2 expression in SGC. Therefore, in our study, we aimed to determine the presence of HSPA2 expression in SGC and its prognostic significance.
Material Method : 44 cases diagnosed with TBK in our department between January 2012 and 2022 were included in our study. The degree of HSPA2 expression in tumoral and non-tumoral areas and the relationship of this expression with prognostic parameters were investigated using immunohistochemical method. **Results:** In our study, HSPA2 staining was observed in all 44 cases. When the histoscore values of tumor and non-tumor areas were compared, the staining was statistically significantly stronger in tumor areas (p<0.05). Additionally, the mortality rate was significantly higher in patients with increased HSPA2 expression (p:0.026). There was no significant relationship between HSPA2 expression and patients age, gender, macroscopic tumor size, pathological stage, histological subtype, lymphovascular invasion, perineural invasion, recurrence and metastasis (all p>0.05). **Conclusion:** The results of our study suggest that HSPA2 expression in SGCs may play a role in tumor development. In addition, although no significant relationship was detected with most prognostic parameters, the finding of a significant relationship between survival and increased HSPA2 expression suggests that high HSPA2 expression in SGCs can be used as a prognostic marker. **Key Words:** Salivary gland carcinomas, HSPA2, prognostic markers

1. GİRİŞ

Tükrük bezi karsinomları (TBK), çeşitli histolojik tipleri, biyolojik davranış çeşitliliği, tedavi şekilleri ve genomik değişiklikleri olan baş-boyun bölgesinden kaynaklanan nadir görülen tümörlerdir. Görülme oranı dünya genelinde 100.000 kişi başına 0,05 ile 2 arasında değişmektedir. Amerika Birleşik Devletleri'nde yılda 2000'den fazla kişinin ölümüne yol açtığı ve görülme sıklığının arttığı bildirilmektedir. Malignitenin doğru teşhisi, optimal cevap alınan uygun tedavinin uygulanmasını sağlamaktadır (1, 2).

Isı Şok Proteinleri (HSP) strese veya yüksek sıcaklığa yanıt olarak hücresel proteinlerin denatürasyonunu veya açılmasını tersine çevirme, engelleme işlevi gören bir protein grubudur. İnsan HSP70 ailesi, HSPA genleri tarafından kodlanan 13 üyeden oluşmaktadır. HSPA2 geni orijinal olarak, testiste spesifik ve yüksek oranda eksprese edilen kemirgen genlerinin insandaki karşılığı olarak karakterize edilmektedir (3, 4) . Son zamanlarda, testis dışı dokuların karsinogenezine olası katılımı nedeniyle artan ilgiye sahiptir. HSP70'ler kanser gelişiminde önemli roller oynar ve genellikle kanser hücrelerinde anormal derecede yüksek seviyelerde eksprese edilmektedir. Heat shock 70 kDa protein 2 (HSPA2), HSP70-2 olarak da bilinmektedir. HSPA2, serviks, mesane, karaciğer, akciğer kanseri gibi malignitelerde anormal seviyelerde eksprese edilen potansiyel kanseri teşvik eden protein olarak tanımlanmaktadır (5-8).

Literatürde farklı kanser türlerinde HSPA2 ekspresyonu araştırılmıştır ancak TBK'de HSPA2 ekspresyonunu araştıran yeterli çalışma bulunmamaktadır. Bu nedenle çalışmamızda TBK'de HSPA2 ekspresyonununun varlığını ve bunun prognostik önemini belirlemeyi amaçladık.

2. MATERYAL VE METOT

2.1. Hastaların Genel Özellikleri

Bu çalışmada, anabilim dalımızda Ocak 2012-2022 tarihleri arasında opere edilen ve tükrük bezi karsinomu tanısı konan, ameliyat öncesi kemo-radyoterapi almayan ve parafin bloklarına ulaşılabilen 44 adet tükürük bezi rezeksiyon materyali incelendi. Hastaların klinik bilgileri hastanemiz otomasyon sisteminden alındı. Histolojik alt tip, lenfovasküler invazyon, perinöral invazyon, patolojik evre (pT), makroskobik tümör çapı, nüks, metastaz, sağkalım gibi önemli prognostik parametreler incelendi. Hastaların takip süresi en az 1 yıl en fazla 11 yıl olarak belirlendi. Hastaların patoloji raporları, camları ve parafin blokları arşivimizden çıkartılarak tümörü en çok temsil eden parafin bloklar seçildi.

2.2. İmmünhistokimyasal Çalışma

Tümörün en yoğun olduğu bloklardan 4 mikron kesitler alındı ve dokular yüklü lamlara 70 derecelik kurutma fırınında 15 dakika yerleştirildikten sonra Roche Ventana otomatik immünohistokimya boyama cihazına (Ventana Roche, ABD) konuldu. Cihazdaki dokular sırasıyla deparafinizasyon ve dehidrasyon işlemlerinden geçirildikten sonra ULTRA Cell Conditioning Solution, hidrojen peroksit, HSPA2 antikorları ile muamele edildi.

İmmünhistokimyasal boyalar iki patolog tarafından değerlendirildi. Nükleer ve stoplazmik boyanma pozitif olarak kabul edildi. Boyama oranı=0 Grade 0, 1-10% = Grade 1, %11-49 = Grade 2, ≥%50 = Grade 3 kabul edildi. Boyama yoğunluğu: boyama yok= Grade-0, zayıf boyama=Grade 1, orta boyama=Grade 2, güçlü boyama=Grade 3 olarak kabul edildi. İmmünoreaktivite skoru, yoğunluk ve oranın çarpılması yöntemi kullanılarak hesaplandı. Histoskor değerleri şu şekilde değerlendirildi; negatif=Grade 0, 1-3; zayıf=Grade 1, 4-6; orta=Grade 2, 7-9; güçlü=Grade 3.

