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Bu sayımızda 4 orijinal makale ve 4 olgu sunumu yer alıyor.

Dergimize çok sayıda olgu sunumu şeklinde makale geliyor.
Bunları titiz bir hakemlik sürecinden geçirdiğimizi ve bazı makaleleri
bu sürecin sonunda kabul edemediğimizi üzülerek bildirmek istiyorum.
Olgu sunumları bilimsel literatüre katkı sunmakla birlikte bilimsel kanıt düzeyi
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ÖZGÜN ARAŞTIRMA/ORIGINAL ARTICLE

Serebral Beyaz Cevherde Diffüzyon Değişiklikleri: Yaş ve Cinsiyetin Etkisi

Diffusion Changes in Cerebral White Matter: The Effect of Age and Gender

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Key Words:
Apparent Diffusion Coefficient
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ÖZ

Amaç: Myelinasyon, doğumdan sonra devam eden dinamik bir süreçtir. MR görüntüleme tekniklerinden biri olan difüzyon ağırlıklı görüntüleme (DAG) ve görünen difüzyon katsayısının (GDK) ölçümü, normal beyin gelişimi için bir kılavuzdur. Bu çalışmanın amacı çocuklarda normal miyelinasyon gelişiminin izlenmesinde DAG ve GDK haritalarının rolünü göstermek ve korpus kallozum (KK) ve temporal bölgelerde (TB) GDK değerlerini belirlemektir.

Gereç ve Yöntem: MR görüntülerinin yeniden değerlendirildiği retrospektif çalışmaya 57'si erkek toplam 112 çocuk (ortalama yaş 98 ± 52,9 ay) dahil edildi. Katılımcılar 0 ile 202 ay arasında dört yaş grubuna ayrıldı. DAG ve GDK haritaları her iki TB'de KK'nın her iki tarafından ve parahipokampal sulkus beyaz cevherinden elde edildi. GDK değerlerinin ortalamaları belirlendi.

Bulgular: Yaş ilerledikçe GDK değerlerinin tüm ölçüm alanlarında düştüğü görüldü ($p< 0,005$). Bu değişiklik TB'nin her iki tarafında ve KK genu ve gövdenin sol yarısında önemliydi. ADC değeri cinsiyete ve ölçülen tarafa göre değişmedi.

Sonuç: GDK değerleri yaş ilerledikçe azalmaktadır. KK ve TB'nin ADC değerleri kullanılarak beyinde normal myelinasyon gelişimi ve ergenliğin neden olduğu değişiklikler diğer patolojilerden ayırt edilebilir.

ABSTRACT

Objective: Myelination is a dynamic process that continues after birth. One of the MR imaging techniques diffusion-weighted imaging (DWI) and measurement of apparent diffusion coefficient (ADC) is a guide for normal brain development. The aim of this study is to show the role of DWI and ADC maps in monitoring the normal development of myelination in children, and to determine ADC values in corpus callosum (CC) and temporal regions (TL).

Material and Method: A total of 112 children (mean age 98 ±52.9 months), 57 of whom were male, were included in the retrospective study in which MRI images were reevaluated. Participants were divided into four age groups between 0 and 202 months. DWI and ADC maps were obtained from both sides of CC and parahippocampal sulcus white matter in both TL. Averages of ADC values were determined.

Results: It was found that ADC values decreased in all measurement areas as the age progressed ($p< 0.005$). This change was significant on both sides of the TL and left half of the CC genu and body. ADC value did not change according to gender and measured side.

Conclusion: ADC values decrease with progressive increase of age. Using ADC values of CC and TL, the development of normal myelination in the brain and changes caused by puberty can be distinguished from other pathologies.

Keçeli M. Serebral beyaz cevherde diffüzyon değişiklikleri: Yaş ve cinsiyetin etkisi. Hitit Med J 2021;3(3):63-70. DOI: 10.52827/hititmedj.88893

Introduction

Brain development in children is a dynamic process that involves white matter maturation. This process is characterized by axonal development and myelination (1,2). The microstructural organization of white matter develops under the influence of these two components (3). Myelination is a continuous process and an accessible marker of maturation in the brain of developing infants. Several researchers have documented the changes in magnetic resonance imaging (MRI) corresponding to myelination of the white matter in neonates and infants; a relatively normal adult appearance can be seen at 2 years of age, and all major fiber tracts can be identified by 3 years of age (4,5). With the development of diffusion-weighted imaging (DWI), it has become possible to evaluate these effects.

Myelination begins at around 20 weeks gestational age and continues up to around 2 years of age. As myelination precedes, the water content of the white matter decreases. Changes in the signal of the white matter due to myelination are demonstrated at different ages on MRI (6,7). An important area in the myelination process is the corpus callosum (CC) (8,9). Sex steroid hormone receptor densities are high in the medial part of the cerebral temporal lobes and cortical gray matter (10). It has been shown that puberty-related myelin maturation differs according to gender (11). However, none of the studies conducted have analyzed the developmental changes of these structures together with this area before and after puberty.

MRI measurements of the Brownian motion of water molecules can be illustrated using DWI, apparent diffusion coefficient (ADC) maps, diffusion tensor imaging (DTI), and tractography (5,8,12,13). ADC is a metric of the magnitude of diffusion within cerebral white matter tissue (14). Callosal microstructural integrity is better explored by DWI and ADC maps (15). ADC values have been reported to better reflect white matter maturation in the fiber pathways than fractional anisotropy (FA) measures (13). Both values can be used to evaluate the white matter structure, especially in major psychiatric illnesses (16,17).

In this study, it was aimed to determine the changes before and after puberty by evaluating the DWI and ADC values of the specific white matter region in children and adolescents.

Material and Method

After obtaining ethics committee permission (KTO Karatay University Medical School, 17.05.2020/decision number: 2020/036), cranial MRI images taken between January of 2018 and 2020, obtained via the standard protocol in our imaging department, of 112 participants (57 males, 55 females, mean age of 98±52.9 months), were reevaluated. Attention was paid to the absence of ethnic differences among the participants. Using the information obtained from the hospital information system, cases of normal physical examinations and laboratory examinations were selected and included in the evaluation. The clinical history of each patient was carefully inspected by a pediatrician to rule out developmental abnormalities, chronic headaches, and migraines. No pathological findings were found in the imaging of these cases, which were imaged due to nonspecific complaints, such as headache and dizziness, except for sinusitis and mastoiditis. Children evaluated by the pediatric psychiatry and genetic diseases departments were excluded from the study. To facilitate interpretation, the participants were divided into four age groups, according to their ages calculated from their birth dates, comprising 0-48 months, 49-96 months, 97-144 months, and 145-202 months.

MRI scans were acquired using a Siemens Magnetom Aera 1.5 T (Global Siemens Healthcare, Erlangen, Germany). A standard head coil was used for radiofrequency transmission and reception of the MR signal, and restraining foam pads were utilized to minimize head motion. Axial plane T1-weighted images were first obtained to verify the head position of the participant and image quality. Next, T2-weighted axial and coronal plane images were acquired, according to an axial plane parallel to the anterior-posterior commissures, for clinical neurodiagnostic evaluations. Then, axial plane fluid-attenuated inversion recovery (FLAIR) sequence images were obtained (Figure 1). In our imaging unit, in daily practice, diffusion-weighted imaging is added in addition to standard sequences in cranial MRI examinations. Specifically, three gradients were acquired in three orthogonal directions. ADC map images obtained in the axial plane in our department were reconstructed in the coronal plane using the standard multi-plane imaging technique in order to take measurements from anatomical structures during image archiving and re-evaluation in the communication system (Figure 2).

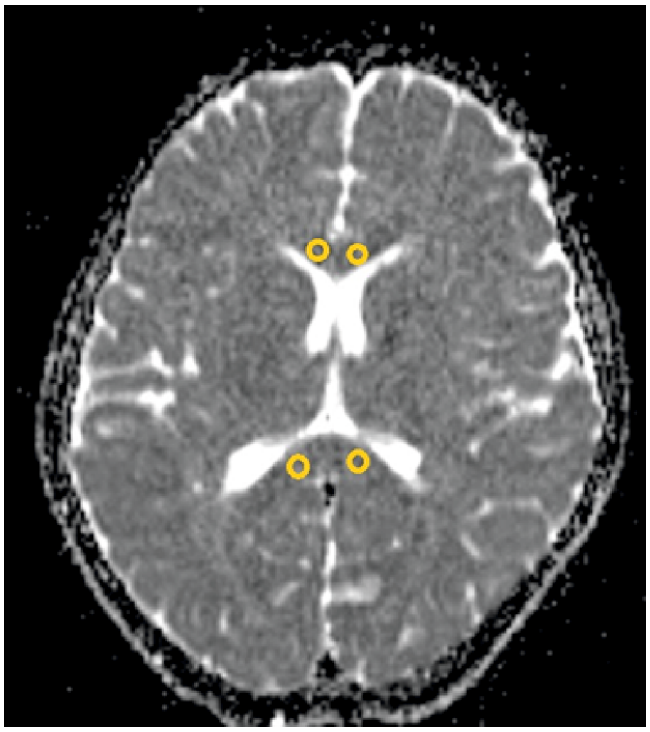

Figure 1. On the ADC map (axial plane) obtained, the regions of interest placed in the corpus callosum genu and splenium.
(RCC head: The head of Corpus Callosum right side,
LCC: The head of Corpus Callosum left side,
RCC bd: The body of Corpus Callosum right side,
LCC bd: The body of Corpus Callosum left side,
RCC spl: The splenium of Corpus Callosum right side,
LCC spl: The splenium of Corpus Callosum left side,
Temp R: Temporal lobe: Cerebral white matter in right parahypocampal sulcus region,
Temp L: Cerebral white matter in left parahypocampal sulcus region.)

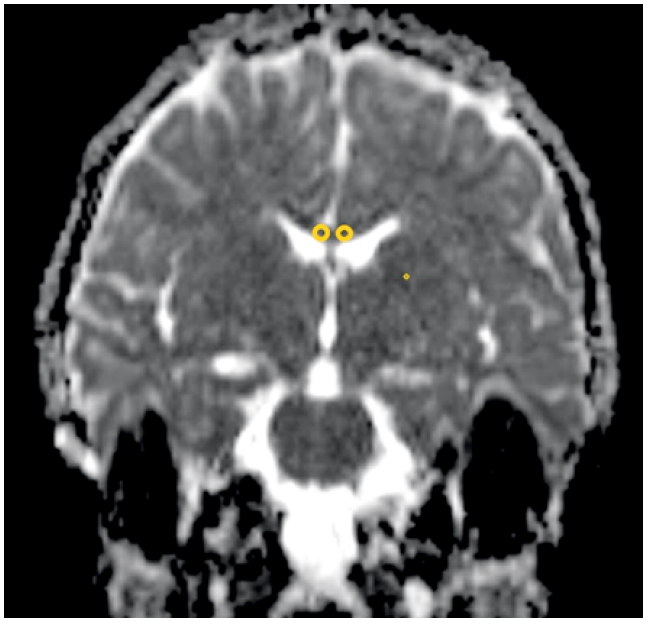

Figure 2. On the ADC map (reconstruction coronal plane) obtained, the regions of interest placed in the corpus callosum genu and splenium.

In our department, imaging of patients in their first year is obtained during physiological sleep after the baby has been fed. Older children who cannot cooperate are left sleepless before the examination and imaged during their physiological sleep. If imaging is not possible under these conditions, sedation is applied. To eliminate the possible effect of sedation on the results, the images to be evaluated were selected from MRI obtained from non-sedated participants. Images with artifacts were not included in the study.

Determination of the cellular density of the tissue, which is one of the advantages of MRI examination, can be made with the ADC map calculated from DWI. Measurements made from areas selected from the ADC map provide diagnostic benefit in the differentiation of many pathologies. With the region of interest (ROI) marking options available to the user, this measurement can be carried out electronically in a safe and simple way. The ADC is used reliably in the differentiation of CNS lymphoma from other malignancies and in the response of CNS tumors to chemotherapy (18). Using this feature of the DWI and ADC map, the corpus callosum and temporal lobe white matter, which have high hormone receptors in puberty development, were used to measure ADC values in the cerebral tissue. Eight ROIs were evaluated for all of the subjects, including the white matter adjacent to the parahippocampal sulcus in the bilateral temporal lobe (TL), bilateral genu, and body and splenium of the CC sections. Landmarks for callosal subregions were adapted from the design reported in the studies of Bonekamp and Prunas (13,16). A round-shaped ROI was placed in these areas on the b=0 DWI and ADC map. Measurement areas were marked manually. Circular ROIs standardized at 5 pixels (corresponding to an area of 0.2 cm2) were placed in the determined regions. In the genu and splenium of the CC, ADC measurements were taken from the axial plane (Figure 1, 3). In the body of the CC, ADC measurements were taken from the reconstructed coronal plane in order to reduce the partial volume artifacts that may occur due to close vicinity with the ventricular system (Figure 2). Since there was no loss of information in the ADC map, which is a mathematical map, with reconstruction algorithms, measurements could be made on these images. In the axial plane, the ADC map was measured from the white matter adjacent to the parahippocampal sulcus adjacent to the temporal horn of the lateral ventricle on both sides (Figure 3). The values obtained from the ADC map were recorded in mm/s2. All of the measurements were performed in all four age groups. The ADC values were compared with the average age in the age group.

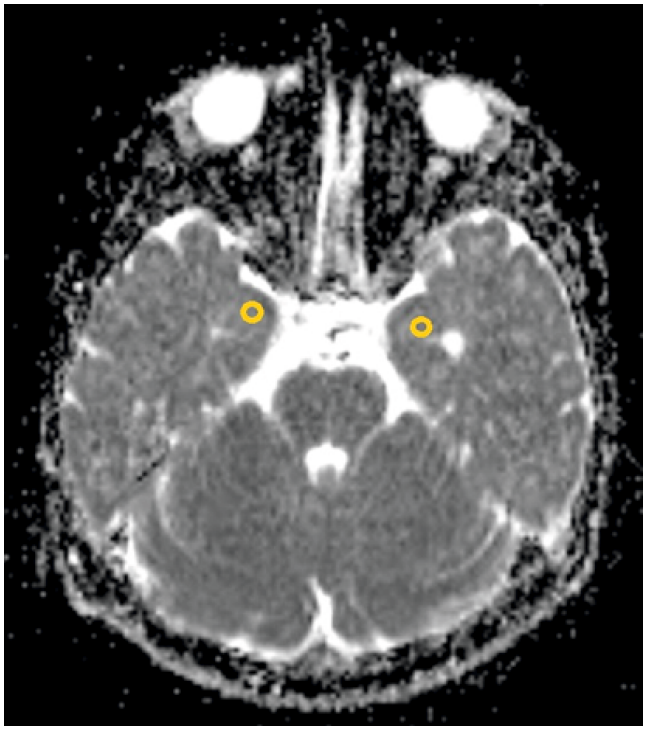

Figure 3. On the ADC map (axial plane) obtained, the regions of interest placed in the parahypocampal region in temporal lobes.

Reevaluation was performed by a single experienced pediatric radiologist who was interested in pediatric neuroradiology. For each participant, each measurement was repeated two times at three-day intervals; the average of the values obtained was recorded. Intrarater reliability was investigated for each measurement.

The sample range of this study was determined by taking the power (strength of the test) for each variable as at least 80% and the type 1 error as 5%. The Kolmogorov-Smirnov (n>50) and skewness-kurtosis tests were employed to determine whether the measurements in the study were normally distributed, and parametric tests were applied after determining that the measurements were normally distributed. Descriptive statistics for continuous variables in this study were as follows: average, standard deviation, minimum, and maximum. For the categorical variables, they were presented as numbers and percentages. The independent t-test and one-way analysis of variance (ANOVA) were applied in comparing the measurements made according to the gender and age groups. The kappa statistical test was used to investigate the reliability of repeated measurements of ADC values made by a single rater. ANOVA was followed by the Duncan multiple range test to determine differences between the different groups. The paired t-test was employed in the comparison of right-left measurements separated in accordance with gender. Pearson correlation coefficients were calculated to determine the relation between the age groups and the measurements. The statistical significance level (α) was taken as 5% in the calculations and IBM SPSS Statistics for Windows 25.0 (IBM Corp., Armonk, NY, USA) was used for the calculations.

Results

The study included 112 participants, 57 of whom were male (50.9%) and 55 of whom were female (49.1%). The average age was 98 ± 52.9 months. Information on the descriptive statistics is shown in Tables 1 and 2.

Table 1. General characteristics of the participants.

		N	%
Sex	Boy	57	50,9%
	Girl	55	49,1%
	Total	112	100,0%
Age (month)	0-48	28	25,0%
	49-96	30	26,8%
	97-144	34	30,4%
	145-202	20	17,9%
	Total	112	100,0%

Table 2. Descriptive information about the ages of the participants.

		N	Mean	Std. Dev.	Min.	Max.
Age (month)	Boy	57	93,00	54,546	12	201
	Girl	55	103,33	51,186	18	202
	Total	112	98,07	52,939	12	202

It was observed that there was a statistically significant and very high level of agreement at all levels in the kappa test, which determines intra-rater agreement in the measurement of repeated ADC values (κ=0.839-0.895 for measurements made from the eight specified regions; $p<0.05$).

The ADC values obtained from the levels determined in CC and the TL level were not related to gender (p=0.240-0.847). Apparently, the gender of the individual did not cause a significant change in the ADC values. The distribution of the average of the ADC values in the determined regions by gender is shown in Figure 4.