2.3. İstatistiksel analiz

Tümöral ve non tümöral dokudaki HSPA2 seviyeleri ki-kare testi ile incelendi. HSPA2 ekspresyonunun prognostik parametrelerle korelasyonları Spearman korelasyon testi kullanılarak değerlendirildi. İki uçlu p değeri için <0,05 anlamlı olarak kabul edildi. İstatistiksel analizler MedCalc yazılımı (ver 16, Ostend, Belçika) kullanılarak yapıldı.

3. SONUÇ

3.1. Hastaların Demografik ve Histopatolojik Özellikleri

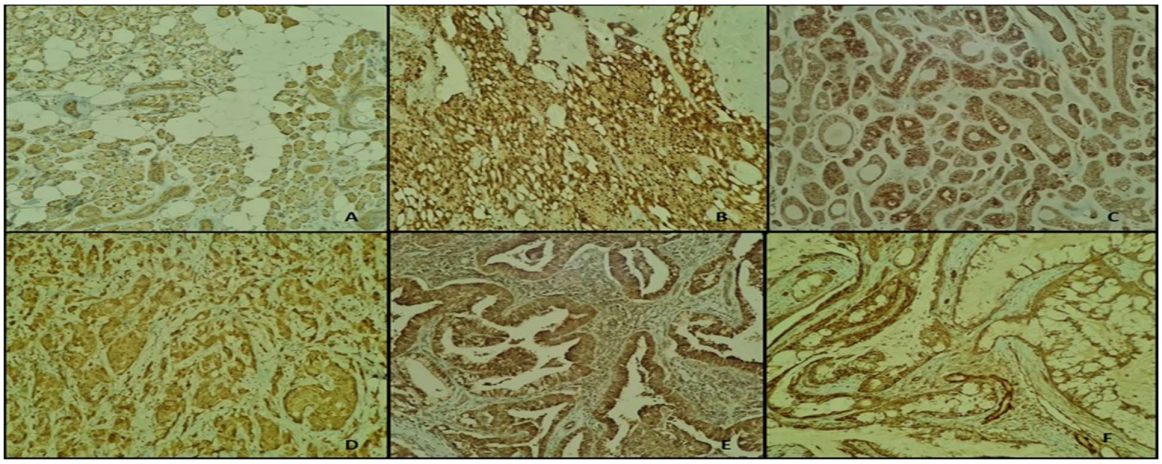
Çalışmamıza dâhil edilen toplam 44 olgunun yaş ortalaması 56 ± 19,1 (11-86) yıl olarak belirlendi. Erkek/kadın oranı 1,4 idi. Olgulardan, 12'si mukoepidermoid karsinom, 10'u epitelyal myoepitelyal karsinom, 4'ü yassı epitel hücreli karsinom, 4'ü adenoid kistik karsinom, 4'ü asinik hücreli karsinom, 3'ü tükürük bezinin duktal karsinomu, 2'si adenokarsinom-NOS, 2'si sekretuar karsinom, 1'i karsinoma ex pleomorfik adenom, 1'i polimorfoz adenokarsinom, 1'i bazal hücreli adenokarsinom idi. Tümörün ortalama makroskopik çapı 2,5 ± 1.3(0.5-5.3) cm idi. 11 olguda lenfovasküler invazyon, 12 olguda perinöral invazyon tespit edildi. Olgulardan 15'i pT1, 16'sı pT2, 7'si pT3, 6'sı pT4 idi. 9 hastada nüks ve metastaz izlendi. Hastaların 14'ü takipten sonraki beş yıl içinde öldü.

3.2. Tükürük Bezi Malignitelerinde HSPA-2 Ekspresyonunun Önemi

Olguların tümöral alan ve tümöral olmayan alanlarındaki HSPA2 seviyeleri ki-kare testi ile incelendi. 44 olgunun tamamında tümöral alanlarda kuvvetli boyanma (histoskor: grade 3) izlenirken komşu tümörsüz alanlarda zayıf (histoskor: grade 1) HSPA-2 boyanması saptandı (Resim 1). Tümörlü ve tümörsüz alanların histoskor değerleri karşılaştırıldığında istatiksel olarak anlamlı bir

şekilde tümörlü alanlarda boyanma daha kuvvetliydi (p<0,05).HSPA-2 ekspresyonu ile klinikopatolojik parametreler arasındaki ilişki Spearman korelasyon analizi ile değerlendirildi. HSPA2 ekspresyonu ile sağ kalım arasında anlamlı ilişki tespit edildi (p:0,026). Diğer taraftan HSPA2 ekspresyonu ile hastaların yaşı, cinsiyeti, makroskopik tümör boyutu, patolojik evre (pT), histolojik alt tip, lenfovasküler invazyon, perinöral invazyon, nüks ve metastaz arasında anlamlı bir ilişki yoktu (tümü p>0.05) (Tablo) (Resim 1)

Resim 1: Tükrük bezinin tümöral ve non tümöral alanlarında HSPA2 ekspresyonu.



A: Non tümöral alanlarda düşük HSPA2 ekspresyonu (HSPA2x200)
B: Asinik hücreli karsinomda HSPA2 ekspresyonu (HSPA2x200)
C: Adenoid kistik karsinomda HSPA2 ekspresyonu (HSPA2x200)
D: Epitelyal myoepitelyal karsinomda HSPA2 ekspresyonu (HSPA2x200)
E: Tükrük bezinin duktal karsinomunda HSPA2 ekspresyonu (HSPA2x200)
F: Mukoepidermoid karsinomda HSPA2 ekspresyonu (HSPA2x200)

Table 1: HSPA2 ekspresyonu ile prognostik parametreler arasındaki ilişki

	HSPA2 EKSPRESYONU			
	Derece 1	**Derece 2**	**Derece 3**	**p Değeri**
Histolojik Tip				
MEK	1	5	6	
EMK	1	2	7	
AKK	1	2	1	0,91
YEHK	1	1	2	
AHK	1	0	3	
Diğer	1	2	7	
LV				
Var	4	0	7	0,69
Yok	2	12	19	
MTÇ				
2≥	2	6	10	
2-4	0	6	13	0,52
4<	4	0	3	
PN				
Var	3	1	8	0,88
Yok	3	11	18	
pT				
Pt1	1	5	9	
Pt2	0	5	11	0,75
Pt3	4	0	3	
Pt4	1	2	3	
Nüks				
Var	0	2	7	0,15
Yok	6	10	19	
Metastaz				
Var	0	2	7	0,15
Yok	6	10	19	
Sağkalım				
Ölü	1	1	12	0,026
Sağ	5	11	14	

MEK: Mukoepidermoid Karsinom EMK: Epitelyal Myoepitelyal Karsinom AKK: Adenoid Kistik Karsimom, YEHK: Yassı Epitel Hücreli Karsinom, AHK: Asinik Hücreli Karsinom,MTÇ: Makroskobik Tümör Çapı LV: Lenfovasküler İnvazyon, PN: Perinöral invazyon, pT: Patolojik Evre

4. TARTIŞMA

TBK, baş ve boyun kanserinin yaklaşık %6,5'ini oluşturan heterojen bir malignite grubudur (1). En son Dünya Sağlık Örgütü'nün Baş ve Boyun Tümörleri sınıflandırması TBK'nin 22 histopatolojik alt tipini ayırt eder bu da her bir alt tipi daha da nadir hale getirir (9). Bu farklı alt tiplerin tanınması ve birbirinden ayırt edilmesi zordur ve farklı alt tipler, hastalığın karmaşıklığına ek olarak farklı klinik özellikler sergilemektedir (10). 5 yıllık genel sağkalım oranı %14.8 iken uzak metastazlı tüm TBK tipleri için ortalama genel sağkalım 15 aydır (11). Sağkalım oranı farklı alt türler arasında büyük farklılıklar göstermektedir (12, 13).

Hastalığın klinikopatolojik çeşitliliği, patolojik incelemenin önemini vurgulayarak, spesifik TBK alt tipine göre uyarlanmış tedavinin önemini artırmaktadır. Bununla birlikte, TBK'nin nadirliği ve kapsamlı heterojenliği, ileriye dönük çalışmalarda büyük ölçekli hasta çalışmalarını engellemektedir. Bu bağlamda erken ve doğru tanının önemi eşsizdir. Kanserin oluşma mekanizmasını anlamak tanıda ve tedavide yol gösterebilmektedir.

HSP strese veya yüksek sıcaklığa yanıt olarak hücresel proteinlerin denatürasyonunu, açılmasını tersine çevirme veya engelleme işlevi gören bir protein grubudur. Geleneksel olarak HSP'ler, hücrelerdeki fizyolojik ve koruyucu rolleri nedeniyle moleküler şaperonlar olarak da bilinmektedir. HSP'ler genellikle moleküler ağırlıklarına göre sınıflandırılır. Isı şokuna bağlı 70-kDa protein 2 (HSPA2), HSP70 ısı şoku proteinleri ailesinin bir üyesidir (14). HSPA2 geni orijinal olarak, testiste spesifik ve yüksek oranda eksprese edilen kemirgen genlerinin insandaki karşılığı olarak karakterize edilmektedir (3, 4). Son zamanlarda, HSPA2, testis dışı dokuların karsinogenezine olası katılımı nedeniyle artan ilgiye sahiptir. HSPA2'nin aşırı ekspresyonu, küçük hücreli olmayan akciğer kanseri, servikal karsinom, özofagus skuamöz hücreli karsinom ve hepatoselüler karsinom dahil olmak üzere birçok insan malignitesinde tanımlanmaktadır (5, 7, 8, 15). Ancak TBK'larda HSPA2 ekspresyonunu araştıran bir çalışma literatürde bulunmamaktadır.

Çalışmamızda HSPA-2 ekspresyonu incelendiğinde 44 olgunun tamamında tümöral alanlarda kuvvetli boyanma izlenirken komşu tümörsüz alanlarda zayıf HSPA-2 pozitifliği saptandı. Tümörlü alanlarda tümörsüz alanlara göre HSPA-2 aşırı ekspresyonu izlendi. Sağkalım ile HSPA2 ekspresyonu arasında anlamlı ilişki bulundu ve artmış HSPA2 ekspresyonu izlenen hastalarda ölüm oranı belirgin derecede yüksekti.

HSPA-2 ekspresyonu ile klinikopatolojik parametreler arasındaki ilişki Spearman korelasyon analizi ile değerlendirildi. HSPA-2 aşırı ekspresyonu ile hastaların yaşı, cinsiyeti, makroskopik tümör boyutu, pT, histolojik alt tip, lenfovasküler invazyon, perinöral invazyon, nüks ve metastaz arasında anlamlı bir ilişki yoktu.