The mean ADC values determined by considering gender were as follows: from CC genu 0.75 × 10-5 mm/sn², from CC body 0.82 × 10-5 mm/sn², from CC splenium 0.77 × 10-5 mm/sn², 0.78 × 10–5 mm/sn², and from TL 0.81 × 10-5 mm/sn². The ADC values and age groups were compared (Table 3), and it was observed that the ADC value decreased with increasing age. A statistically significant correlation was found between the ADC values obtained

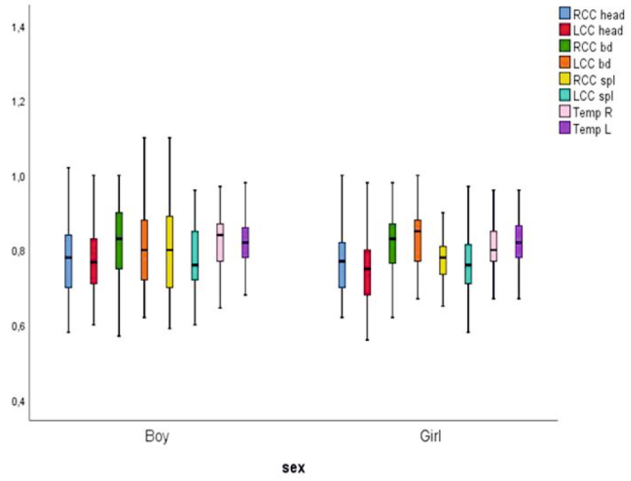

Figure 4. This graph shows the change of ADC values according to genders and their ADC mean values according to the cerebral regions examined.

from the genu and body sections from the left part of the CC and both parts of the TL and the age groups (p<0.05). This correlation was weaker at the other measurement points (p = 0.45-0.50).

The ADC values obtained from the genu part of the right part of the CC in the 0-48 and 49-96 month age groups were similar. The 0-48 month age group had higher ADC values than the 97-144 and 145-202 month age groups. Similarly, the ADC values obtained from the left side genu of the CC in the 0-48 and 145-202 month groups were similar. Higher values were found in the 0-48 month group than those of 49-96 and 97-144 month groups.

The 0-48 and 49-96 month age groups were similar with regards to the measurements conducted on the body section in the right part of the CC. The values were higher in the 0-48 month age group than in the other age groups. In the measurements obtained from the same level in the left part of the CC, values of the 0-48 month age group were higher than those of the other age groups.

In measuring the ADC values performed on the splenium level of the CC, the 0-48 and 49-96 month age groups were similar, while the values in these groups were higher than those of the 97-144 and 145-202 month age groups. The 145-202 month age group had a lower value than the other age groups in the left part.

A statistically significant difference was found on both sides in the measurements performed at the TL level according to age (p<0.05). In the right part, the 0-48 month age group had higher values than the other age groups. In the left part, the 0-48 and 97-144 month age groups were different from each other.

Table 3. The comparison results of ADC values by age groups (ignoring gender).
ADC: apperant diffusion coefficient,
RCC head: The head of Corpus Callosum right side,
LCC: The head of Corpus Callosum left side,
RCC bd: The body of Corpus Callosum right side,
LCC bd: The body of Corpus Callosum left side,
RCC spl: The splenium of Corpus Callosum right side,
LCC spl: The splenium of Corpus Callosum left side,
Temp R: Temporal lobe: Cerebral white matter in right parahypocampal sulcus region,
Temp L: Cerebral white matter in left parahypocampal sulcus region.

		N	Mean ($x10^{-5}$)	Std. Dev.	Min.	Max.	*p.
RCC genu	0-48 month	28	,8089^{a}	,10436	,60	1,02	,045
	49-96 month	30	,7767^{ab}	,09904	,62	,95	
	97-144 month	34	,7521^{b}	,08580	,62	,92	
	145-202 month	20	,7410^{b}	,07518	,58	,86	
	Total	12	,7709	,09493	,58	1,02	
LCC genu	0-48 month	28	,8150^{a}	,13407	,60	1,20	,003
	49-96 month	30	,7382^{b}	,08218	,60	,90	
	97-144 month	34	,7265^{b}	,08395	,56	,89	
	145-202 month	20	,7645^{ab}	,07338	,62	,88	
	Total	112	,7585	,10193	,56	1,20	
RCC bd	0-48 month	28	,8671^{a}	,09786	,68	1,20	,010
	49-96 month	30	,8273^{ab}	,09483	,66	,97	
	97-144 month	34	,8009^{b}	,10760	,57	1,00	
	145-202 month	20	,7760^{b}	,08494	,62	,90	
	Total	112	,8201	,10194	,57	1,20	
LCC bd	0-48 month	28	,8700^{a}	,08287	,68	1,00	,007
	49-96 month	30	,8067^{b}	,08079	,68	1,00	
	97-144 month	34	,7974^{b}	,12094	,57	1,10	
	145-202 month	20	,7810^{b}	,08849	,66	,90	
	Total	112	,8151	,10074	,57	1,10	
RCC spl	0-48 month	28	,8229^{a}	,12073	,64	1,10	,050
	49-96 month	30	,8080^{a}	,11391	,60	1,10	
	97-144 month	34	,7774^{b}	,08621	,60	,96	
	145-202 month	20	,7480^{b}	,09833	,59	,98	
	Total	112	,7917	,10735	,59	1,10	
LCC spl	0-48 month	28	,7971^{a}	,07798	,65	,97	,012
	49-96 month	30	,8033^{a}	,09245	,65	1,10	
	97-144 month	34	,7609^{ab}	,11102	,60	1,10	
	145-202 month	20	,7285^{b}	,06268	,58	,89	
	Total	112	,7755	,09107	,58	1,10	
Temp R	0-48 month	28	,8621^{a}	,06315	,76	,98	,001
	49-96 month	30	,8097^{b}	,05968	,68	,89	
	97-144 month	34	,7822^{b}	,06503	,62	,88	
	145-202 month	20	,7720^{b}	,09534	,51	,95	
	Total	112	,8113	,07545	,51	,98	
Temp L	0-48 month	28	,8675^{a}	,06484	,74	1,00	,002
	49-96 month	30	,8317^{ab}	,11151	,70	1,23	
	97-144 month	34	,7865^{b}	,06391	,68	,92	
	145-202 month	20	,7845^{b}	,07134	,67	,96	
	Total	112	,8165	,08533	,67	1,23	

**Significance levels according to ANOVA test results*
a, b: shows differences between groups (Duncan post-hoc test)

It was observed that the ADC values obtained from the right and left parts of the CC and TL did not statistically significantly vary between the age groups (p=0.14-0.859).

Correlation analysis results between age groups and the ADC values are shown in Table 4, separated by gender, where it can be seen that a statistically significant negative correlation was observed in the male patients between the age groups and the ADC values obtained from the genu section of the right part of the CC. The degree of this relation was 37.2%. On the other hand, no statistically significant correlation was observed in the female patients between the age groups and the obtained values. A negative correlation was observed in the females between the age groups and the ADC measurements performed on the splenium section of the left part of the CC. The degree of this correlation was 39.5%. On the other hand, no significant correlation was observed in the males. An inverse relationship was found between the ADC values and age, although the correlation was not high. The diffusion restriction and ADC value decreased as the age of the participants increased.

Table 4. The gender-separated correlation analysis between age and ADC values. Abbreviations are the same as in table 3.

		Boy (n=57)	Girl (n=55)
		Age (month)	Age (month)
RCC genu	r	-,372**	-,176
	p	,004	,199
LCC genu	r	-,307*	-,119
	p	,020	,388
RCC bd	r	-,320*	-,323*
	p	,015	,016
LCC bd	r	-,306*	-,283*
	p	,020	,036
RCC spl	r	-,228	-,282*
	p	,088	,037
LCC spl	r	-,237	-,395**
	p	,076	,003
Temp R	r	-,348**	-,354**
	p	,008	,008
Temp L	r	-,225	-,218
	p	,092	,110

*$p<0.05$; **$p<0.01$; r:Pearson corelation coefficient

Discussion

The aim of this study was to show the changes in the size of the diffusion of water molecules in the determined age groups and white matter areas. ADC is a measure of the magnitude of diffusion of water molecules within tissue, and it is commonly clinically calculated using DWI. The ADC values are calculated automatically by software and then displayed as a parametric map that reflects the degree of diffusion of water molecules through different tissues. Then, by use of a dedicated workstation, ADC measurements are recorded for a given region by drawing ROIs on the ADC map (19). The ADC of tissue is expressed in units of mm2/s. The ADC value of the white matter in adults, regardless of gender, is roughly 0.670 to 0.802×10-5 mm/s2. There is no unanimity regarding the boundaries of the range of normal diffusion, but ADC values less than 1 to 1.1×10-5 mm2/s are generally acknowledged in adults as indicating restriction. However, this is entirely dependent on the organ being imaged and the pathology (14).

The FA is a quantitative index that provides information on the spatial orientation of fiber tracts and reflects the axonal tract coherence forming the white matter microstructure. Thus, the FA is high if axonal integrity and directionality are maintained, while it is low in areas of axonal loss and/or axonal demyelination. The white matter microstructure organization can thus be described by both ADC and FA, which are indeed considered as complementary indexes, showing alterations of white matter when increased and decreased, respectively (20). To further support the influence of myelination, a strong correlation was found between the FA and nb0 (b=0) changes. It has been suggested that T2 shortening is caused by the water loss induced by the development of the hydrophobic inner layer of the myelin sheath. Strong correlations between the nb0 and FA in many regions have suggested that myelination, or at least axonal properties that mature concomitantly with myelination, are an important facet of the FA increase. However, myelination is not the sole determining factor for anisotropy (5).

The FA values and DTI method used in previous studies were not used as an assessment tool in this study. In the presented study, only ADC value measurements were used. The aim was to determine the interpretability of the normal myelination process with the diffusion value obtained, without the need for an additional procedure in daily radiology practice. Another aim was to obtain basic mathematical values that would provide simpler evaluation without the need for advanced technical applications in order to demonstrate diffusion changes that might occur with pubertal process and evaluate pubertal pathologies.

According to the results of this study, differences were found in ADC values showing the mathematical value of diffusion in children in different age groups and in certain parts of CC and TL white matter. The ADC values obtained from the genu, body, and splenium of the CC and from the

TL white matter from both sides were found to be higher when compared to the other areas in the study. The most significant statistical changes in these regions were obtained in the genu and left part of the body parts of the CC and bilateral TL white matter areas. When all of the measurements were interpreted, it could be understood that the ADC values decreased with age. Non-myelinated white matter has high water and low molecular contents, and so it showed non-restricted ADC values. Neil et al. imaged newborns at 36 h after birth and measured the ADC values in all of the subjects. They reported that a correlation existed between the ADC values and the gestational age of the newborns, suggesting the potential role of brain water in the elevation of ADC values in neonates (21). With the progression of myelination, there is a drop in the water content and progressive increase of the molecular contents, and consequently. more restricted ADC values, as confirmed by Forbes et al., Löbel et al., and Zhai et al. (22-24). They used diffusion to detect the progression of myelination and their results showed a significant decrease in the ADC values in the white matter with an increase in the age of their subjects. In this study, it was observed that the ADC values decreased with age in both genders in all of the regions where the measurements were taken. In both genders, in subjects who were over 145 months of age, it was seen that the values taken in some regions had increased. However, these increases were not statistically significant.

Faadel et al., in their study of the brain images of healthy infants, reported that the average of the ADC values obtained from the CC genu and splenium were 1.35×10-5 mm^2/s and 0.98×10-5 mm^2/s, respectively (25). In the same study, it was found that the same values gradually decreased in children aged 3 years ($p<0.05$). In the current study, in accordance with this result, it was seen that the ADC value decreased as the age increased. The reason why these values were different from each other may have been the different designs of the age groups. Differences due to the tissues or measurement changes of the participants caused by technical characteristics may have been the cause.

In this study, it was found that the ADC values obtained from the CC and TL did not vary according to gender. The ADC values obtained from the genu and body parts on the left side of the CC and TL on both sides varied according to age. A non-significant statistical connection was observed between the values obtained from the other parts of CC and age. This finding confirmed that myelination development varies regionally. Findings obtained in this study were in agreement with those of previous studies on the sequence of the myelination process (8,15,20). Autopsy studies have shown that the corticospinal tract, parts of the CC, and the superior cerebellar peduncles mature early, which was in concordance with MRI studies. The late maturation of the association tracts was also confirmed by histological analyses. On the other hand, autopsy studies have shown that the fornix, which has relatively high FA in newborns, does not reach full myelination until 2 years of age (4,5). This study concluded that axonal membranes play a primary role in myelination. However, fornix measurements were not taken because it was not possible to determine the fornix levels correctly in the ADC map.

Sex steroid hormone receptor density is high in the parahippocampal region of the temporal lobe. In the presented study, diffusion changes in white matter adjacent to this area were measured. In all of the age groups, the ADC values from the TL were significantly higher than those obtained from the CC ($p<0.05$). This finding suggested that there is less myelination at the TL level. The ADC values obtained in the TL decreased significantly with age. No studies on diffusion changes in the temporal lobe and parahippocampal region white matter could be found in the literature. The ADC values obtained from children without pubertal pathology can be considered normal and may help in the assessment of children with pubertal abnormalities.

There were limitations that cannot be ignored in this study. In the neurological examination notes obtained from the patient records, it was learned that some of the school-aged children used their right hands. This information was available for 5% of the subjects. Apart from this, information on this subject was not available. The choice of right-hand or left-hand usage of the other enrolled children was unknown. In the retrospective study, sex hormones lab results were not available for all of the participants. Therefore, their pubertal status was determined clinically. These were the biggest limitations. The measurements were made by a single radiologist. When performed by different observers, the repeatability of the measurements would be more reliable. To increase reliability, an inter-rater reliability assessment was conducted for repeated ADC value measurements. Another limitation was the presence of uncontrollable parameters in the diffusion measurements. The ADC map reflects not only true diffusion, but depends on spatial orientation microscopic perfusion and pulse sequence timing. Of these parameters, only sequences used for imaging could be standardized. Moreover, a limitation to keep in mind was that the extent of myelination was not the only interpretation of the changes in the ADC. However, one of the goals of the study was to find answers to questions with standard sequences in daily practice. Therefore, this risk was accepted.

Conclusion

DWI and ADC measurements can be applied in the study of normal brain development and myelination. ADC values decrease as age increases, regardless of gender. Using ADC values is helpful in the assessment of the myelination development in certain areas of white matter in the brain. Practically obtaining age-related changes in ADC values may help distinguish white matter pathologies from expected age-related changes.

Yazarlık katkısı: Fikir/Hipotez: MK Tasarım: MK Veri toplama/Veri işleme: MK Veri analizi: MK Makalenin hazırlanması: MK Makalenin kontrolü: MK

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ÖZGÜN ARAŞTIRMA/ORIGINAL ARTICLE

Yanık Sonrası Gelişen Bakteriyel Translokasyon Üzerine Amifostin'in Etkisi: Deneysel Çalışma

Effect of Amifostine on Bacterial Translocation After Burn Injury: An Experimental Study

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Yanıklar

ÖZ

Amaç: Bağırsak epitel bariyerinin bozulmasının yanık yaralanmasını takiben meydana geldiği gösterilmiştir. Bu süreç, patojenlerin bağırsak lümeninden sistemik dolaşıma ve uzak organlara yer değiştirmesine yol açarak sepsis riskini artırır. Bu çalışmanın amacı, sıçan yanığı yaralanma modelinde amifostinin bakteriyel translokasyon üzerindeki etkisini incelemektir.

Gereç ve Yöntem: Toplam 27 erkek Wistar albino sıçanı dokuzlu üç gruba ayrıldı. Grup I bir kontrol grubuydu. Grup II ve grup III, toplam vücut yüzey alanının %30'u üzerinde üçüncü derece yanıklara maruz bırakıldı ve grup III'e intraperitoneal olarak 200 ml/kg amifostin uygulandı, ardından üçüncü derece yanıklardan sonra 10 ml/kg/gün idame dozu uygulandı. 48 saat sonra karaciğer, dalak, mezenterik lenf düğümleri ve çekumdan doku ve kan örnekleri alındı ve kültür ekimi yapıldı.

Bulgular: Kan kültürleri tüm gruplarda negatifti. Kontrol grubunda kolonizasyon sadece çekumda görülürken, grup II ve III'te karaciğer, dalak, mezenterik lenf nodları ve çekumda kolonizasyon tespit edildi. Bakteriyel kolonizasyon en sık çekum ve mezenterik lenf düğümlerinde bulunurken, grup II ve III arasında çekum (p = 0,298) ve mezenterik lenf düğümlerinde (p = 0,418) bakteri sayıları önemli ölçüde farklılık göstermedi.

Sonuç: Amifostin tek başına yanık yaralanmaları ile ilişkili bakteriyel translokasyonu kontrol etmede etkili değildir. Bakteriyel translokasyonu etkileyen bir dizi faktör olduğu için bu sonuçlar dikkatle yorumlanmalıdır.

Key Words:
Amifostine
Bacterial Translocation
Burns

ABSTRACT

Objective: Disruption of the intestinal epithelial barrier has been shown to occur following burn injury. This process can lead to translocation of pathogens from the gut lumen to the systemic circulation and distant organs thereby increasing the risk for sepsis. The aim of this study was to examine the effect of amifostine on bacterial translocation in a rat burn injury model.

Material and Method: A total of 27 male Wistar albino rats were divided into three groups of nine. Group I was a control group. Group II and Group III were subjected to third-degree burns over 30% of the total body surface area, and group III was administered amifostine 200 ml/kg intraperitoneally, followed by a 10 ml/kg/day maintenance dose after undergoing third-degree burns. After 48 hours, tissue and blood samples were obtained and cultured from the liver, spleen, mesenteric lymph nodes, and cecum.

Results: Blood cultures were negative in all groups. In the control group, colonization appeared only in the cecum, but in groups II and III, colonization was found in the liver, spleen, mesenteric lymph nodes, and cecum. While bacterial colonization was most frequently found in the cecum and mesenteric lymph nodes, bacterial counts did not significantly differ in the cecum (p = 0.298) and mesenteric lymph nodes (p = 0.418) between groups II and III.

Conclusion: Amifostine alone is not effective in controlling bacterial translocation associated with burn injuries. These results should be interpreted with caution as there are a number of factors that affect bacterial translocation.

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Objective

Burns, which are among the most common types of trauma, may result in death due to sepsis and infectious complications depending upon the severity of the injury (1). A systemic inflammatory response affecting distant organs may develop early after a burn (2). In addition to skin inflammation, irritation has also been reported in the lungs, liver, and intestines (3). Mesenteric vasoconstriction has reportedly developed in the intestines due to a burn, and that vasoconstriction resulted in a hypoxic environment around the intestines (4). Hypoxia causes oxidative stress, cell death, and an impaired epithelial barrier. As intestinal permeability increases, bacterial translocation develops in the mesenteric lymph nodes playing an important role in the pathogenesis of sepsis, which is the main cause of mortality in burn patients (5,6).

Amifostine, with an organic triphosphate structure, is thought to act as a free radical scavenger (7). Due to its cell protective effects, amifostine has been developed as a shielding agent against radiation and chemotherapy damage. Its polyamine-like structure and sulfhydryl group enable it to affect cellular processes and protect cells from the harmful effects of chemotherapeutics and ionizing radiation (8). It is thought that amifostine may also have anti-oxidant and cell protective effects on the blood-gut barrier. The effect of amifostine on bacterial translocation has been evaluated in a limited number of studies including one involving a radiation enteritis model (9).

In the present experimental study we aimed to evaluate the effect of amifostine on bacterial translocation induced by a burn injury. If this study demonstrates that amifostine prevents bacterial translocation, prophylactic use of amifostine in burn patients may reduce patients' comorbidity and reduce the secondary harmful effects of burn.

Material and Method

The study protocol was approved by the Baskent University School of Medicine Ethics Committee for Animal Experiments on 06/08/2013 (no. DA 13/05), which is in line with the National Institutes of Health Guide for the Care and Use of Laboratory animals (NIH Publications No. 8023, revised 1978). Animals were obtained from the Baskent University Production and Research Center. The experiments were performed at Baskent University School of Medicine Research Unit Laboratories. The study included 27 male Wistar albino rats weighing 180 to 350 g (mean: 286 g). All animals were cared for under optimal standard conditions.

Study Design

The rats were divided into three groups of nine rats as follows: group I (control group), group II (burn injury group) and group III (burn injury + amifostine treatment group).

After all rats in groups were anesthetized via intraperitoneal injection, the burn process was initiated by exposing the skin for ten seconds to a brass plate which had been heated for two minutes (Figure 1). The method reported by Gilpin et al. was used to calculate 30% of the body area (10). The third-degree burn was confirmed by histopathologic methods. Following the burn initiation in group III, a 200 mg/kg amifostine (Ethyol®, Er-Kim, Turkey) loading dose (intraperitoneal) followed by a 10 mg/kg/day (subcutaneous) maintenance dose was administered.

Figure 1: Third degree burn formation on rats

After 48 hours, following a sterile laparotomy, blood samples were taken from the portal vein and tissue samples were taken from the liver middle lobe, spleen, mesenteric lymph nodes, and cecum. Microbiological assessment was performed on the tissues and blood samples. When bacterial growth was observed, the type and number of colonies were recorded.

Microbiological Assesment

In order to prevent contamination in the microbiological examination, first blood and finally cecum samples were taken. Samples were placed in sterile 5 mL tubes containing thioglycollate broth (BD, USA). Samples other than blood were homogenized with tissue dissociator (gentleMACS Dissociator, Germany).

Blood samples, which taken from the portal vein of the rat were inoculated on blood agar, MacConkey Agara, two Scheadler Agara and Sabouraud Dextrose Agara using single spore method. Dilutions of tissue samples were obtained using a homogenizer. 100 microliter samples

from each dilution, were inoculated on blood agar, MacConkey Agara, two Scheadler Agara and Sabouraud Dextrose Agara using single spore method. One of the Schaedler Agar pairs was incubated under anaerobic conditions and the other under aerobic conditions for at least 48-72 hours at 37 °C. All other media were incubated at 37 °C for 24-72 hours under aerobic conditions.

Colonies growing on the plates were counted and typed using standard microbiological methods. The number of colony forming units (colony forming units-CFU) per gram of tissue was calculated according to the formula given below.

Number of bacteria (CFU/gram) = Number of bacteria in 1cc (CFU/ml) / Tissue weight (g)

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 9.0) program. The logarithmic transformation (log10) was performed because bacterial numbers varied widely among the groups. The data are expressed as the mean and standard deviation. A one-way ANOVA and *t* test were used to compare groups. A *P* value < 0.05 was considered significant.

Results

In the control group, there were no bacteria found in any area except the cecum. In the burn group, one rat had bacteria recurrence in the liver, one in the spleen, eight in the mesenteric lymph nodes, and nine in the cecum. Likewise, in the burn + amifostine group, one rat had bacteria in the liver, one in the spleen, eight in the mesenteric lymph nodes, and nine in the cecum (Table 1). The most frequently observed bacteria were *Escherichia coli* and *Enterococcus faecalis* (Table 2).

Table 1. Pathogen occurrence according to areas and groups.

	Control	Burn	Burn + Amifostine
Blood	-	-	-
Liver	-	1/9 (11%)	1/9 (11%)
Spleen	-	1/9 (11%)	1/9 (11%)
MLN †	-	8/9 (89%)	8/9 (89%)
Cecum	9/9 (100%)	9/9 (100%)	9/9 (100%)

†*MLN: Mesenteric lymph nodes*

In all groups the most frequent occurrence of bacteria was observed in the cecum; however, there was no difference between groups in terms of bacterial count (p = 0.298) (Table 3). It was observed that the most frequent occurrence of bacteria other than in the cecum was found in the mesenteric lymph nodes; however, no significant difference was observed between the groups (p = 0.418).

Discussion

It has been shown that after burns injuries, intestinal permeability leads to increases in bacterial translocation to mesenteric lymph nodes or distant organs and bacterial translocation is in turn associated with sepsis and mortality (11). In our study for the first time, the effect on bacterial translocation in a burn model treated with amifostine was evaluated. Although amifostine has cell-protective and anti-oxidant properties, it has not been found to be effective in bacterial translocation.

Bacterial translocation has been described in association with ileus, colorectal cancer, cirrhosis, obstructive hepatitis, acute pancreatitis, abdominal surgeries, bowel transplantation, hemorrhagic shock, and heart diseases (5,12-14). Despite the fact that the presence of bacterial translocation has been confirmed in a number of studies, only a few studies have identified factors that have an impact on bacterial translocation. Among these identified factors, immunodeficiency is considered to be most important. Vaishnavi stated that bacterial translocation is constantly seen in healthy individuals but only becomes clinically important when immunity is inadequate (15). In addition to insufficient immunity, factors such as changes in the normal ecological balance of the gut, barrier permeability, trauma, and oxidative stress have also been implicated in bacterial translocation. It was hypothesized that amifostine would have an effect on bacterial translocation due to its anti-oxidant properties; however, a positive result was not obtained from our tissue samples. The most likely reason for these results is that bacterial translocation has a multi-dimensional etiology. Since this was a pilot study, our findings should be interpreted cautiously.

The effect of amifostine on bacterial translocation has only been assessed in one study thus far to the best of our knowledge. Recently, the study by Taş et al. evaluated the effect of amifostine on bacterial translocation created by radiation enteritis (9). In their study, amifostine did not have an effect on bacterial translocation when administered at the same dosage and in a similar manner as in our study. However, unlike in our study, amifostine reportedly reduced bacterial overgrowth. Amifostine has the capacity to repair DNA fragmentation after radiation damage, which can explain this difference (16). Taş et al. concluded that amifostine alone is not sufficient to prevent bacterial translocation (9).

Table 2. Pathogen analysis of tissue cultures.

	Test subject	1	2	3	4	5	6	7	8	9
LIVER	Control	-	-	-	-	-	-	-	-	-
	Burn	-	-	-	-	-	*E. faecalis* 11	-	-	-
		-	-	-	-	-	-	-	-	-
	Burn	-	-	*E. coli* 6	-	-	-	-	-	-
	+Amifostine	-	-	*E. faecalis* 6	-	-	-	-	-	-
SPLEEN	Control	-	-	-	-	-	-	-	-	-
		-	-	-	-	-	-	-	-	-
	Burn	-	-	-	-	-	*E. faecalis* 28	-	-	-
		-	-	-	-	-	-	-	-	-
	Burn	-	-	-	-	-	-	-	*E. coli* 4	-
	+Amifostine	-	-	-	-	-	-	-	-	-
MLN†	Control	-	-	-	-	-	-	-	-	-
		-	-	-	-	-	-	-	-	-
	Burn	*E. coli* 157	*E. coli* 6	*E. coli* 24	*E. faecalis* 4	*E. faecalis* 3		*E. faecalis* 21	*E. coli* 31	*E. faecalis* 10
		E. faecalis 19	*E. faecalis* 56	*E. faecalis* 73						
	Burn	*E. coli* 40	*E. coli* 17	*E. coli* 16	*E. faecalis* 13		*E. faecalis* 4	*E. faecalis* 4	*E. coli* 3	*E. coli* 13
	+Amifostine			*E. faecalis* 80					*E. faecalis* 3	
CECUM	Control	*E. coli* 5.952	*E. coli* 95	*E. coli* 41.026	*E. coli* 9.615	*E. coli* 1.238	*E. coli* 114	*E. coli* 534	*E. coli* 64.815	*coli* 6.250
		E. faecalis 20.833	*E. faecalis* 269	*E. faecalis* 15.385	*KNS* 19.231		*E. faecalis* 170	*E. faecalis* 76	*E. faecalis*	*E. faecalis* 2.500
	Burn	*E. coli* 2.121	*E. coli* 123	*E. coli* 839	*E. coli* 1.200	*E. coli* 1.600	*E. coli* 3.000	*E. coli* 625	*E. coli* 833	*E. coli* 250
		E. faecalis 1.818	*E. faecalis* 123	*E. faecalis* 140		*E. faecalis* 240	*E. faecalis* 5.000	*E. faecalis* 15.625	*E. faecalis* 4.167	
	Burn	*E. coli* 160.000	*E. coli* 240.000	*E. coli* 30.000	*E. coli* 15.000	*E. coli* 33.333	*E. coli* 50	*E. coli* 50	*E. coli* 200	*E. coli* 85.714
	+Amifostine	*E. faecalis* 600.000		*E. faecalis* 10.000		*E. faecalis* 33.333	*E. faecalis* 50	*E. faecalis* 50	*E. faecalis* 467	*E. faecalis* 57.143

†*MLN: Mesenteric lymph nodes.*

Table 3. Comparison of groups in terms of pathogens recurrence in the cecum.

Group	Average number of bacteria	
	MLN†	Cecum
Control		3.70 ± 0.97
Burn	1.36 ± 0.64	3.30 ± 0.63
Burn + Amifostine	1.13 ± 0.48	4.10 ± 1.46
P-value	0.418	0.298

†*MLN: Mesenteric lymph nodes*

The limitation of our study is the lack of pathological assessment of the tissue samples taken. In future studies, the antioxidant effect of amifostine can be demonstrated with pathological examination and its preventive effect on bacterial translocation can be evaluated.

As a conclusion in the prevention of bacterial translocation produced by a burn model, amifostine has limited activity. We found that despite its cell-protective and antioxidant properties, amifostine is not effective in reducing bacterial translocation associated with burn injury in a rat model.

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HMJ

ÖZGÜN ARAŞTIRMA/ORIGINAL ARTICLE

Somali'de Bulunan "Mogadişu Türkiye Recep Tayyip Erdoğan Eğitim ve Araştırma Hastanesi" Kliniklerine Başvuran Hastalarda Hepatit B ve Hepatit C Virüs Enfeksiyonu Seroprevalansının Retrospektif Olarak Değerlendirilmesi

Evaluation and Comparison of the Seroprevalence of Hepatitis B and Hepatitis C Virus Infection in Patients Admitted to Clinics at the "Mogadishu, Turkey Recep Tayyip Erdogan Training and Research Hospital" in Somalia

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ÖZ

Amaç: Somali Mogadişu'daki Türk hastanesine başvuranların hepatit B ve hepatit C seroloji bulgularını değerlendirmeyi ve mevcut prevalansının belirlenmesi.

Gereç ve Yöntemler: Hastaların demografik bulguları ve hepatit test sonuçları (HBsAg, anti-HBs antikoru ve anti-HCV) dosyalarından geriye dönük olarak kaydedildi.

Bulgular: Çalışmamıza yaş ortalaması 34 (31/61) yıl olan 75.903 (%49,8) erkek ve 76.363 (%50,2) kadın olmak üzere toplam 152.266 hasta dahil edildi. Anti-HCV için test edilen 67.749 hastanın 1.278'i (%1,9) pozitif bulundu. 27.208 hastanın (%32,2) HBV için doğal veya aşı bağışıklığı geliştirdiği bulundu. Anti-HCV (+) olanların genel olarak 55 yaşından büyük, HBsAg (+) olanların ise genellikle 55 yaşından küçük olduğu [OR: 6,02 (5,28-6,87): %95, CI] bulundu.

Sonuç: Çalışmamızda Somali popülasyonunda HBsAg ve anti-HCV seroprevalansının (sırasıyla %8,2 ve %1,9) halen istenilen seviyelerin üzerinde olduğu söylenebilir. Anti-Hbs antikor düzeylerinin %32,2 düzeyinde olması, aşılama programlarının geliştirilmesinin ve yaygınlaştırılmasının önemini vurgulamaktadır.

ABSTRACT

Objective: To evaluate hepatitis B and hepatitis C serology findings and to determine the current prevalence of those who had applied to the Turkish hospital in Mogadishu, Somalia.

Material and Method: The demographic findings and hepatitis test results (HBsAg, anti-HBs antibody, and anti-HCV) of the patients were recorded retrospectively from their files.

Results: A total of 152,266 patients, 75,903 (49.8%) male and 76,363 (50.2%) female, with a mean age of 34 (31/61) years, were included in our study. 1,278 (1.9%) of 67,749 patients who were tested for anti-HCV were found to be positive. 27,208 patients (32.2%) were found to have developed natural or vaccine immunity for HBV. It was found that those with anti-HCV (+) were generally older than 55 years and that those with HBsAg (+) were generally younger than 55 years [OR: 6.02 (5.28-6.87): 95%, CI].

Conclusion: In our study, it can be said that HBsAg and anti-HCV seroprevalence (8.2% and 1.9%, respectively) in the Somalia population is still above desired levels. The fact that anti-Hbs antibody levels are at 32.2% underscores the importance of the development and popularization of vaccination programs.

Introduction

Acute and chronic viral hepatitis are important public health problems, especially in developing countries. According to the World Health Organization (WHO), two billion people worldwide (one third of the global population) have been infected with the hepatitis B virus (HBV), and more than 240 million are inactive carriers. However, hepatitis C virus (HCV) infection, for which a vaccine protection program has not been developed yet, has become a significant viral hepatitis factor. Sub-Saharan Africa accounts for almost a fifth of infections worldwide, and more than six million people in Latin America are thought to be infected with HCV (1).

It is expected that HBV and HCV seroprevalence will undergo a dynamic change in parallel with the development of preventive and curative services in the health system in Somalia over recent years. In this study, we there fore aimed to evaluate hepatitis B and hepatitis C serology findings and to determine the current prevalence of those, who had applied to the Turkish hospital in Mogadishu, Somalia.

Material and Method

Permission for the study was obtained from the Non-Invasive Clinical Research Ethics Committee of the The Noninvasive Clinical Research Ethics Committee of Mogadishu, Turkey Recep Tayyip Erdogan Training and Research Hospital (MSTH/813). It was aimed to evaluate the results of hepatitis markers obtained from patients admitted between January 2017 and June 2019 to the Somalia Mogadishu Turkey Recep Tayyip Erdogan Training and Research Hospital. The demographic findings of the patients, antigen and antibody test results for HBV and HCV infection (HBsAg, anti-HBs antibody, and anti-HCV), liver function test were recorded retrospectively from the patient files. Patients whose HBsAg and Anti-HCV seroprevalence were included in the prevalence calculation were classified as being either active disease or inactive carriers. The presence of the anti-HBs antibody alone was evaluated as previous hepatitis b infection or immunization with vaccine.

Serology

HBsAg II, anti-HCV II and anti-HBs II tests were performed according to the manufacturer's recommended standard procedures. The mandatory dilution algorithm of the assay is an initial measurement of a 1:100 (for the Elecsys 2010 and Cobas e411, Roche Diagnostics GmbH, Mannheim, Germany). HBsAg, anti-Hbs antibody and anti-HCV concentrations were measured by means of an electro-chemiluminescence immunoassay (ECLIA) (Cobas e411, Roche Diagnostics, Mannheim, Germany). Serum HBsAg was determined qualitatively. The signal-to-cut-off signal (S/Co) ratio was used for interpretation of the initial results. Values higher than 1.00 (≥1.00) indicated a reactive result, values between ≥0.90 and samples with nonreactive and results considered to be negative for HBsAg and Anti-HCV did not require further testing. All tests including calibrations and controls were performed and interpreted in accordance with the manufacturers' recommendations.