Bizim çalışmamıza benzer şekilde Zhang ve ark. özofagus karsinomlarında, Garg ve ark. mesane ve serviks karsinomlarında, Scieglinska ve ark. küçük hücreli dışı akciğer karsinomlarında, Fu ve ark. hepatoselüler karsinomlarda HSPA-2 aşırı ekspresyonunu göstermişlerdir (5-8, 15). Tüm bu çalışmalar ve bizim çalışmamız HSPA-2'nin karsinogeneziste etkili olabileceğini göstermektedir.

Zhang ve ark. HSPA-2 aşırı ekspresyonunun özofagus karsinomunda pT, klinik evre, pN ve nüks ile ilişkili olduğunu belirtirken Garg, Scieglinska, Fu ve arkadaşları, serviks, mesane, küçük hücreli dışı akciğer karsinomları ve hepatoselüler karsinomlarda HSPA-2 ekspresyonu ile TNM evre+sağkalım arasında anlamlı ilişki bulmuşlardır (5-8, 15). Çalışmamızda farklı organları kapsayan literatürdeki çalışmalara benzer şekilde artmış HSPA2 ekspresyonu izlenen hastalarda ölüm oranı belirgin derecede yüksekken TBK'nin çoğu prognostik parametresi ile HSPA2 ekspresyonu arasında anlamlı ilişki izlenmedi. Bunu çalışmamızın kısıtlılığı olarak da düşündüğümüz vaka sayımızın azlığına, histolojik tiplerin homojen dağılmamasına ve takip süremizin kısa olmasına bağlıyoruz.

5. SONUÇ

Çalışmamızın sonuçları TBK'lerde HSPA2 ekspresyonunun gösterilmesi açısından önemlidir. Literatürdeki çalışmalar ve çalışmamızdaki bulgular birlikte değerlendirildiğinde HSPA-2'nin tümör gelişiminde ve progresyonunda önemli rol oynayabileceğini düşünüyoruz. Ayrıca her ne kadar çoğu prognostik parametre ile anlamlı ilişki tespit edilmese de sağ kalım ile artmış HSPA2 ekspresyonu arasında anlamlı ilişki bulunması TBK'da yüksek HSPA2 ekspresyonunun prognostik belirteç olarak kullanılabileceğini düşündürmektedir. Diğer taraftan HSPA2 ekspresyonu ve TBK'lerdeki prognostik parametreler arasındaki ilişkiyi daha net açıklayacak veriler elde edebilmek için homojen dağılımlı, geniş hasta gruplu ve farklı histolojik alt tipleri içeren çalışmaların yapılması gerekliliğini düşünüyoruz.

Çıkar çatışması: Çalışmamızda çıkar çatışması olmadığını beyan ederiz.

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AKUT BİLİNÇ KAYBI İLE TANI ALAN MEDULLOBLASTOM OLGUSU

A CASE OF MEDULLOBLASTOM DIAGNOSED WITH ACUTE LOSS OF CONSCIOUSNESS

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Abstract / Özet

Giriş: Akut bilinç kaybı çocuklarda hayatı tehdit eden önemli bir durumdur. Santral sinir sistemi enfeksiyonları, intoksikasyonlar, metabolik-endokrin nedenler, status epileptikus, intrakranial kanamalar ve kitleler bilinç kaybının önemli nedenleri arasındadır. Bu olgu sunumu akut bilinç kaybı ile başvuran hastalarda öncesinde hiçbir belirti ve semptom olmasa bile intrakranial tümörlerin akılda tutulması gerektiğine dikkat çekmektedir.

Anahtar kelimeler: Medulloblastom, Bilinç değişikliği, Adölesan çocuk.

Objective: Acute consciousness disorders are an important life-threatening condition in children. Central nervous system infections, intoxications, metabolic-endocrine causes, status epilepticus, intracranial hemorrhages and masses are among the important causes of loss of consciousness. This case report draws attention to the fact that intracranial tumors should be kept in mind even if there are no previous signs and symptoms in patients presenting with acute consciousness disorders.

Keywords: Medulloblastoma, Loss of consciousness, Adolescent.

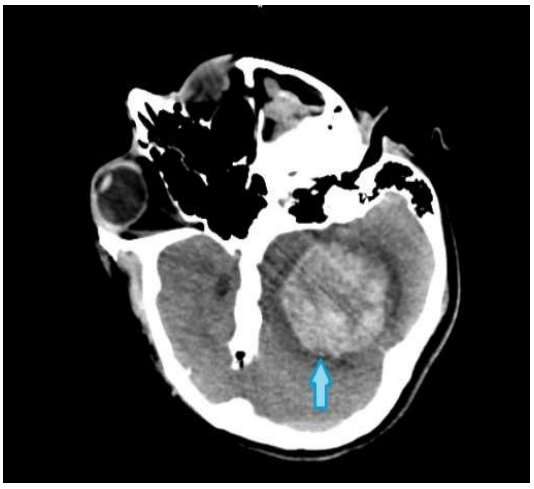
1. GİRİŞ

Akut bilinç kaybı çocuklarda hayatı tehdit eden önemli bir durumdur (1). Santral sinir sistemi enfeksiyonları, intoksikasyonlar, metabolik-endokrin nedenler, status epileptikus, intrakranial kanamalar ve kitleler bilinç kaybının önemli nedenleri arasındadır (1,3). Bu çalışmada akut bilinç kaybı ile başvurup medulloblastom tanısı alan hasta sunulmuştur.

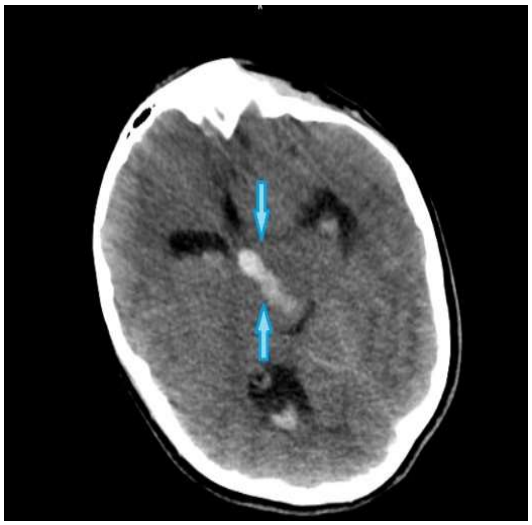
2. OLGU

On dört yaşında kız hasta ani bilinç kaybı şikâyeti ile hastanemiz çocuk acil kliniğine başvurdu. Alınan ilk anamnezde öncesinde tamamen sağlıklı olduğu ifade edilen hasta ailece piknik yaptıkları esnada önce başının ağrıdığını söylemiş. Sonra aniden bilinç kaybı yaşamış. Beş dakikadan kısa süre içinde bilinci açılmış. Hasta getirilirken yolda tekrar bilinç kaybı gelişmiş. Başvuru sırasında yapılan fizik muayenesinde; genel durumu kötü glasgow koma skalası 5 puan idi. Pupiller bilateral fiks dilate, ışık refleksi bilateral negatif, babinski bilateral pozitifti. Kalp tepe atımı 70/dk ritmik, oksijen satürasyonu %30 idi. Tansiyon arteriyel alınamadı. Hastaya ileri yaşam desteği basamakları uygulandı ve entübe edildi. Hastanın alınan kan tetkiklerinde özellik yoktu. Elektrokardiyografide özellik saptanmadı. Hasta stabilize edildikten sonra akut patolojiler açısından beyin bilgisayarlı tomografi çekildi. Tomografide 3. ve 4. ventrikülü dolduran hemorajik saha ve posterior fossadan lateral ventriküle uzanan kitle imajı (Resim 1, 2) izlenmesi üzerine hasta beyin cerrahi kliniğine intrakranial kitle ve intrakranial hemoraji ön tanıları ile konsülte edildi. Acil operasyona alınan hasta post operatif takip ve tedavi amacı ile çocuk yoğun bakım kliniğine devralındı. Operasyon esnasında alınan patoloji materyali medulloblastom olarak raporlandı. Yapılan ileri tetkik ve görüntülemeler sonucunda hasta inoperable kabul edildi. Beş aylık takibi sonrasında hasta ex oldu.

Resim 1: Posterior fossada 45*43 mm ebatlı 4. ventriküle uzanan intrakranial kitle



Resim 2: 3. ve 4. Ventrikülü dolduran hemorajik alan



3. TARTIŞMA

Bilinç kaybı, beyin faaliyetlerindeki bir bozulma nedeni ile uyku halinden hiçbir uyarıya cevap vermeme haline kadar giden bilincin kısmen ya da tamamen kaybolması halidir. Akut bilinç kaybı çocuklarda hayatı tehdit eden önemli bir durumdur. Ani kötüleşen çocuklarda çoğu zaman kliniğe eşlik eder. Santral sinir sistemi enfeksiyonları, intoksikasyonlar, metabolik-endokrin nedenler, status epileptikus, intrakranial kanamalar ve kitleler bilinç kaybının önemli nedenlerindendir (1,3). Bilinç kaybı ile gelen vakalarda sebebin ortaya çıkarılması hızlı tedavi ve sekelsiz iyileşme için büyük önem arz etmektedir. Olgumuzda piknik esnasında akut bilinç kaybı gelişmesi, hastanın adölesan yaşta olması ilk olarak intoksikasyon olabileceğini akla getirmiştir. Ancak yapılan nörogörüntülemede karşımıza beklenmedik bir şekilde kafa içi yer kaplayan bir kitle çıkmıştır. İleri evre medulloblastom tanısı alan bu kitlenin öncesinde hiçbir şekilde belirti ya da bulgu vermemiş olması oldukça dikkat çekici olmuştur.

Medulloblastom santral sinir sisteminin posterior fossaya yerleşim gösteren primitif nöroektoderm kökenli tümörüdür. Pediatrik yaş grubunda en sık görülen primer malign beyin tümörü olma özelliği taşır. Klinik bulgular hastaların yaşı, tümörün boyutu ve yayılımına göre çeşitlilik arz eder. Ergen yaş grubunda çoğunlukla ilk bulgu baş ağrısı ve kusmadır. Nöbet, çift görme, şaşılık, gözlerde kayma, yürüyüş bozukluğu, nörojenik mesane, bağırsak disfonksiyonu gibi çeşitli semptomlarla hastalar başvurabilir. Semptomların başladığı zamandan tanı konulmasına kadar geçen zaman dilimi düşük derece tümörlerde ortalama on ay iken, yüksek derece tümörlerde ise iki ila yedi ay arasında

değişkenlik göstermektedir (2). Medulloblastom hastalarında semptomların başlangıcı ve tanı sürecinin ayları bulması alışılagelmiş bir durumken bizim olgumuzda ileri evre bir medulloblastomun daha önceden herhangi bir belirti bulgu vermemesi ve akut bilinç kaybı ile başvurması ilgi çekici olmuştur.