Statistical Analysis

The SPSS 26.0 (IBM Corporation, Armonk, New York, United States) program was used for analysis of variables. The compatibility of univariate data to normal distribution was evaluated using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used together with Monte Carlo results to compare two independent groups with each other according to the quantitative data. In the comparison of categorical variables, the Pearson Chi-Square test was tested with Exact results and the column proportions were compared with each other and expressed according to the Benjamini-Hochberg corrected p-value results. The Odds ratio was used with 95% confidence intervals to show how many times those with a risk factor were higher than those without. Sensitivity, specificity, positive predictivity and negative predictivity ratios for the relationship between the classification separated by the cut-off value calculated according to the variables of the groups and the actual classification were analyzed and expressed by ROC (Receiver Operating Curve) curve analysis. Quantitative variables were expressed as median (percentile 25 / percentile 75) in the tables, while categorical variables were presented as n(%).Variables were examined at a 95% confidence level, and a p-value of less than 0.05 was considered to be significant.

Results

A total of 152,266 patients, 75,903 (49.8%) male and 76,363 (50.2%) female, with a mean age of 34 (31/61) years, were included in our study.

Out of 84,505 patients tested for HBV, 6,893 (8.2%) were found to have HBsAg (+). 1,278 (1.9%) of 67,749 patients, who were tested for anti-HCV, were found to be positive. 27,208 (32.2%) patients were found to have developed immunization through natural immunization or vaccine for HBV (Table 1).

Table 1. Demographic results of HBsAg (+) or anti-HCV (+) patients.

	Total (n=8171)	Anti-HCV (+) (n=1278)	HBsAg (+) (n=6893)	*P*
Gender	n (%)	n (%)	n (%)	
Female	3376 (41.3)	495 (38.7)	2881 (41.8)	0.041
Male	4795 (58.7)	783 (61.3)	4012 (58.2)	1.13 (1.01 - 1.28) or
	Median (Q1 / Q3)	**Median (Q1 / Q3)**	**Median (Q1 / Q3)**	
Age (year)	47 (31 / 61)	65 (51 / 73)	43 (30 / 59)	<0.001
ALT (IU/L)	23 (16 / 35)	27 (18 / 43)	22 (16 / 33)	<0.001
AST (IU/L)	27 (21 / 39)	34 (23 / 61)	26 (21 / 36)	<0.001
T. Bil. (mg/dL)	0.51 (0.36 / 0.79)	0.58 (0.4 / 0.95)	0.5 (0.35 / 0.76)	<0.001
D. Bil. (mg/dL)	0.2 (0.13 / 0.33)	0.26 (0.16 / 0.53)	0.2 (0.12 / 0.31)	<0.001

Pearson Chi Square Test (exact), Mann Whitney U test (Monte Carlo), Q1: Percentile %25, Q3: Percentile %75

A total of 1,278 anti-HCV (+) patients and 6,893 HBsAg (+) patients included in our study were compared in terms of demographic findings and LFTs. While viral serology positivity was higher in men in both groups, the incidence of Anti-HCV (+) was found to be 1.13 times higher than the frequency of HBsAg in men (p=0.041) (Table 1). Patients with anti-HCV (+) were older, and their LFT and bilirubin levels were found to be higher than those of HBsAg patients (p<0.001) (Table 1).

Patients who were tested for anti-HCV and for HBV were evaluated separately. The anti-HCV test was found to be positive in 1,278 (1.9%) of 67,749 patients, who were tested for anti-HCV. HBsAg positivity was detected in 6,893 (8.2%) of 84,505 patients who underwent a hepatitis B test. (Table 2).

In our study, when the characteristics of the patients with anti-HCV (+) and HBsAg (+) were interpreted through ROC curve analysis; it was found that those with anti-HCV (+) were generally older than 55 years and that those with HBsAg (+) were generally younger than 55 years [OR: 6.02 (5.28-6.87): 95%, CI]. In patients with anti-HCV (+) ALT >32.54 IU/mL (OR:1.92, CI: 1.7-2.18), AST >36.86 IU/mL (OR: 2.72, CI: 2.41-3.08), T. Bil >0.28 mg/dL (OR: 1.53, CI: 1.35-1.72) and D. Bil. >0.25 mg/dL (OR: 2.09, CI: 1.85-2.36) predicted anti-HCV positivity (CI; 95%) (p<0.001) (Table 3).

Discussion

In Somalia, the civil war has been on-going for decades, with insufficient numbers of qualified medical staff and limited access to modern laboratory facilities also posing significant screening and vaccination challenges for viral hepatitis (2). Therefore, HBV and HCV infections transmitted by blood, sexually and via the perinatal route are still the most important preventable and treatable causes of death for Somalian people. As a result of our study, we can conclude that due to the high prevalence of HBsAg and anti-HCV, people living in the Somalia Mogadishu region are still at a serious public health risk in this respect.

HBV infection causing liver cirrhosis and hepatocellular carcinoma (HCC) is endemic worldwide. Africa is the region with the second highest number of inactive carriers following the Western Pacific regions. Chronic HBV infection is very common, especially in Asia and sub-Saharan Africa. Approximately 15-40% of individuals with chronic HBV infection have an increased risk for the development of cirrhosis, fulminant hepatitis, and HCC (3,4). Analyzes on the global distribution of chronic HBV infection were classified according to HBsAg prevalence by low (<2%), intermediate (2%-7%) and high (≥8%) prevalence regions (5). Somalia is also a region in the world with a high rate of HBV seroprevalence (>8%)(6,7). In our study,

Table 2. Test results for hepatitis B and/or hepatitis C virus infection.

	Negative n (%)	Positive n (%)	Total n (%)
Tested for HCV infection (anti-HCV)	66471 (98.1)	1278 (1.9)	67749
Tested for HBV infection (HBsAg)	77612 (91.8)	6893 (8.2)	84505
Anti-HBsAb (+) and HBsAg (-)	57297 (67.8)	27208 (32.2)	84505

The proportions were calculated as the number of positives or the number of negatives / numbers in the total column.

Table 3. ROC Curve analysis for HBsAg and anti-HCV results.

Cut-off value		Anti-HCV (+) (n=1278)	HBsAg (+) (n=6893)	Odds Ratio (%95 CI)	(SE.)	*P*
Age	>55	902 (31.5) ^{npv} (70.6) ^{sp}	1963	6.02 (5.28 / 6.87)	0.746 (0.007)	<0.001
	≤55	376	4930 (92.9) ^{ppv} (71.5) ^{sn}			
ALT	>32.54	519 (22.3) ^{npv} (40.6) ^{sp}	1807	1.92 (1.70 / 2.18)	0.581 (0.009)	<0.001
	≤32.54	759	5086 (87.0) ^{ppv} (73.8) ^{sn}			
AST	>36.86	604 (26.1) ^{npv} (47.3) ^{sp}	1706	2.72 (2.41 / 3.08)	0.616 (0.009)	<0.001
	≤36.86	674	5187 (88.5) ^{ppv} (75.3) ^{sn}			
T. Bil.	>0.28	683 (18.7) ^{npv} (53.4) ^{sp}	2960	1.53 (1.35 / 1.72)	0.562 (0.008)	<0.001
	≤0.28	595	3933 (86.9) ^{ppv} (57.1) ^{sn}			
D. Bil.	>0.25	590 (22.7) ^{npv} (46.2) ^{sp}	2006	2.09 (1.85 / 2.36)	0.599 (0.008)	<0.001
	0.25	688	4887 (87.7) ^{ppv} (70.9) ^{sn}			

Roc Curve Analysis (Youden index J - Honley & Mc Nell), AUC: Area under the ROC curve, SE: Standard Error, npv: negative predictivity value, ppv: positive predictivity value

we found that the current HBsAg seroprevalence is still 8.2%.

Development of a vaccine for HBV makes a significant contribution to this struggle. A HBV vaccine has been available since the early 1980s, and a dramatic reduction in the frequency of chronic HBV infection has been achieved through regular HBV vaccination programs. The WHO recommends that the HBV vaccine should be integrated into national vaccination programs in all countries. However, HBV vaccines are not widely available in low-income countries.

Current studies on this subject are generally carried out with refugees in the USA, which is in receipt of significant levels of immigration from these regions. Previous reports have documented the frequency of HBsAg among US refugees as 3-15% (8-10). In a recently published study, the overall frequency of HBsAg in Somali refugees, who immigrated to the United States, was found to be 2.9%, which is equal to approximately 10 times the rate of HBV infection in the general US population (11). However, the frequency of HBsAg varies between 8.2 - 40.1% in general screening and seroprevalence studies in the population of Somalia and patients diagnosed with HCC (12). In our study, the HBsAg seroprevalence of the Somali population was found to be lower when compared to the results of previous local studies and it was found to be significantly higher than the level in refugee studies. This may be attributed to the fact that people who have the opportunity to emigrate from Somalia enjoy better socioeconomic conditions generally and have access to vaccines and early treatment.

Hepatitis B is estimated to cause 87,890 deaths annually in sub-Saharan Africa, but the incidence of cirrhosis in individuals in sub-Saharan Africa is difficult to determine. Liver biopsy is not a routine procedure and non-invasive elastography is almost impossible to access (13). However, several studies have reported that HBV infection is responsible for 80% of patients diagnosed with HCC in sub-Saharan Africa (14-16). In sub-Saharan Africa, the age-standardized incidence of HCC rises to 41-2 per 100,000 people per year (17). The reported frequency of HCC and cirrhosis may only reflect a very small percentage of the actual incidence due to the inadequacy of regular recording systems (18).

As a result of the cohort studies conducted; male gender, a family history of HCC, a cirrhosis background, a high HBsAg concentration, a high HBV DNA concentration, having HBV genotypes A and C, core-promoter mutations and aflatoxin exposure were associated with an increased risk for HCC (17). Therefore, effective intervention requires a clear understanding of the dynamics of viral outbreaks.

Many countries in sub-Saharan Africa are currently in the process of developing viral hepatitis management guidelines and strategic plans to work towards the eradication of viral hepatitis. Major challenges for HBV eradication

in sub-Saharan Africa are as follows: reduction of mother-to-child transmission (materno-fetal) with the administration of a HBV birth dose vaccine and full coverage for the HBV vaccination program; identifying individuals infected with HBV, access to affordable diagnostic assays to provide an effective link to care and treatment with nucleoside analog therapy for HBV-infected individuals; and reducing the social stigma associated with HBV diagnosis.

Despite all the scientific advances and increasing knowledge of HCV, HCV infection still remains a "hidden pandemic"(19). HCV prevalence has recently decreased to 0.1% in developed countries (20). HCV is still considered endemic in developing countries with insufficient genotype data. The largest population of individuals infected with HCV was found to be in Asia (3.6% of the global population), followed by Africa (3.2% of the global population) and Latin America (1.4% of the global population), respectively (21). Most of these regions face many structural, cultural, social and political obstacles in responding to this epidemic. Social and educational programs should be encouraged, especially in countries that still ignore and stigmatize certain behaviors that lead to HCV infection. Raising awareness of HCV infection in the general population can be beneficial in two ways: First, people who are aware request treatment. Second, encouraging appropriate behavior helps to limit the risk of disease progression. A national action plan with national guidelines for the treatment of HCV infection should be supported (22).

It is noteworthy that HCV positivity is more common in older ages and LFT levels are found to be higher. This situation can be interpreted with the increase of awareness in the society and the decrease in contagiousness as a result of the early diagnosis of HCV in recent years (23). In addition, the increase in the frequency of metabolic syndrome, DM, hepatosteatosis with age may have contributed to the elevation of LFT.

In a study based on the prevalence of serological markers for HBV and HCV in 596 children, who lived in a residential institution in Somalia in 1992, it was reported that the prevalence of HBsAg was 16% and anti-HCV was 1.5%(4, 24). In our study, we found that anti-HCV seroprevalence was 1.9% in the local population, close to the levels stated in the previous literature data. This result may be significant in terms of its indicating that increasing awareness about HCV, teaching people about transmission pathways, and highlighting the importance of the widespread use of regular screening and follow-up programs are still not sufficient.

HCV infection is a global public health problem that affects millions of people worldwide. HCV-infected individuals have a 2.4 times increase in the risk of all-cause death, a 26.5 times increase in the risk of liver-related death, and a 1.8 times increase in the risk of non-liver-related death compared to the non-infected population (25). HCV has a great heterogeneity in both the prevalence of infection and the distribution of viral genotypes. This poses a serious health burden globally in terms of morbidity and mortality. In our study, the rate of anti-HCV prevalence was particulalrly highwith HCV-related morbidity and mortality difficult to determine, since the rates of compliance of patients with follow-up systems and treatments are very low.

Our study has some important limitations. First of all, HBV and HCV seroprevalence were evaluated via HBsAg, anti-HBs antibody and anti-HCV levels. Although patients living in the same region were included in our study, seroprevalence was evaluated in separate groups due to differences in the file scanning system. This situation is attributable to social security problems in the region, identity card complexities and difficulties with respect to data retrieval from the hospital registration system. Since the HBV-DNA and HCV-RNA levels and genotyping results of the patients could not be obtained, data related to the development of active infection, chronic hepatitis, liver cirrhosis and HCC could not be obtained. This situation can be explained by the regular patient follow-up problem in the region where our hospital is located and the inadequacies of laboratory capacity. However, our study's results are important with respect to their determination of seroprevalence in the region and given the very large patient cohort and resultant size of the data used patient population.

As such, based on our study, we can say that HBsAg and anti-HCV seroprevalence (8.2% and 1.9%, respectively) in Somalia is still above desired levels. The fact that anti-HBs antibody levels are 32.2% reveals the importance of the development and popularization of vaccination programs. It is vital to ensure that Somalian people have access to adequate and regular hepatitis B vaccination programs for viral hepatitis (normal population, pregnancy and neonatal follow-up, etc.), adequate medical care, a reliable drug supply and equal access to medical follow-ups.

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ÖZGÜN ARAŞTIRMA/ORIGINAL ARTICLE

Sağlıklı İnsanlarda Vücut Kitle İndeksi ile Sedimantasyon Arasındaki İlişki

Correlation Between Body Mass Index and Erythrocyte Sedimentation Rates in Healthy Participants

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Anahtar Sözcükler:
Beden Kitle İndeksi
HDL
Lipoprotein
Monosit
Sedimentasyon Hızı

Key Words:
Body Mass İndex
Erythrocyte Sedimentation Rate
HDL
Lipoprotein
Monocyte

ÖZ

Amaç: Uzun yıllardır kullanılan ucuz, kolay ve hızlı bir test olan sedimantasyon hala birçok durumda tanıya yardımcı olmaktadır. Bu çalışmada, sağlıklı bireylerde sedimantasyon, kolesterol değerleri ve monosit yüksek dansiteli lipoprotein oranı (MHR) ile vücut kitle indeksi arasındaki ilişki değerlendirilmiştir.

Gereç ve Yöntem: Ocak 2020 ile Aralık 2020 tarihleri arasında; iç hastalıkları kliniğine belirgin şikayeti olmadan, rutin sağlık kontrolü ve check-up için başvuran 689 sağlıklı bireylerin sonuçları retrospektif olarak değerlendirilmiştir. Hastaların demografik özellikleri, vücut kitle indeksi ve kan parametreleri değerlendirilmiştir. Katılımcılar; vücut kitle indeksine göre; Grup 1 (normal kilolu), Grup 2 (aşırı kilolu) ve Grup 3 (obez) olarak sınıflandırılmıştır.

Bulgular: Gruplar arasında; vücut kitle indeksi ile; boy, kilo, sedimantasyon değeri, glikoz, monosit sayısı, total kolesterol, düşük dansiteli lipoprotein, yüksek dansiteli lipoprotein dışı kolesterol ve MHR arasında anlamlı bir ilişki saptanmıştır. Kadınların sedimantasyon değeri erkeklerden anlamlı olarak fazla saptanmıştır. Vücut kitle indeksi ile sedimantasyon değeri (r=0.346, p=0.001), glikoz (r=0.239, p=0.001) ve monosit sayısı (r=0.096, p=0.013) arasında anlamlı bir korelasyon bulunmuştur.

Sonuç: Bu çalışmanın neticelerine göre sedimantasyon hızı sağlıklı bireylerde VKI ile ilişkili bir parametre olarak sağlıklı bireylerde inflamasyon şiddetini göstermek için kullanılabilir. Sedimantasyon değeri yüzyıl önce bulunmasına rağmen kullanışlılığını devam ettirmektedir.

ABSTRACT

Objective: Erythrocyte sedimentation rate (ESR) is a cheap, fast, and readily available test. It is still being used for many medical conditions to help diagnose and evaluate diseases. This study inspected the association of ESR, cholesterol levels, and monocyte to high-density lipoprotein ratio (MHR) with body mass index in healthy populations.

Material and Method: This study is an observational, retrospective study. It has been conducted in a university hospital with people admitting to internal medicine outpatient clinics between January 2020 and December 2020. Demographic characteristics, body mass indexes, and laboratory parameters of 689 patients were evaluated. Participants were divided into three groups according to body mass indexes; Group 1 (normal weight), Group 2 (overweight), Group 3 (obese). Data obtained from three groups were compared.

Results: There were significant associations between body mass index and height, weight, ESR, glucose, monocyte counts, total cholesterol, low-density lipoprotein, Non-HDL cholesterol, and MHR among groups. ESR was significantly higher in women compared to men. There were significant correlations between body mass index and ESR (r=0.346, p=0.001), glucose (r=0.239, p=0.001) and monocyte count (r=0.096, p=0.013).