4. SONUÇ

Çocuk acil başvurularının önemli nedenlerinden biri akut bilinç kayıplarıdır. Nedenin ortaya çıkarılması hızlı tedavi ve sekelsiz iyileşme için önemlidir. Medulloblastom çocukluk çağının sık rastlanılan malign beyin tümörlerinden biri olup ilk bulgu olarak bilinç kaybı ile nadir de olsa başvurabilir. Bu olgu sunumu akut bilinç kaybı ile başvuran hastalarda öncesinde hiçbir belirti ve semptom olmasa bile intrakranial tümörlerin akılda tutulması gerektiğine dikkat çekmektedir.

Çıkar çatışması: Çalışmamız ile ilgili hiçbir şekilde (mali vs.) çıkar çatışması olmadığını beyan ederiz.

Mali Destek: Bu çalışmada herhangi bir mali destek alınmamıştır.

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İZOLE KEMİK KİTLESİ: GRANÜLOSİTİK SARKOM OLABİLİR Mİ?

ISOLATED BONE MASS: GRANULOCYTIC SARCOMA?

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Abstract / Özet

Giriş: Granülositik sarkom (GS) granülositik prekürsör hücrelerin ekstramedüller yayılımından kaynaklanan lokalize bir tümördür ve literatürde; chloroma, monositik sarkom, myeloid sarkom, myeloblastom, ekstramedüller myeloid hücreli tümör olarak da adlandırılmaktadır. Genellikle kemik, periost, yumuşak doku, lenf nodları veya deride lokalize olur. En yaygın paranazal sinüsler ve orbita etkilenir. GS ayrıca akut miyeloid löseminin nadir bir başlangıç prezentasyonudur. **Olgu:** Bu olgumuzda bacak ağrısı ve üst solunum yolu enfeksiyonu bulgularıyla başvuran 2 yaş 10 aylık kız hasta sunulmaktadır. Hastamıza yapılan parmak ucu periferik kan ve kemik iliği aspirasyon yayma değerlendirmesinde blastik hücre popülasyonu görülmemiştir. Çocukluk çağı lösemileri bu nedenle ayırıcı tanıda dışlanmış olup tanıda gecikmeye neden olmuştur. Olgunun şu an yoğun kemoterapi ile tedavisi ve sağ kalımı devam etmektedir. **Sonuç:** Çocuklarda ekstramedüller kitle varlığında ayrıntılı muayene ve görüntüleme yöntemleri ile araştırılmalıdır. Akut lösemi tanısı ayırıcı tanıda yer almalıdır. Bu olgu sunumunda, torasik kostada destrüksiyona neden olan nadir bir granülositik sarkom vakasına yer verilmiştir. **Anahtar kelimeler:** akut miyeloid lösemi, granülositik sarkom, miyeloproliferatif hastalık, çocuk

Introduction: Granulocytic sarcoma (GS) is a localized tumor arising from extramedullary invasion of granulocytic precursor cells and is also called chloroma, monocytic sarcoma, myeloid sarcoma, myeloblastoma, extramedullary myeloid cell tumor in the literature. It is usually localized in bone, periosteum, soft tissue, lymph nodes or skin. The paranasal sinuses and orbit are most commonly affected.GS is also a rare initial presentation of acute myeloid leukemia. **Case report:** In this case report, we present a 2 years and 10 months old female patient who presented with leg pain and upper respiratory tract infection. No blastic cell population was observed in fingertip peripheral blood and bone marrow aspiration smear evaluation. Childhood leukemias were therefore excluded in the differential diagnosis, leading to a delay in the diagnosis. The patient is currently being treated with intensive chemotherapy and his survival continues. **Conclusion:** In the presence of extramedullary mass in children, it should be investigated with detailed examination and imaging methods. Acute leukemia should be included in the differential diagnosis. In this case report, a rare case of granulocytic sarcoma causing destruction of the thoracic costa is presented. **Keywords:** acute myeloid leukemia, granulocytic sarcoma, myeloproliferative disease, child

1. GİRİŞ

Granülositik sarkom granülositik prekürsör hücrelerin ekstramedüller yayılımından kaynaklanan lokalize bir tümörüdür ve literatürde; chloroma, myeloblastoma, monositik sarkom, ekstramedüller myeloid hücreli tümör, myeloid sarkom olarak da adlandırılmaktadır. Ender olarak görülür. Bu sarkomlar; akut myeloid lösemili (AML) hastalarda hastalığın seyri sırasında veya henüz kemik iliği invazyonu olmadan önce görülebilir (1). Granülositik sarkom ayrıca myelodisplastik sendrom, kronik myeloid lösemi, kronik idiopatik myelofibroz, hipereozinofilik sendrom ve polisitemia vera ile ilişkili olarak da görülebilir (2). Kemik, periost, yumuşak doku, lenf nodları veya deriyi tutabilmektedir. En yaygın paranazal sinüsler ve orbita tutulur. Ayrıca genitoüriner sistem, gastrointestinal sistem, safra yolları, tükrük bezleri, meme, serviks, mediasten, plevra, kalp, periton, santral sinir sistemi de tutulabilir (3). Ayırıcı tanıda özellikle Burkitt lenfoma, blastik tipi, diffuz büyük hücreli lenfoma ve çocukluk çağının rabdomyosarkom, nöroblastom ve primitif nöroektodermal tümörler grubu yuvarlak mavi hücreli malign tümörleri önemlidir. Kemik iliği tutulumu olmadan, izole kitle ile tanı konabilir, kemik iliği tutulumu ve kitle eş zamanlı olabilir ya da tedavi sürecinde kitle ortaya çıkabilir. En sık birliktelik gösterdiği mutasyonlar translokasyon (8,21), invazyon (16), 11q23 MLL yeniden düzenlenmesidir.