Conclusion: According to the results of this study, ESR is a parameter associated with BMI, and it may reflect the magnitude of inflammation taking place in obesity.

Introduction

Erythrocyte sedimentation rate (ESR) is determined by measuring aggregation of cellular components of blood sample in a vertically placed test tube containing anticoagulants in one hour and is reported as millimeters/hour. It has been used for many years and is still an important and usable inflammatory marker in many conditions (1). ESR is directly affected by acute phase reactant proteins circulating in the blood (2). Proteins related to inflammation, such as fibrinogen and immunoglobulins, decrease negative electrically repulsive charge at the surface of erythrocytes and increase ESR (3). Inflammatory cytokines are reported to be increased in obesity (4). Inflammation in obese patients results in an increase in fibrinogen and immunoglobulin levels (5,6). These proteins increase ESR (7). Thus, it has been presumed that obesity and inflammation have associations.

ESR increases in many conditions. In a study with older people, ESR was significantly higher in participants with high cholesterol levels (8). An association between body mass index (BMI) and ESR has been reported previously in patients with diabetic polyneuropathy (9). Monocyte counts were reported to be elevated in obese people (10). Monocyte to high-density lipoprotein ratio (MHR) and ESR is being used to reflect the magnitude of inflammation. These values were higher in patients with metabolic syndrome than people who do not have metabolic syndrome (11). MHR was also reported to be high in patients with polycystic over syndrome (12). Association between BMI and MHR and ESR in healthy populations was not sufficiently inspected previously.

Cholesterol levels increase as the body mass index of relevant people increases (13). A study reported that non-high-density lipoprotein levels (non-HDL) increase as BMI increase (14). The association between BMI and cholesterol levels in the healthy population is not clear yet.

The purpose of this study is to evaluate the association between BMI and lipid parameters [High-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides and total cholesterol levels], ESR, and MHR in the healthy population.

Material and Method

This study was conducted in a tertiary university hospital with 689 participants admitted to internal medicine outpatient clinics and had an observational retrospective design. Participants who did not have any active complaints and were admitted to the hospital for annual routine occupational examinations or check-ups between 1 January 2020 and 31 December 2020 were evaluated. People who accepted to participate in the study were enrolled and patients who had the previous history of hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary diseases, renal or hepatic failures, active infectious diseases, rheumatic diseases, malignancies, who were using antihyperlipidemic medications and people who were under 18 years age were excluded. This study was approved by Lokman Hekim University Non-Interventional Clinical Research Ethics Committee (App. No: 2021/032) and conducted in compliance with the Declaration of Helsinki and good clinical practices updates.

Participants' demographic characteristics; age, gender, height, weight measurements were recorded at admission, laboratory parameters ESR, glucose, HDL, LDL, triglycerides, total cholesterols levels were analyzed after blood samples were taken, and MHR was calculated after obtaining related results; all data were recorded. Non-HDL cholesterol was calculated by subtraction of HDL value from total cholesterol value. BMI was calculated by the division of body weight in kilograms to the square of body height in meters. Participants were divided into three groups according to BMI values; Group 1 (normal weight); 19-<25, Group 2 (overweight); 25-30 and Group 3 (obese); 30 and over. ESR and cholesterol levels may be directly affected by the age and gender of participants. For this reason, participant distribution in groups was tried to be balanced, and groups similar in means of age and gender were tried to be constituted.

Blood samples were obtained after 12 hours of fasting. Complete blood counts were analyzed using an XN-1000 analyzer (USA). Glucose, LDL, HDL, triglycerides, and total cholesterol levels were analyzed by Roche Hitachi Cobas 501 (Switzerland) device. Erythrocyte sedimentation rates were measured automatically using the Biosed 100 (Italy) device in blood sample tubes.

Statistical Analysis

SPSS for Windows 25.0 statistical software package (SPSS Inc., Armonk, NY, USA) was used for statistical analysis of the data. Data distributions or normality tests were evaluated by the Shapiro-Wilk test. Data were presented as mean ± standard deviation for normally distributed variables, as median (minimum-maximum) for non-normal distributed variables. The comparisons between groups were evaluated by One Way ANOVA tests. Associations between data were inspected by the Pearson

correlation test. P values below 0.05 were considered significant.

Results

A total of 689 participants was enrolled, and 432 (62.6%) were males, and 257 (37.4%) were females. The average age of participants was 39.39±10.72 (males 39.40±10.60 and females 39.38±10.93). Demographic characteristics and laboratory parameters of participants are shown in Table 1. Mean ESR for men was 10.80±8.52 mm/hr and 18.17±11.56 mm/hr for women (p=0.001). The mean BMI value of men was 26.84±4.02, and women's was 28.31±6.25 (p=0.001). The number of participants in Group 1 was 247 (35.8%), Group 2 was 248 (35.9%), and Group 3 was 194 (28.3%).

There were significant differences between BMI and height, weight, ESR, glucose, monocyte counts, total cholesterol, LDL, Non-HDL cholesterol, and MHR between groups in healthy participants in this study. Comparison of data about demographic characteristics and laboratory parameters are shown in Table 2.

Table 1. Demographic characteristics and means of laboratory parameters of participants.

Parameters	Mean ± Standard Deviation
Age (years)	39.39±10.72
Height (meter)	1.72±0.10
Weight (kilograms)	81.15±15.46
Body mass index (kg/m^2)	27.39±5.02
Glucose (mg/dL)	96.23±15.94
Hemoglobin (g/dL)	14.73±1.71
Mean Platelet volume (µm^3)	10.25±0.88
Monocytes (x10^9/L)	0.57±0.18
Erythrocyte sedimentation rate (mm/h)	13.55±10.38
Total Cholesterol (mg/dL)	184.59±40.49
Low density lipoprotein (mg/dL)	109.09±35
High density lipoprotein (mg/dL)	49.75±19.76
Triglycerides (mg/dL)	139.08±93.43
Non HDL Cholesterol (mg/dL)	134.84±42.60
Triglyceride/High density lipoprotein ratio	3.27±2.99
Monocyte/High density lipoprotein ratio	0.125±0.052
Non HDL Cholesterol/HDL ratio	3.00±1.40

Table 2. Comparison of demographic characteristics and laboratory parameters of participants according to BMI.

Parameter	Normal weight (n=247)	Overweight (n=248)	Obese (n=194)	p value
Age (years)	38.32±11.54	40.10±9.36	43.98±11.19	0.142
Height (meter)	1.74±0.09	1.72±0.09	1.70±0.10	<0.001
Weight (kilograms)	69.92±10.23	79.84±9.24	97.11±13.79	<0.001
Mean Platelet volume (µm^3)	10.26±0.85	10.21±0.91	10.30±0.88	0.543
Monocyte count (x10^9/L)	0.55±0.18	0.58±0.16	0.60±0.19	0.009
Erythrocyte sedimentation rate (mm/h)	9.85±9.09	13.80±7.66	17.95±12.92	<0.001
Glucose (mg/dL)	93.29±10.03	95.61±14.10	100.74±22.17	<0.001
Total Cholesterol (mg/dL)	185.26±37.70	188.81±42.59	178.34±40.60	0.025
Low density lipoprotein (mg/dL)	109.81±32.77	113.06±36.88	103.10±34.63	0.011
High density lipoprotein (mg/dL)	51.26±27.74	48.40±12.66	49.54±14.19	0.270
Triglycerides (mg/dL)	132.24±73.98	148.23±114.35	136.09±85.01	0.142
Monocyte/High density lipoprotein ratio	0.116±0.0047	0.127±0.0050	0.131±0.0061	0.009
Non-HDL Cholesterol (mg/dL)	134±41.31	140.42±43.71	128.79±42.10	0.016
Triglyceride/HDL ratio	3±2.29	3.5±3.41	2.92±1.63	0.165
Non-HDL Cholesterol/HDL ratio	2.91±1.17	3.16±1.41	2.92±1.63	0.085

There were significant correlations between BMI and ESR (r=0.326, p=0.001), glucose levels (r=0.239, p=0.001) and monocyte count (r=0.096, p=0.013) but there were no correlation between BMI and MHR (r=0.055, p=0.204). Correlations were shown in Figure 1a, 1b, 1c.

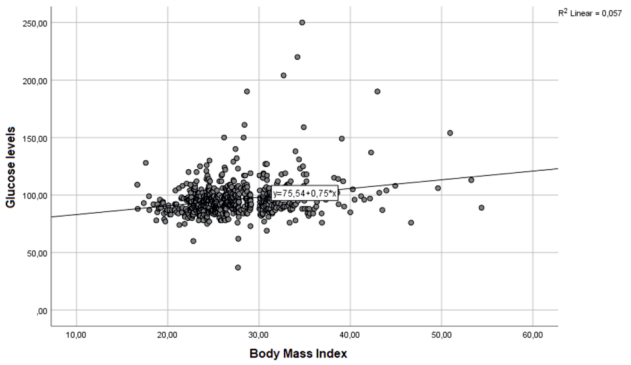

Figure 1a. Correlations between BMI and glucose levels.

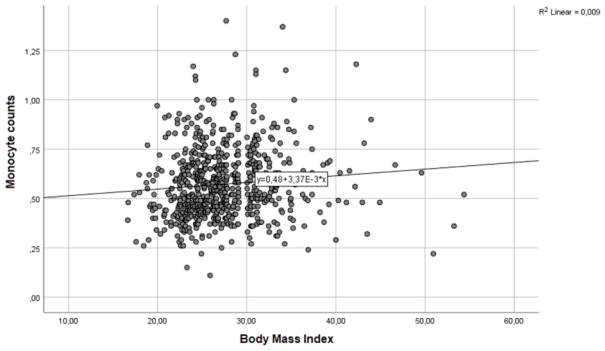

Figure 1b. Correlations between BMI and monocyte counts.

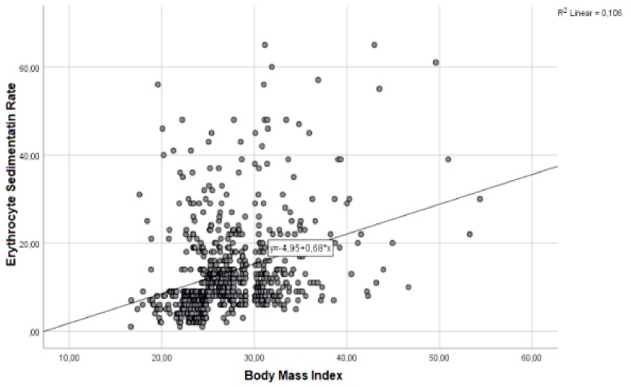

Figure 1c. Correlations between BMI and ESR, glucose levels and monocyte counts.

Discussion

In this study, as BMI increased, glucose, monocyte counts, ESR, and monocyte/HDL ratios were also found to be increasing. There were significant correlations between BMI and ESR, glucose, and monocyte count levels. When effects of age and gender are negated, increase in BMI was most associated with increased ESR levels.

It has been reported that obesity causes a low level but persistent inflammation (15). ESR is a general tool for evaluating the acute phase; it may help predict the magnitude of inflammation and may be used in many conditions, including rheumatic diseases (16). An association between ESR and enhancement in erythrocyte aggregation in obese patients was reported before, and this association was found to be independent of cholesterol levels (17). Obesity, with increased adipose tissue, results in a pro-inflammatory condition because of secreted cytokines and adipokines from activated immune system cells such as macrophages and lymphocytes (18). Cytokines, tumor necrosis factor-alpha, and interleukin-6 secreted from adipocytes were accused of the pro-inflammatory condition in adipose tissue (19). As a result of inflammatory cytokines, acute phase reactants such as ESR will increase (20). In a study with 10745 patients, ESR and inflammatory markers were elevated, related to increasing BMI (21). Interestingly, when obese people lose weight, inflammatory cytokine levels decrease (22). In this study, ESR values of participants were found to be increased with increasing BMI values, and the highest ESR values were recorded in the obese group, and these participants are expected to have concomitant inflammation. This finding is concordant with previous studies (15-19).

In a study, the relationship between erythrocyte aggregation and insulin resistance and glucose levels was reported. This relationship was found to be resulted from emerging acute phase reactants in response to inflammation (23). Similarly, this study also reveals the highest glucose levels in obese participants, and there is a significant correlation between BMI and glucose levels.

Monocytes are activated with inflammatory conditions, and by releasing cytokines, they aggravate inflammation (24). A study from Germany reported that monocyte counts were increasing in obese people (10). MHR is increased in inflammatory conditions like polycystic over syndrome (12). Also, the ratio of MHR was previously reported to be related to metabolic syndrome and obesity (25). In this study, there was an association between monocyte counts and MHR, but there was no association between BMI and HDL.

ESR was reported to be higher in females compared to males. Thus, laboratory normal values were determined differently according to gender, higher in females (26). This study is congruous and female participants had higher ESR values.

A study reported that non-HDL levels increase with increasing BMI values (14). In a study with diabetic

patients, LDL and total cholesterol levels were higher in overweight patients than patients with normal weight and obese patients (27). This study also reports highest non-HDL, LDL, and total cholesterol levels in the overweight group, similarly. Lipid profiles of overweight were worse than obese patients, which reminds obesity paradox. In previous studies, the obesity paradox was explained by the uneven distribution of fat throughout the body; for this reason, lean body mass and fat mass may be considered for better evaluation of BMI (28).

This study has some limitations. It has a retrospective design. In all participants, inflammatory parameters other than ESR, monocyte counts, MPV, and MHR were not evaluated. Confounding factors, such as diet and socioeconomic status of participants, were not considered in the evaluation of hyperlipidemia and obesity. Also, waist circumference and waist to hip circumference ratios were not available in every participant. Thus metabolic syndrome could not be evaluated.

Conclusion

This reported study reveals associations between BMI and ESR, glucose, monocyte counts, and MHR. BMI was most associated with increased ESR. As the oldest and widely used one of these parameters, ESR is correlated with BMI and is an effective tool to evaluate inflammation. In people who do not have concomitant diseases, there is a need for further studies about factors affecting erythrocyte aggregation and changes in ESR value.

Yazarlık katkısı: Fikir/Hipotez: RA Tasarım: RA, MBK, KSY Veri toplama/Veri işleme: RA, MBK, KSY Veri analizi: RA, MBK, KSY Makalenin hazırlanması: RA, MBK, KSY Makalenin kontrolü: RA, MBK, KSY.

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OLGU SUNUMU/CASE REPORT

Nadir Bir Eritema Nodusum Nedeni Olarak Epstein-Barr virüs: Bir Olgu Sunumu ve Literatür Taraması

A Rare Cause of Erythema Nodusum: Epstein-Barr virüs: A Case Report and Review of the Literature

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Rash

ÖZ

Eritema nodozum en yaygın septal pannikülit şeklidir. Vakaların %50'sinde hiçbir neden bulunamaz. Tanımlanmış nedenlerin en önemlilerinden biri enfeksiyonlardır. Epstein-Barr virüs de nadir bir eritema nodozum nedenidir. On beş yaşında kız hasta bir gün süren ateş ve bacaklarda daha belirgin ağrılı kızarık lezyonlar nedeni ile acil servise başvurdu. Fizik muayenesinde ön kol iç yüzünde ve bacaklarda en büyüğü 3X5 cm olan eritemli zemin üzerinde bulunan ağrılı nodüller dışında bulgu yoktu. Ön planda eritema nodozum düşünülen hasta servise yatırıldı. Yapılan tetkiklerden tam kan sayımı normal bulundu. Akut faz reaktanları yüksek bulunan hastanın alınan boğaz, idrar ve kan kültürlerinde üreme saptanmadı. Etiyolojiye yönelik yapılan mikrobiyolojik testlerden sadece anti-viral kapsid antijen (VCA)-IgM/IgG testi pozitif saptandı. Epstein-Barr virüse bağlı eritema nodozum tanısı alan hasta semptomatik tedavi ile takip edildi. Yatışının 8. gününde ağrısı ve lezyonları gerileyen hasta taburcu edildi. Epstein-Barr virüsün en sık cilt bulgusu makulopapüler döküntü olsa da eritema nodozum saptanan hastalarda akılda bulundurmalıdır.

ABSTRACT

Erythema nodosum is the most common form of septal panniculitis. In 50% of cases, no cause can be found. Epstein-Barr virus is a rare cause of erythema nodosum. A fifteen-year-old girl presented to the emergency department with fever and painful hyperemic lesions more prominent on the legs. Physical examination revealed no pathological findings except of the painful nodules, on the forearm and legs, the largest of which was 3X5 cm. The patient was hospitalized with diagnose of erythema nodosum. Complete blood count was normal. Acute phase reactants were found elevated. Cultures were found negative. Only anti-viral capsid antigen-IgM/IgG tests were found to be positive. The patient was followed up with symptomatic treatment. The patient, whose pain and lesions regressed, was discharged (8th day). Although the most common skin manifestation of Epstein-Barr virus is maculopapular rash, Epstein-Barr virus should also be kept in mind when erythema nodosum is detected.

Giriş

Eritema nodozum (EN), herhangi bir antijene veya tetikleyiciye yanıt olarak meydana gelen aşırı duyarlılık reaksiyonu sonucu oluşan en yaygın septal pannikülit şeklidir. Aynı zamanda inflamatuvar nodüllerin de en sık nedenidir. Vakaların yaklaşık %50'sinde hiçbir neden bulunamaz ve durumun idiyopatik olduğu kabul edilir. Tanımlanmış nedenlerin en önemlilerinden biri enfeksiyonlardır (1).