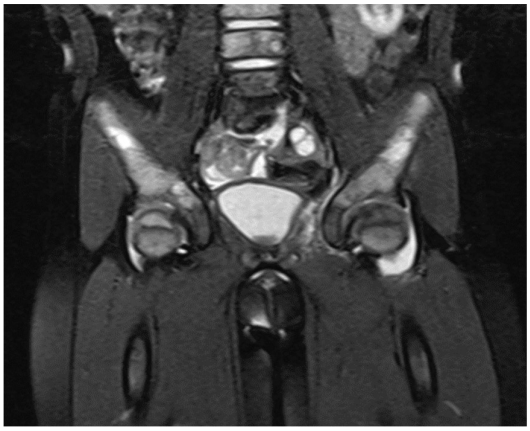
2. OLGU

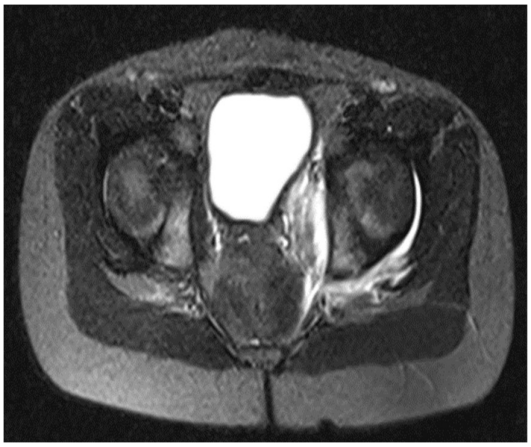
2 yaş 10 aylık kız hasta yeni başlayan bacak ağrısı, yürüyememe ve birkaç haftadır olan öksürük, ateş, şikayetlerinin olması üzerine hastanemize başvurdu. Hastanın başvurusunda özgeçmiş ve soygeçmişinde özellik yoktu. Sistem muayenesinde karaciğer kot altı 2cm palpe edildi. Laboratuvarda; lökosit sayısı: 12140/mm3 (4000-10000) hemoglobin: 11,6 g/dL, trombosit: 646000/mm3 (150000-400000) sedim:60 mg/h, laktat dehidrogenaz enzimi (LDH): 370 U/L (135-214), Anti nükleer antikor: negatif, Anti Streptolizin O <50, C3: 1,82, C4:0,348 olarak bulundu. Hastanın periferik kan yayması normal olarak değerlendirildi. Hastanın radyolojik değerlendirilmesinde kalça manyetik rezonans görüntülemesi yapıldı Kalça eklemlerinde artmış sıvı, sol kalça eklemi sinoviyumunda kontrastlanma ve eklem çevresinde yumuşak doku ödemi, pelvis kemiklerinde hiperintens lezyonlar görüldü (Resim1,2). Hastanın çekilen bilgisayarlı toraks tomografisinde altıncı kostada destrüksiyona neden olan yaklaşık 33x13 mm boyutlarında yumuşak doku kitlesi görüldü (Resim 3) Kemik ağrısı olan hastaya kemik iliği aspirasyonu yapıldı ve atipik hücre veya blastik hücre popülasyonu saptanmadı. Flow sitometrik inceleme bu neden ile planlanmadı.

Ayırıcı tanıda öncelikle Ewing sarkomu, osteosarkom, langerhans hücreli histiyositoz düşünüldü. Hastaya toraksik bölgedeki kitleden yapılan tru-cut biyopsisi patolojik incelemesinde "Küçük Yuvarlak Hücreli Tümör" tanısı konuldu. Patolojide öncelikle primitif nöroektodermal tümörler/ Ewing sarkomu grubu tümörler düşünüldü. Hastanın kemik iliği incelemesinin normal olması ve mevcut radyoloji ve patoloji sonuçlarının neticesinde hastaya metastatik primitif nöroektodermal tümörler/ Ewing sarkomu tanısı konuldu JCO (journal of clinical oncology) 2020 protokolü başlandı. "Vinkristin-Topotekan-Siklofosfamid/ifosfamid-Etoposid/Vintistin-Doksorubusin-Siklofosamid" tedavileri verildi.

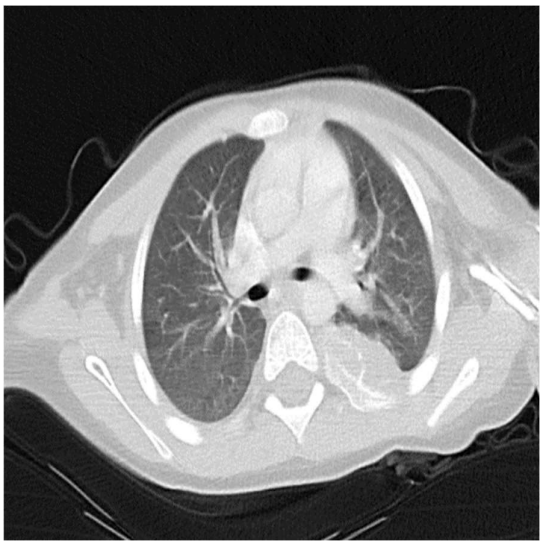
Hastanın tedavisinin devamında radyoterapi alıp almayacağına karar vermek için ilk biyopsi yapılan bölgeden eksizyonel biyopsi yapıldı. Biyopsi patoloji incelemesi sonucu AML olarak sonuçlandı. Biyopsi materyalin ön tanısı AML olmadığı için genetik tetkik gönderilemedi. Hastaya tekrar kemik iliği incelemesi yapıldı ve normal olarak değerlendirildi. Hastaya kemik kitlesi ile prezente olan granülositik sarkom tanısı konuldu. AML BFM 2019 Protokolü başlandı. Doku uygun verici adayı olmayan hastanın kemik iliği remisyonda seyrettiği için kemik iliği nakil kolunda değerlendirilmemiş olup idame tedavisine devam edilmektedir.