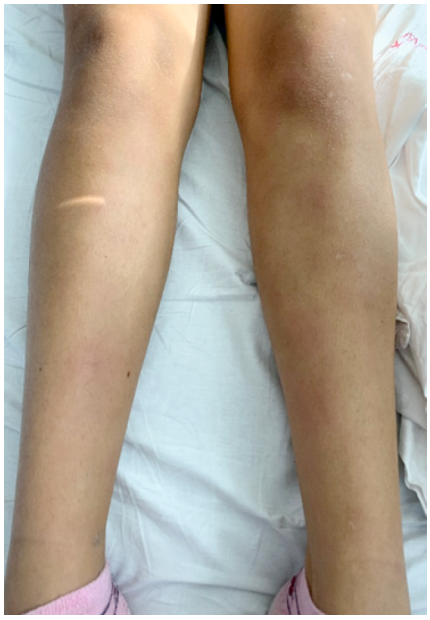
Epstein-Barr virüs (EBV); ateş, eksudatif farenjit, lenfadenopati, hepatosplenomegali ve atipik lenfositoz ile karakterize enfeksiyöz mononükleoza ve birçok sistemde etkilenmeye neden olabilecek bir virüstür (2). En sık meydana gelen cilt bulgusu makulopapüler döküntüdür. Daha seyrek olarak ise çocuklarda sıklıkla aksiller bölgeyi tutan tek taraflı laterotorasik ekzantem, "hedef" lezyonlar ve bol mukoz membran tutulumu ile karakterize Stevens-John-

son sendromu, EN, eritema multiforme ve kriyoglobulinemi ile ilişkili soğuk ürtiker görülebilmektedir (3). Bu vakada; EBV'nin nadir bir cilt bulgusu olan EN ile başvurup tetkiklerinde EBV saptanan 15 yaşında bir olgu sunularak, EN etiyolojisinde EBV'nin de akılda bulundurulması gerektiği vurgulanmak istenmiştir.

Olgu Sunumu

On beş yaşında kız hasta ateş ve bacaklarda daha belirgin olmak üzere her iki ön kol ve bacak ön yüzde ortaya çıkan ağrılı ve kızarık lezyonlar nedeni ile acil servise başvurdu. Ateşinin bir gün önce başladığı, dirençli olmadığı, döküntülerin oluşmasıyla da hastaneye başvurduğu öğrenildi. Akut gastroenterit nedeniyle çocuk enfeksiyon servisinde 6 gün takip ve tedavisi yapılan hasta 5 gün önce taburcu olmuştu. Son 2 ay içinde çevresinde ateşli veya döküntülü hastalık geçiren biri ile teması yoktu. Evinde kedi beslediği öğrenilen hastanın özgeçmiş ve soy geçmişinde başka özelik saptanmadı. Fizik muayenesinde bilateral ön kol iç yüzünde ve bacak ön yüzünde en büyüğü 3x5 cm olan eritemli zemin üzerinde bulunan ağrılı nodüller dışında patolojik bulgu yoktu (Şekil 1,2). Lezyonlar ilaç erüpsiyonu veya alerjik döküntü olarak değerlendirilmedi. Öncelikle EN düşünülen hasta ileri tetkik ve tedavi düzenlenmesi için servise yatırıldı. Tetkiklerinde hemoglobin değeri 12g/L, beyaz küre sayısı 14520uL, nötrofil sayısı 11880uL, lenfosit sayısı 1960uL, monosit sayısı 630uL, trombosit sayısı 362000uL, C Reaktif protein 104mg/L, sedimentasyon 125mm/h saptandı. Periferik yaymasında blast, atipik hücre veya downey hücresi görülmedi, ancak viral enfeksiyon ile uyumlu olarak değerlendirildi. Böbrek ve karaciğer fonksiyon testleri, koagulasyon testleri ile tam idrar tetkiki (TİT) normal sınırlarda idi. Evinde bulunan kedi ile sık teması olması ve *Bartonella Henselae* ajanına yönelik spesifik test gönderilme imkanı olmadığı için ek bir fizik muayene bulgusu olmamasına da rağmen hastaya ampirik azitromisin tedavisi başlandı. Gaita mikroskopisinde özellik yoktu. Gaitada Rota, Adeno antijen testleri negatifti. İmmunglobulin (Ig) E ve IgG düzeyleri yaşına göre uygun seviyelerde idi. Anti nükleer antikor (ANA) ve Anti dsDNA negatif bulundu. Tüberküloz için yapılan PPD testi negatif olarak değerlendirildi. Spesifik mikrobiyolojik ajanlara yönelik yapılan incelemelerde; grup A streptokok (GAS) hızlı antijen testi, Brucella tüp aglütinasyon testi ve Rose Bengal testi, HbsAg, Anti-HCV, Anti-HIV, Toxoplazma-IgM, Sitomegalovirüs (CMV)-IgM, Parvovirüs-IgM, *Mycoplasma pneumoniae*-IgM testleri negatif saptanırken EBV antiviral kapsid antijen (VCA)-IgM ve anti-VCA-IgG testi pozitif saptandı. Epstein-Barr nükleer antijeni (EBNA) antikorları ise negatif idi. Kan, boğaz, idrar ve gaita kültürlerinde üreme olmadı. Dirençli ateşi olmayan hastanın EBV enfeksiyonu saptanması nedeniyle azitromisin tedavisi 3. günde kesilerek semptomatik tedavi ile takip edildi. Batın ultrasonografi ve ekokardiyografi (EKO) normal olarak değerlendirildi. Göz muayenesinde patoloji saptanmadı. Hasta genel durumu ve beslenmesi iyi olması, lezyonlarının gerilemesi, ateşi ve ek şikâyeti olmaması nedeniyle yatışının 8. günü taburcu edildi. Olgu sunumu için hastadan bilgilendirilmiş onam alınmıştır.

Şekil 1. Ön Kolda Bulunan Eritema Nodozum Lezyonları.



Şekil 2: Bacaklarda Bulunan Eritema Nodozum Lezyonları.

Tartışma

Panniküllit, deri altı yağ dokusunun yama veya nodüller ile karakterize ani gelişen ve nadir görünen iltihaplanmasıdır. Eritema nodozum, panniküllitin en yaygın klinik sunumudur. Yılda yaklaşık 100.000 kişide 1-5 oranında görünür. En yüksek insidans 15-30 yaş arası genç kadınlarda olmakla birlikte bu yaş grubunda erkek/kadın oranı 1:6'dır. Çocuklarda ise cinsiyetler arası oran 1:1'dir (4). Hastamız 15 yaşında ve kız olup, EN'nin en yüksek insidansa sahip olduğu yaş aralığı ve cinsiyette idi.

Eritema nodozum tanısı klinik olarak konmaktadır. Genellikle pretibial bölgede ani başlayan ağrılı ve kızarık nodüller ile karakterizedir. Hastalığın

tanısında kullanılan klinik kriterler; 1. Ağrılı, eritematöz veya mor renkte, nodüller veya yama şeklinde, genellikle 1-5 cm boyutunda, sınırları düzensiz ve belirsiz lezyonlar 2. Simetrik tibial ön yüzeyde meydana gelen lezyonlar (diğer cilt alanlarına ulaşsın veya ulaşmasın) 3. Ani ortaya çıkan ve 8 haftadan kısa süren lezyonlar 4. Ülserasyon veya yara izi olmaksızın gerileme (4). Lezyonların en sık yerleşim yeri tibial ön yüzeydir, ancak önkol, uyluk, göğüs ve hatta yüzü veya ekstansör yüzeyi de tutulabilir (5). Hastamızın tanısı klinik olarak, ani başlayan, hiperemik zemin üzerinde, en büyüğü yaklaşık 3x5 cm olan, bilateral alt ekstremite ön yüzlerde daha belirgin olmakla birlikte ön kolda da bulunan ağrılı nodüllerin bulunması ile konuldu.

Kapsamlı araştırmalara rağmen EN'li hastaların yarısında etiyolojik bir neden bulunamamaktadır (4). Tespit edilen nedenler arasında enfeksiyonlar, ilaçlar, aşılar, gebelik, inflamatuar barsak hastalıkları, sarkaidoz, otoimmun hastalıklar, paraneoplastik hastalıklar sayılabilir (1). Enfeksiyoz nedenler arasında en sık araştırılması gerekenler streptokokal enfeksiyonlar (GAS farenjit), tüberküloz, EBV, CMV, Varicella Zoster Virüs, Kabakulak başta olmak üzere salmonella, şhigella, mikoplazma gibi bakteriyel, hepatit A, B, C, HIV ve parvovirüs B19 gibi viral, Toxoplasma *gondii*, *Ascaris lumbricoides*, *Entamoeba histolytica* gibi paraziter, Aspergillus ve *Candida albicans* gibi mantar kaynaklı enfeksiyoz etkenler de araştırılmalıdır (6). Hastamızın akut faz reaktanları yüksek idi. Biyokimyası ve TİT normaldi. Anamnezinde alerji veya ilaç erüpsiyonu düşündürecek özelik yoktu. Serum IgE düzeyi normal sınırlarda idi. Otoimmun hastalıklar açısından bakılan ANA ve Anti dsDNA negatif bulundu. Yakın zamanda gastroenterit nedeni ile yatış hikayesi olması sebebiyle bakılan eski ve yeni gaita tetkiklerinde (Rota antijen, Adeno antijen, gaita mikroskopisi, gaita kültürü) özelik saptanmadı. PPD testi negatif olarak değerlendirildi. EKO'da kardiyak patoloji saptanmadı. Boğaz, idrar ve kan kültüründe üreme olmadı. GAS hızlı antijen testi, Brucella tüp aglütinasyon testi ve Rose Bengal testi, HbsAg, Anti-HCV, Anti-HIV, Toxoplazma, CMV, Parvovirüs, *Mycoplasma pneumoniae*-IgM testleri negatif saptanırken, Anti-VCA-IgM ve IgG testleri pozitif, EBNA antikorları negatif saptandı. Böylece hastamızda ortaya çıkan EN'nin akut EBV'ye bağlı olduğunu tespit etmiş olduk.

Epstein-Barr virüs, insan popülasyonunun büyük bir bölümünü enfekte eden ve periferik kanda bulunan hafıza B hücrelerinde latent formda kalan bir herpes virüsüdür. Gelişmiş ülkelerde, EBV enfeksiyonu prevalansı çocuklarda %60-80'e ve erken yetişkinlik döneminde %95'e yaklaşmaktadır (7). Yaygın görünmesinin en önemli nedeni yakın teması ile kolayca bulaşabilmesidir ve bu bulaşın büyük bir kısmını oluşturmaktadır. Diğer bulaşma yolları ise kan transfüzyonu, allograft transplantasyon, cinsel ilişki ve hane halkı veya bakıcı ile yakın temastır (8). EBV, bademcikler ve adenoidler gibi lenfoid dokulardaki B hücrelerini enfekte etmek için mukozal epitelden geçer ve 30-50 günlük inkübasyon süresi boyunca, viral replikasyon ve yayılma, lenforetiküler sistem yoluyla gerçekleşir (7). Hastamızın son 2 ay içinde yakın çevresinde ateşli, döküntülü hastalık geçiren biri ile teması yoktu.

Epstein-Barr virüs enfeksiyonları genellikle asemptomatik seyretmektedir. Eğer semptomatik ise ana belirtiler ateş, farenjit, lenfadenopati ve splenomegalidir. Ayrıca EBV; aseptik menenjit, ensefalit, miyelit, optik nörit, kraniyal sinir felci, transvers miyelit, Alice Harikalar Diyarında sendromu, Guillain-Barré sendromu gibi nörolojik belirtilere, dalak yırtılması, agranülositoz, hemolitik anemi ve hemofagositik lenfohistiyositoz (HLH) gibi hematolojik belirtilere neden olabilmektedir. Nadir olarak ta hastalarda pnömoni, orşit ve miyokardit görülebilir (2,9). Hastamızda ateş ve eritema nodozum dışında klinik belirti yoktu. Göz muayenesi ve EKO normal olarak değerlendirildi. Organomegali saptanmadı.

Epstein-Barr virus'e bağlı cilt döküntüsü, genellikle ilk olarak gövde ve üst ekstremitelerde, ardından yüze ve ön kollara uzanan eritemli, makulopapüler bir döküntüdür. Bir haftaya kadar sürebilir. Varsayılan bakteriyel enfeksiyonu tedavi etmek için kullanılan penisilin (özellikle amoksisilin ve ampisilin), başlanmasından 7-10 gün sonra aşırı duyarlılık deri reaksiyonunun gelişmesine yol açabilir. Bu döküntü, ekstansör yüzeyler ve basınç noktaları üzerinde gelişen ve gövde ve ekstremitelere yayıldıkça birleşik hale gelen maküler bir döküntüdür (7). EBV'ye bağlı nadir de olsa EN de görülebilmektedir (3). Bizim de hastamızda EBV'nin sık görünen deri bulgularından ziyade nadir bir cilt bulgusu olan EN saptandı.

Epstein-Barr virüs'ünün tanısında klinik bulgular yanında laboratuvar tetkiklerinden faydalanılmaktadır. Hemogramda anemi, lökopeni, trombositopeni görülebilmektedir. Ancak lenfositoz ve monositoz daha sık bulunmaktadır. Periferik yaymada atipik lenfositlerin %10 ve üzerinde saptanması önemli bir destekleyici bulgudur (10). EBV enfeksiyonu tanısı için en yaygın kullanılan test, VCA'ya karşı gelişen antikor düzeylerinin saptanmasıdır. Enfeksiyonun erken dönemlerinde anti-VCA-IgG yüksek titrede ortaya çıktığından ve yaşam boyu orta düzeylerde kaldığından, tek başına aktif enfeksiyonun varlığını belirlemek için yararlı değildir. Bunun tersine, anti-VCA-IgM antikorunun tespit edilmesi, aktif ve yeni enfeksiyonları tanımlamak için yararlıdır. EBNA'ya karşı gelişen antikorlar ise enfeksiyo-

nun başlangıcından belirli bir süre geçmesi ile ortaya çıkmaktadır. Anti-VCA-IgM pozitif ve EBNA antikorunun negatif saptanması kuvvetle akut EBV enfeksiyonunu düşündürmektedir. Aksine çok yüksek EBNA antikor düzeyleri aktif enfeksiyonu dışlayabilmektedir (2,9). Hastamızda anti-VCA-IgM ve anti-VCA-IgG pozitif olarak saptanırken EBNA antikoru ise negatif bulundu. Hematolojik parametrelerde anomali yoktu. Ancak periferik yayma viral enfeksiyon ile uyumlu saptandı.

Çoğu EN vakası kendi kendini sınırlar ve dikkatli gözlem dışında hiçbir tedavi gerektirmez. Tedavi esas olarak semptomatiktir. Rahatsızlığı azaltmak için genellikle yatak istirahati ve bacak kaldırma önerilir. Steroid olmayan antiinflamatuvar ilaçlar (örn. ibuprofen, naproksen, indometasin) ağrı tedavisinde ilk seçenek tedavidir. Pediatrik yaş grubunda asetilsalisilik asit kullanımından kaçınılmalıdır. Sistemik kortikosteroidler, ağrının azaltılmasında ve lezyonların çözülmesinde hızlı bir şekilde etkili olabilir ve şiddetli vakalarda düşünülebilir ancak kullanılmadan önce tüberküloz gibi bulaşıcı nedenler dışlanmalıdır (1,11). EBV'de de tedavi genellikle semptomatiktir. Kısa süreli kortikosteroidler ile yapılan tedavinin bazı akut semptomlar üzerinde yararlı bir etkisi olabilmesine rağmen, potansiyel yan etkiler nedeniyle, kullanımı yalnızca; hava yolu obstrüksiyonu muhtemel belirgin tonsiller iltihabı olan hastalar, masif splenomegali, miyokardit, hemolitik anemi veya HLH ile birlikte olan hastalar için düşünülmelidir (2). Hastamızda tanının EBV lehine sonuçlanması nedeniyle mevcut antibiyotik tedavisi kesilerek analjezik ile izlendi ve yatışının 8. gününde lezyonları gerilemesi üzerine hasta taburcu edildi.

Epstein-Barr virüs ve EN birlikteliği nadir görülen bir durumdur. Biz de bu olgu ile EBV'nin nadir bir cilt bulgusu olan EN'li 15 yaşında bir hastayı sunarak Türk literatürüne bir katkıda bulunmak istedik.

Yazarlık katkısı: Fikir/Hipotez: ÖK, DKİ, HKT, ÖYU, AN, AK. Tasarım: ÖK, DKİ, HKT, ÖYU, AN, AK. Veri toplama/Veri işleme: ÖK, DKİ, HKT, ÖYU, AN, AK. Veri analizi: YB. Makalenin hazırlanması: HKT, ÖYU, AN. Makalenin kontrolü: ÖK, DKİ, AK.

Etik Kurul Onayı: Gerekli değildir.

Hasta Onayı: Olgu sunumu için hastadan izin alınmıştır.

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OLGU SUNUMU/CASE REPORT

Primer Kadın Üretra Karsinomu: Bir Olgu Sunumu

Primary Carcinoma of the Female Urethra: A Case Report

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Key Words:
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ÖZ

Kadınlarda primer üretra kanseri literatürde son derece nadir karşılaşılan bir durumdur. Bu olgu sunumunda hematüri yakınması ile başvuran ve primer üretra kanseri tanısı konulan 79 yaşındaki kadın hastanın literatür bilgileri altında tartışılması amaçlanmıştır.

ABSTRACT

Primary urethral carcinoma in women is rare in the literature. The aim of the present case report was to discuss with literature the 79 years old female patient who presented with hematuria complaint and was found to have primary urethral cancer.

Introduction

Urethral cancers are rare in women. They account for approximately 0.02% of all cancers in women. As with other types of cancer in the urinary system, there are no specific diagnostic symptoms. Dysuria, hematuria, urethrorrhagia, weak urine stream, pollakiuria, acute urinary retention, recurrent urinary tract infections, perineal pain are major complaints with which patients apply to clinics. This nonspecific clinical presentation often leads to delays in diagnosis, and urethral cancers are highly aggressive for both sexes (1). An in-depth analysis shows that studies into female urethral cancers with large case series are quite limited. Unlike other urogenital system tumors such as kidney, bladder and prostate, there is no detailed information about risk factors, diagnosis, follow-up and treatment approaches (2). Aim of the present case report was to demonstrate clinical approach we used, with a literature review, for a 79 years old female patient who applied to our clinic with hematuria complaint and had primary urethral cancer diagnosis.

Case Report

Seventy-nine years old woman admitted to our clinic about three months ago with intermittent hematuria complaint. Our patient, who was in the postmenopausal period, had a 20-year history of smoking packs. She had no surgery, radiotherapy or chronic disease except for dementia. In the medical history of our patient, it was determined that urethral catheterization was not performed for any reason. Results of laboratory examinations were as follows: serum creatinine 1.01 mg/dl, urea 36.11 mg/dl, hemoglobin 11.14 g/dl and white blood cell count 9100/mm^3. Urine analysis confirmed gross hematuria (RBCs full number), albumin +1, white blood cells 6-11/high power field (HPF), negative nitrite and casts absent. Plain abdominal x-ray appeared normal. Renal ultrasonography showed normal kidney measurements and echogenicity and it excluded hydronephrosis, masses or stones. On axial contrast-enhanced computed tomography examination, the 2 cm size mass lesion showing predominantly peripheral contrast enhancement, with a slightly irregular border, soft

tissue density, which is indistinguishable from the muscle plans extending to the periurethral area by filling the urethra. No pathological lymph node was detected in the parailiac or inguinal region adjacent to the mass lesion (Figure 1a,b). Images were evaluated by two radiologists, and no finding was found indicating metastatic disease within the limitations of contrast-enhanced computed tomography. Detailed physical examination showed papillary tumor mass in external urethral meatus. In cystourethroscopy, tumors were observed throughout the urethra. On the other hand, no tumor was observed in both bladder neck and bladder. It was observed that the lesion was fragile and hyperemic in the endoscopic evaluation, however it did not cause complete obstruction in the urethra. Cold cup biopsy was taken from the mass during endourological evaluation. In pathological evaluation of specimens, malignant tumoral infiltration was observed in the form of trabecular, insular and solid areas, indicating invasiveness in large areas. Tumoral structures were found to consist of large hyperchromatic malignant cells with pleomorphic nucleus, unclear margins, narrow eosinophilic cytoplasm and high nucleus/cytoplasm ratio. These cells had solid trabecular development forming focal follicle-like structures in some places. It was observed that they had quite pronounced pleomorphism and bizarre nuclear forms in some places with frequent and atypical mitosis (Figure 2a, b). Pathologists of our clinic reported that the tumor was an invasive high-grade urothelial carcinoma. Radical cystourethrectomy was performed with bilateral pelvic lymph node dissection, hysterectomy, salpengectomy and anterior vaginal wall excision followed by ileal urinary diversion. In accordance with the results of the urethra biopsy examination, histological evaluation of radical cystourethrectomy material showed tumor cells with large hyperchromatic and pleomorphic nucleus, unclear margins and pale eosinophilic cytoplasm. These tumor cells were observed to have frequent and atypical mitosis (Figure 2c). Pathology showed high grade urethral carcinoma (TCC) without metastases in other urogenital organs examined within the surgical specimen. After a

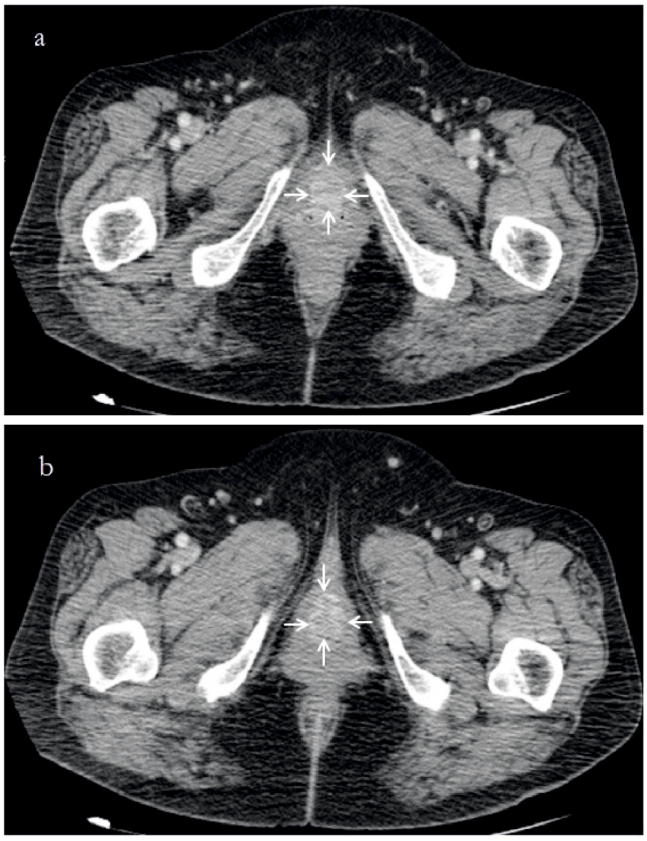

Figure 1a,b. The 2 cm size mass with predominantly peripheral contrast enhancement in the urethra in whole abdominal contrast-enhenced tomography.

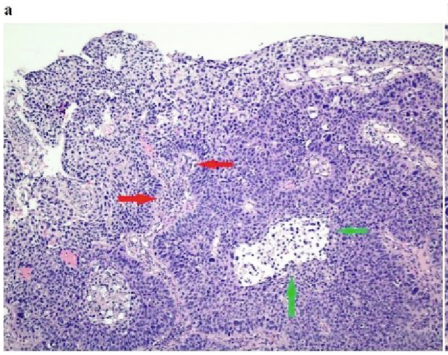

Figure 2a. Cold cup urethra biopsy material. Infiltration of malignant tumor which had invasion in large areas and developed as trabecular, insular and solid areas. Tumor areas include fibrovascular stromal proliferation (red arrows) and cystic necrotic areas (green arrows) (Magnification x 10).

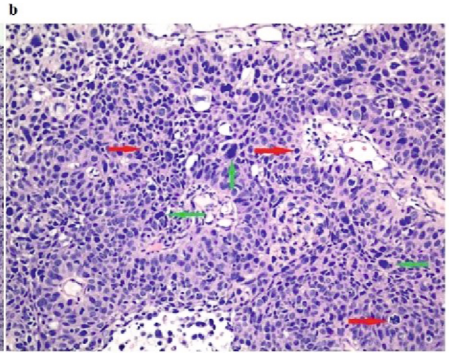

Figure 2b. Urethra biopsy material. Malignant cells with hyperchromatic and pleomorphic nucleus, unclear margins, narrow eosinophilic cytoplasm and high nucleus/cytoplasma ratio and with solid trabecular development forming focal follicle-like structures in some areas. Pleomorphism in cells is quite prominent and occasionally bizarre nuclear forms (green arrows) and frequent and atypical mitosis (red arrows) are observed (Magnification x 40).

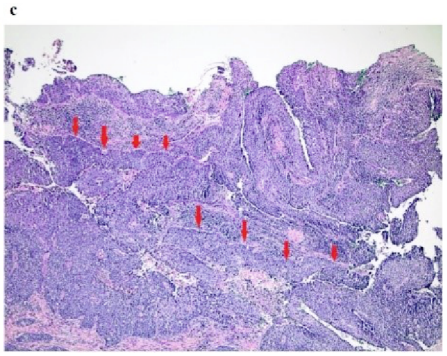

Figure 2c. Radical cystourethrectomy material. Tumor cells with coarse hyperchromatic and pleomorphic nuclei, whose borders are not clearly selected, are observed. Frequent and atypical mitosis are evident in tumor cells (red arrows) (Magnification x 40).

three-month postoperative follow-up, she was asymptomatic without any findings in the physical examination and in whole abdomen contrast-enhanced computed tomography. The patient was consulted to the medical oncology department, and after detailed evaluation, adjuvant chemotherapy was not suggested. The patient's follow-ups are still continuing in our clinic. Written consent was obtained from the patient.

Discussion

Urethral cancers account for only 0.003% of all urogenital malignancies in women. In broad-based epidemiological studies, on the other hand, this cancer was reported to have an annual incidence rate of 1.5 cases per million in the USA. The female urethral lumen is covered by transitional epithelial cells proximally and by a non-keratinized stratified squamous cell layer distally (1). Many factors such as recurrent urinary tract infections, urethral diverticulum and human papillomavirus are blamed for its etiology (3). Traditional imaging methods such as voiding cystourethrography and retrograde urethrography could help in diagnosis. Urethrography often shows focal, irregular narrowing of the urethra. However, extraluminal or periurethral spread cannot be characterized with these imaging methods. A high-resolution transvaginal, transperineal and transurethral ultrasonography performed by an experienced radiologist help in diagnosis, but time consuming and the operator-dependent nature of the examinations constitute some disadvantages in this approach. In computed tomography, urethral cancers are observed as a contrast-enhanced mass in soft tissue attenuation. In magnetic resonance imaging, squamous cell carcinomas or transitional cell carcinomas of urethra exhibit heterogeneous contrast enhancement with hypointense signal feature in T1A images and hypointense-intermediate signal feature in T2A images compared to normal corporal tissue whereas adenocarcinomas are relatively hyperintense in T2A images. On the other hand, both computed tomography and magnetic resonance imaging are very important for clinicians in assessing the local and systemic spread of the urethral tumors (4,5). Because distant staging should concentrate on chest and liver, with CT of the thorax and abdomen in all patients with invasive disease (6). As with urethral tumours in males, MRI has limited utility in depicting stage I disease. However, the target-like appearance of the normal urethra on axial T2-weighted images will be disrupted in stage II lesions. With stage III and IV disease, differentiation of primary urethral lesions from those of the vulva or vagina may be difficult (5). Nevertheless, the gold standard for the diagnosis of patients is cystourethroscopy with urethra biopsy. In terms of pathological evaluations, previous studies showed that about 45% of the cases had transitional epithelium cell carcinoma, 29% adenocarcinoma and 19% squamous cell carcinoma (3). Race, advanced age, lymph node positivity, non-squamous histology and advanced stage were found to be associated with poor prognosis in urethral tumors (6). On the other hand, it was revealed that survival is better in distal tumors compared to proximal tumors. However, it was mentioned that primary urethral carcinomas are a highly aggressive malignancies, and 5-year survival rate varies between 40 and 60%. There is no standardized treatment approach accepted worldwide (7). Treatment is planned according to the tumor localization, clinical stage and clinical condition of patient. Local mass excision and partial urethrectomy are often of limited use in distally located superficial urethral cancers not reaching large sizes. This approach has disadvantages such as high recurrence rates and vulnerability to complications such as urinary incontinence and urethral stenosis (8,9). Another surgical approach is anterior exenteration (total urethrectomy, pelvic lymphadenectomy with cystectomy, salpingectomy, hysterectomy and resection of the anterior wall of the vagina) and urinary diversion (2). It is observed that tumor load in particular is preferred by masses of excess proximal origin. Previous studies reported that disease free survival rate was over 70% when tumors of non-aggressive histological subgroups were treated with anterior exenteration alone (10). We think that major surgical approaches in the treatment of female urethral cancers are very important in order to keep tumoral survival at an ideal level, even if the patients' age and cobormid status elevated.

Another treatment protocol is radiotherapy. Milosevic et al. (11) applied radiotherapy for 34 patients with urethral tumors, observed tumor recurrence in 21 patients and reported a 45% seven-year survival rate for the disease. In the same study, 16% of patients were reported to have very serious complications related to the treatment (11). In a similar study, Garden et al. reported that five-year local control rates after radiotherapy was 64%, and 49% of these patients had local complications and 15% of them had serious complications (12). It is very difficult to fight with urethral tumors with only chemotherapy agents. In many studies, it was shown that the rates of recurrence were above 25% in treatment regimens using only this treatment approach (3). On the other hand, most author preferred adjuvant polychemotherapy for locally advanced female urethral cancers such as pT3-4 disease and for

selected high risk. To this end, gemcitabine, cisplatin, and ifosfamide, or cisplatin, 5-fluorouracil and gemcitabine are frequently used treatment strategies. These chemotherapy protocols could be combined with surgical approach or with radiotherapy, or all three approaches could be used together (1). For our case, combined treatment was not required due to the lack of remote organ dissemination and perfect removal of malignant formations.

Urethral cancers are rarely seen in women, and since this oncological pathology has nonspecific findings, delays are experienced in diagnosis and treatment protocols. Detailed gynecological examination and imaging methods such as magnetic resonance or computed tomography are very important in the diagnosis of female urethral cancer. On the other hand, biopsy taken under cystourethroscopy is essential for the diagnosis to be confirmed.

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HMJ

OLGU SUNUMU/CASE REPORT

Covid-19 Pnömonisi ile İlişkili Pnömotoraks Olgu Sunumu

A Case Report with Pneumothorax Associated with Covid-19 Pneumonia

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Anahtar Sözcükler:
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Pneumonia
Pneumotorax
Thoracic Tube

ÖZ

Covid-19 ilk olarak Çin'de 2019 Aralık ayında görülmüş olup, yüksek bulaşıcılığa sahiptir ve tüm dünyada hızla yayılmaya devam etmektedir. Mart ayında Dünya Sağlık Örgütü tarafından pandemi olarak bildirilmiştir. Covid-19 sonrası pnömoni sık görülür. Yapılan çalışmalarda sekonder pnömotoraks nadirdir. Görülme oranı % 1-2 arasında olup ciddi solunum sıkıntısı ve ölüme neden olabilmektedir. Olgu sunumunda Covid-19 nedeniyle serviste yatan 71 yaşında, ani nefes darlığı ve göğüs ağrısı olan sonrasında satürasyonları düşünce yapılan görüntülemede sağda pnömotoraks geliştiği görülen hastadan bahsettik. Covid-19 nedeniyle takip edilen hastalar ani gelişen solunum sıkıntısında spontan pnömotoraks açısından dikkatli değerlendirilmelidir.

ABSTRACT

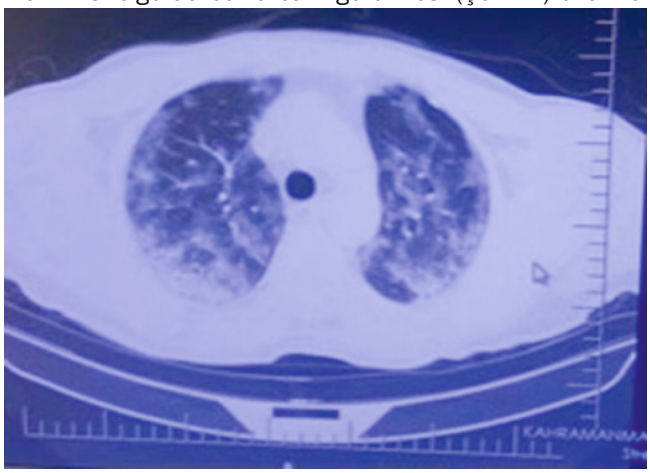
Covid-19 was first seen in China in December 2019, and it was highly contagious and It was reported as a pandemic by the World Health Organization in March. Postcovid-19 pneumonia is quite common. Secondary pneumothorax due to pneumonia is rarely seen in the literature. Its rate is between % 1-2 and it can cause severe respiratory distress and death. The hospitalized patients due to Covid-19 suddenly suffered from severe shortness of breath and chest and imaging revealed right lobe pneumothorax. Physicians should be careful in terms of pneumothorax in patients with sudden respiratory distress during the active Covid-19 disease.

Giriş

Covid-19 ilk olarak Aralık 2019'da Çin'in Wuhan kentinde tespit edildikten sonra küresel bir salgın olarak ilan edilmiştir. Covid-19 hastalığı asemptomatik şiddetli akut solunum sendromuna kadar geniş bir yelpaze içerir. Hastada tipik olarak ateş, öksürük ve nefes darlığı gibi solunum semptomları görülür. Radyolojik görüntüleme, Covid-19 pnömonisinin tanı ve takibinde önemli rol oynar. Radyolojik görüntülemede genellikle alt lobları tutan periferik veya posterior dağılıma sahip yamalı buzlu cam opasiteleri görülür(1). Güncel literatürde spontan pnömotoraks % 1'den az insidansla Covid-19 pnömonisinin nadir bir komplikasyonudur(2). Bununla birlikte, vaka sayısı arttıkça, Covid-19 enfeksiyonu çeşitli diğer solunum patolojileriyle ilişkili olarak giderek daha fazla tanınmaktadır. Bu olgu sunumunda Covid-19 pnömonisi ile takip edilen hastada meydana gelen pnömotoraks olgusu litaratür eşliğinde sunulacaktır.