Resim 1 ve 2: Sakral MR'da, sol kalça eklemi çevresinde posteriorda yoğun yumuşak doku ödemi, sol asetabulum posterior duvar, iskial ramus çevresinde periost reaksiyonu ve buna bağlı kontrastlanma





Resim 3: Sol hemitoraks posteriorda 6. posterior kotta destrüksiyona neden olan yaklaşık 33x13 mm boyutlarında yumuşak doku kitlesi.



3. TARTIŞMA

Lösemiler çocukluk çağı kanser vakalarının yaklaşık üçte birinini oluşturur. Lösemilerin %80'ini akut lenfoblastik lösemi, %15'ini ise AML'ler oluşturur (4). Çocukluk çağında GS, AML seyri sırasında %4-5 oranında gözlemlenir (1). Kloromalar hemen hemen her yerde, en yaygın olarak kafatası, orbita ve paranazal sinüslerde bildirilmiştir (4). Granülositik sarkomlar, lösemik hücrelerin orbita, fasyal sinüs, uzun kemikler, paravertebral alan, ve lenf nodlarını invaze etmesiyle oluşan ekstrameduller kitlelerdir (5) En sık yerleşim yerleri cilt (%13-22), ardından kemiğin subperiosteal alanıdır (6). Hastamızda ise altıncı posteriyor kotta destrüksiyona neden olan yumuşak doku kitlesi mevcuttu. Granülositik sarkomlar çoçuklarda löseminin prezentasyonu, nüksü olarak veya hastalığın seyri sırasında herhangi bir zamanda ortaya çıkabilir (7). Bizim olgumuzda olduğu gibi, bazen AML'nin klinik başlangıcından önce gelirler ve tanı konması zordur.

Bu hastalarda tanı anında detaylı bir ayırıcı tanı yapılması önemlidir. Tanıya yönelik seçilecek doğru inceleme yöntemleri hastalığın seyrini etkilemekte ve hızlı tedaviye başlamada rol oynamaktadır. Hastalara tanı anında GS tanısı koymak zordur. GS primer myeloid neoplazi tanısı olmaksızın izole kitle şeklinde vücudun her yerinde ortaya çıkabilmektedir. Bu nedenle benzer histomorfolojiye sahip tümörler ile ayırıcı tanı yapılması önemlidir. Neiman ve arkadaşlarının 61 vakalık GS serisinde; vakaların %44'ü ilk başvuruda doğru tanı almış. İzole kemik tümörü ile başvuran, lösemi tanısı alması gereken hastaların ise sarkom veya malign lenfoma tanısı aldığını bildirmiştir (8). Byrd ve arkadaşları 154 izole GS vakasının 71'inde (%46) konulan ilk tanının yanlış olduğunu bildirdi. Bahsedilen birinci tanı genellikle nonhodgin lenfoma veya sarkomdu (6). Reinhardt ve arkadaşlarının çalışmasında 34 çocuktan 12'sinde (%35) tanı gecikti veya başlangıçta yanlış konuldu (7). Yapılan başka bir çalışmada vakaların %35'inde ilk tanı anında hata bildirilmişti (7, 9). Bizim hastamızda başta Ewing sarkomu tanısı almıştı, AML'ye sekonder GS tanısını başvurusunun dokuzuncu ayında alabildi. AML'nin kemik iliği dışındaki izole tutulumlarının AML olarak ele alınması gerektiği kabul edilmektedir (10). Ekstramedüller hastalığın prognostik önemi tartışmalıdır. Bazı merkezler kötü prognoz olarak değerlendirirken (10) , birçok merkezde daha iyi sağ kalım oranları bildirilmektedir. Bu nedenle bu hastaları standart AML kürleri ile tedavi etmektedir (1, 10). Biz de hastamıza standart AML kemoterapi kürü ile tedavi uyguladık. İzole GS'nin tedavisinde tek başına lokal radyoterapi endikasyonu yoktur ve kemoterapi ile kombinasyon halinde prognozu iyileştirmez (11). Bu yüzden hastamıza radyoterapi uygulanmadı.

4. SONUÇ

Granülositik sarkom, AML'nin geliş bulgusu olarak hayli seyrektir. Çocuklarda ekstramedüller kitle varlığında, detaylı bir fizik muayene ve hedefe yönelik görüntüleme yöntemleri ile araştırılmalı ve bir akut lösemi tutulumu olabileceği ayırıcı tanıda yer almalıdır. Küçük yuvarlak mavi hücreli tümörler, bazen patolojik olarak tanıda zorluklar yaşanmasına sebep olabilmektedir. Tedaviye cevap alınamadığı durumlarda biyopsinin tekrarlanması, esas tanıya ulaşmak ve tedaviyi yönlendirmek için faydalıdır.

Çıkar çatışması: Yazarlar çıkar çatışması olmadığını beyan eder.

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