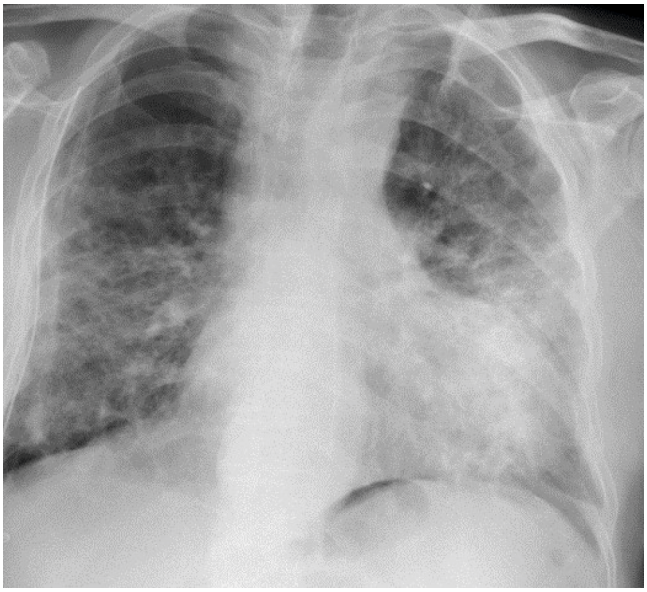
Olgu Sunumu

Yetmiş bir yaşında erkek hastanın ateş, öksürük şikayeti olup çekilen akciğer bilgisayarlı tomografisinde her iki akciğerde buzlu cam görülmesi (Şekil 1) üzerine



Şekil 1. Toraks bilgisayarlı tomografide bilateral buzlu cam görünümü izlenmektedir.

PCR testi alındıktan sonra göğüs hastalıkları servisine yatırıldı. Ek hastalık olarak Hipertansiyona sahipti. Yatış esnasında tansiyonu normal, oda havasında satürasyonunu % 92 idi. Lökosit: 9.71 mcL, C-reaktif protein: 105 mg/L, prokalsitonin: 0.195 ng/mL, D-dimer: 760 ng/ml, Kreatinin: 1.2 mg/dl, Ferritin: 282 ml/ng, Fibrinojen: 468 mg/ng, Covid-19 PCR testi pozitifti. Plaquanil tablet 200 mg oral, Aveloks 400 mg intravenöz flakon, Clexane 0.6 mg hazır enjektör subkutan, Prednol tablet 40 mg intravenöz olarak verildi. Servis takiplerinde şikayetleri gerileyen, C-reaktif protein değeri düşen hasta yatışının yedinci gününde aniden nefes darlığı gelişmesi ve satürasyonları düşmesi üzerine yapılan fizik muayenede, sağ hemitoraksta solunum sesi azalması tespit edildi ve akciğer bilgisayarlı tomografisi istendi (Şekil 2a ve 2b). Sağda pnömotoraks tespit edilen hastanın sağ tarafına göğüs dreni takıldı ve bir haftada pnömotoraksın tam olarak rezorbe olduğu görüldü (Şekil 3). Hasta takibe alınarak taburcu edildi. Hastadan bilgilendirilmiş gönüllü onam formu alınmıştır.

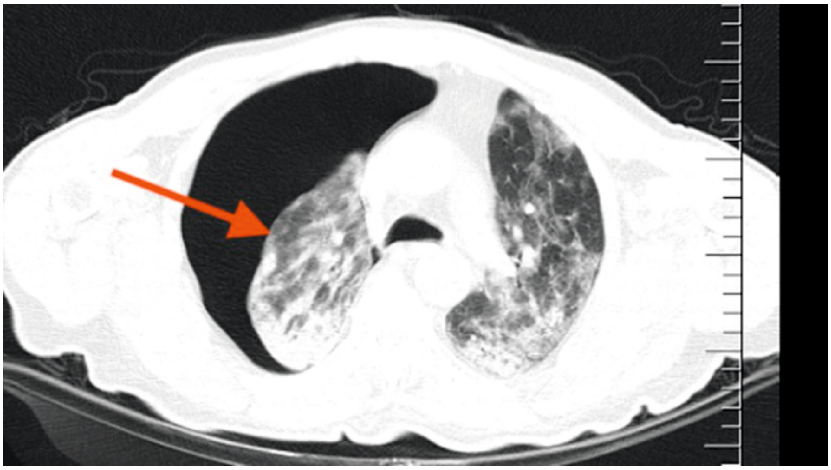


Şekil 3. Toraks tüpü takılması sonrası pnömotoraksın gerilediğini gösteren akciğerin direkt grafi görünümü.

Tartışma

Covid-19 enfeksiyonu genellikle gribal semptomlar ile seyretmekte olup en tipik semptomları kuru öksürük, ateş, nefes darlığı, yorgunluk, kas ağrısı ve boğaz ağrısıdır. Pnömoni başlıca ateş, öksürük, nefes darlığı ve akciğer görüntülemesinde iki taraflı infiltrasyonla karakterize olup enfeksiyon'un en sık görülen ciddi belirtisidir. Komorbid hastalığı olanlarda ölüme neden olabilmektedir. Covid-19 enfeksiyonunda ARDS'ye (Akut respiratuar stres sendromu) varan solunum yetmezliği, kardiyak aritmi ve kardiyak iskemiye kadar giden kardiyak problemler, tromboembolik olaylar, sitokin sendromu gibi inflamasyon ilişkili komplikasyonlar gözlenebilmektedir. Ayrıca sekonder infeksiyonlar ve nörolojik komplikasyonla oluşabilmektedir (3). Pnömotoraks, gelişen nadir komplikasyonlardan biridir. Pnömotoraks, iki plevral tabaka arasındaki boşlukta akciğer parankiminin çökmesine neden olan havanın varlığı ile karakterizedir. Spontan pnömotoraks primer ve sekonder olabilir. Primer spontan pnömotoraks klinik bir akciğer hastalığı olmayanlarda gelişen bir durumdur. Sıklıkla küçük apikal subplevral kabarcıklar ve büllerin rüptürüne bağlı olarak gelişir. Sigara içimi ve genetik yatkınlığın gelişimde etkili olduğu düşünülmektedir. Sekonder spontan pnömotoraks ise altta yatan hastalığı olan kişilerde gelişen pnömotorakstır. En sık sebep kronik obstrüktif akciğer hastalığı olmakla birlite kistik fibrozis, primer veya metastatik akciğer maligniteleri, nekrotizan pnömoni gibi

Şekil 2a. Akciğer direkt grafisinde sağda pnömotoraks izlenmektedir.



Şekil 2b. Toraks bilgisayarlı tomografisinde sağda pnömotoraks izlenmektedir.

durumlar diğer sebepler arasındadır. Kendiliğinden olabilir veya amfizem benzeri kronik obstrüktif akciğer hastalığı, tümörler, interstisyel akciğer hastalıkları, bağ dokusu hastalıkları ve enfeksiyonlar gibi diğer hastalıklara ikincil olarak gelişebilir. Koronavirüs enfeksiyonu 2019'un sonuna doğru başlamıştır ve hala etkisini yoğun bir şekilde sürdürmektedir. Zaman geçtikçe koronavirüs enfeksiyonunun hem akciğer hem de akciğer organ dışı üzerine etkisi daha iyi görülmektedir. Aynı zamanda koronavirüsün mutasyona uğraması da hastalarda klinik spektrumda değişikliklere yok açabilmektedir. Koronavirüs enfeksiyonu sonrası pnömotoraks literatürde bildirilmekle birlikte sık olmayan durumlardan biridir. İngiltere'de 16 merkezde koronavirüs enfeksiyonu nedeniyle takip edilen 71 hastada pnömomedİastinum veya pnömotoraks izlenmiştir. Bu hastaların ikisinde, iki ayrı pnömotoraks izlenmiştir. Bu hastalar değerlendirildiğinde olguların daha çok erkeklerde izlendiği ileri yaşlarda (70 yaş üzeri) sağ kalımın gençlere göre daha az olduğu, yirmi sekiz gün sağ kalım izlendiğinde her iki cins arasında bir fark izlenmediği görülmüştür (4). Bir başka çalışmada 3368 hasta retrospektif olarak değerlendirilmiştir ve bu hastaların 6'sında (% 0.66) pnömotoraks izlenmiştir. Bu 6 hastanın 4'ü kadın 2'si ise erkek hastadır, bu hastaların 4'ünde hastane takibinde ölüm gerçekleşmiştir (5). Covid-19 enfeksiyonu olgularında altta yatan başka bir hastalığı olan vakalar bildirilmekle birlikte akciğer hastalık öyküsü olmayan kişilerde de pnömotoraks izlenmiştir (6). Bu vakalarda pnömotoraksın etyopatogenezi bilinmemekle birlikte, Covid-19 enfeksiyonuna bağlı pnömoni ile ilişkili fibroz, uzun süreli inflamasyon ve iskemi, alveollerin hasar görmesine ve plevral boşluğa hava sızıntılarının ortaya çıkmasına neden olabilir (7). 11 Mart 2020 tarihinde Çin'de yapılan bir çalışmada pnömotoraks ile kombine Covid-19 enfeksiyonu olan hastalarının mortalite oranı % 42.9 kadar yüksek olup, pnömotoraksın Covid-19 enfeksiyonu olan hastalarda kötü prognoz işareti olabileceğinden hasta takibinde çok dikkat edilmelidir. Hastanın erken tanı ve tedavisi, iyi prognozu açısından bir fırsattır. Vakamız da 71 yaşında bir erkek hastaydı ve özgeçmişinde bilinen bir akciğer hastalığı yoktu. Literatürde pnömotoraks gelişen hastalarda mortalite riski arttığı bildirilse de hastamızda entübasyon ihtiyacı olmadı ve ölümle sonuçlanmadı.

Sonuç olarak Covid-19 enfeksiyonu çok çeşitli klinik bulgularla kendini gösterebileceği gibi daha az sıklıkla pnömotoraks ile de prezente olabilir veya takip sırasında oluşabilir. Bu hastalarda mortalitenin daha sık olabileceği ve altta yatan bir başka bir akciğer hastalığı olmayanlarda bile gelişebileceği akılda tutulmalıdır.

Yazarlık Katkısı: Fikir/Hipotez: HŞ, Tasarım: HŞ, Veri toplama/Veri işleme: HŞ, Makalenin hazırlanması: HŞ, Makalenin kontrolü: HŞ.

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OLGU SUNUMU/CASE REPORT

Lenfadenopatinin Nadir Teşhis Konulan Bir Nedeni: Kedi Tırmığı Hastalığı

A Rare Diagnosed Cause Of Lymphadenopathy: Cat Scratch Disease

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ÖZ

Kedi tırmığı hastalığı Bartonella henselae isimli bakterinin neden olduğu zoonotik bir enfeksiyon hastalığıdır. Olgu sunumumuzda 27 yaşında uzun süren yüksek ateş, iştahsızlık, kilo kaybı, terleme, halsizlik, baş ağrısı ve bilateral servikal lenfadenopati ile başvuran, birçok bakteriyel ve viral ajan açısından araştırılan, lenfoproliferatif hastalıklar ve malignite açısından tetkik edilen hastamız ele alınmıştır. Eksizyonel biyopsi yapılan ve histolojik incelemede granülomatöz lenfadenit görülen, serolojik incelemede B. henselae antikorları yüksek titrede pozitif tespit edilen hastamızın anamnezi derinleştirilip şüpheli kedi teması açısından sorgulandığında 3 ay önce sağ dizinde bulunan açık yaranın kedi tarafından yalandığı öğrenilmiştir. Kedi tırmığı hastalığı akut, subakut ve kronik lenfadenopatinin önemli bir nedenidir. Ülkemizde sporadik olarak görülmekle birlikte son yıllarda yapılan serolojik çalışmalar enfeksiyonun tanı konulandan çok daha yaygın olduğunu ortaya koymuştur. Kedi tırmığı hastalığı lenfadenopati ile başvuran hastalarda ayırıcı tanıda mutlaka akla getirilmelidir.

ABSTRACT

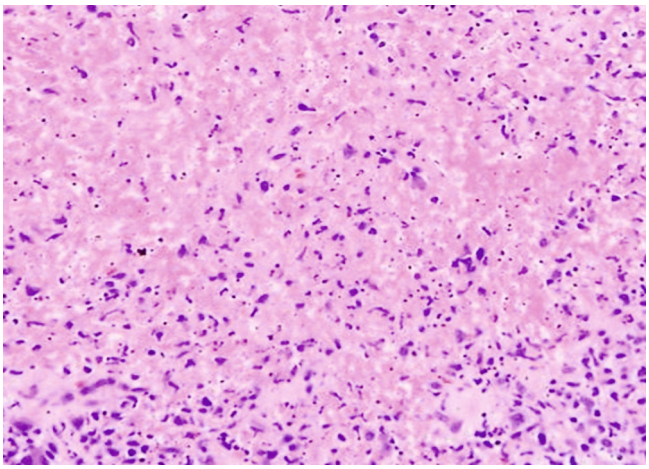
Cat scratch disease is a zoonotic infectious disease caused by a bacterium called Bartonella henselae. In our case report, a 27-year-old patient who presented with prolonged fever, loss of appetite, weight loss, sweating, weakness, headache and bilateral cervical lymphadenopathy. Excisional biopsy was performed and histological examination revealed granulomatous lymphadenitis. B. henselae antibodies were positive in serological examination. Anamnesis was deepened and questioned in terms of suspicious cat contact, it was learned that the open wound on his right knee was licked by the cat 3 months ago. Cat-scratch disease is an important cause of acute, subacute and chronic lymphadenopathy. Although it is sporadic in our country, serological studies conducted in recent years have revealed that the infection is much more common than diagnosed. Cat scratch disease should be considered in the differential diagnosis of patients presenting with lymphadenopathy.

Giriş

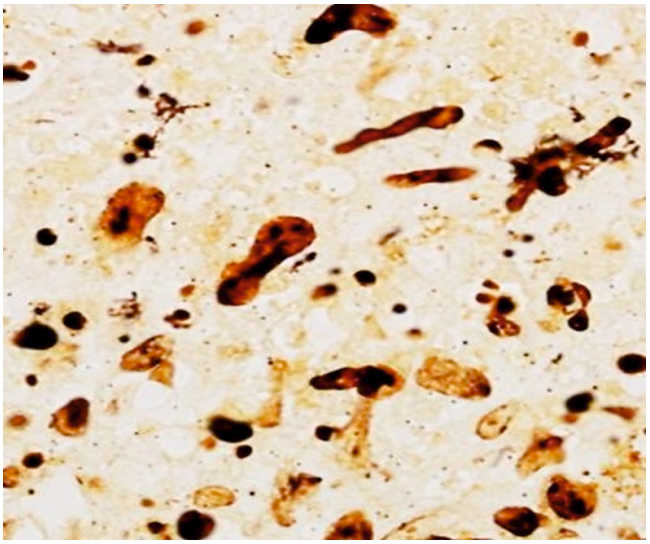
Kedi tırmığı hastalığı gram negatif, hücre içi bir basil olan Bartonella Henselae'nin insanlara kedi tırmalaması, kedi ısırması veya kedi yalaması ile derideki çatlaklardan kedi tükürüğü ile bulaşması sonucu ortaya çıkan bir enfeksiyon hastalığıdır (1,2). Hastalık çocuklarda, erkeklerde, sonbahar ve kış mevsimlerinde daha sık görülmektedir (3,4). Seyir tipik ve atipik olmak üzere iki farklı şekilde olabilir. Sık görülen tipik formda inoklülasyon bölgesinde eritematöz papül, püstül, vezikül veya nodül şeklinde primer lezyon ortaya çıkar ve takiben bölgenin drene olduğu alanda lenfadenopati gelişir. Hastalık kendini sınırlayan, benign bir seyir gösterir (5). Nadir görülen atipik form ise uzun süreli ateş, oküler, nöral ve hepatosplenik tutulum ile prezente olabilir (6). Teşhiste; anamnez, fizik muayene, serolojik ve histolojik inceleme birlikte kullanılır. (7). Hafif vakalarda antibiyoterapi gerekli değildir, destekleyici tedavi verilir. Orta-ağır dereceli prezentasyonda antibiyoterapi gerekir ve ilk tercih azitromisindir (8). Olgu sunumuzda uzun süreli ateş, servikal lenfadenopati, hepatosplenik tutulum ile seyreden birçok enfeksiyon etkeni, lenfoproliferatif hastalıklar ve malignite açısından tetkik ettiğimiz ve atipik seyirli kedi tırmığı hastalığı tanısı koyduğumuz 27 yaşındaki hastamızı ele aldık.

Olgu Sunumu

Hastamız bilgilendirilmiş olup, kendisinden bilgilendirilmiş gönüllü onam formu alınmıştır. 27 yaşında erkek hasta ateş, baş ağrısı ve halsizlik şikayetleri ile acil servisimize başvurmuştu, muayenesinde ateş 37,8 olması dışında özellik saptanmayan hastaya covid polimeraz zincir reaksiyonu (PZR) bakılmış, negatif sonuçlanması üzerine semptomatik tedavi başlanmıştı. İki hafta sonra hasta şikayetlerinin gerilememesi ve boyun bölgesinde şişlik şikayeti ile kulak burun boğaz hastalıkları polikliniğimize başvurmuştu. Yapılan fizik muayenesinde ateş 39,6 olan ve bilateral servikal lenfadenopati tespit edilen hastanın tetkiklerinde lökosit: 15,910 10*3/mL, %80,6 nötrofil, C-reaktif protein (CRP) 147 mg/L (0.01-5) olması üzerine boğaz ve kan kültürü alınmış, amoksisilin 875 mg+klavulonik asit 125 mg 2x1 başlanmıştı. Hasta 1 hafta sonra şikayetlerinin şiddetlenmesi üzerine iç hastalıkları polikliniğimize başvurdu. Anamnezi derinleştirildiğinde boyun bölgesindeki lenfadenopati ile uyumlu şişliğin yaklaşık 2,5 aydır var olduğu ancak son günlerde büyüdüğü öğrenildi. İştahsızlık, kilo kaybı, halsizlik tabloya eşlik ediyordu ve ateşi 38,2 derece idi. Tetkiklerinde lökosit: 17,300 10*3/mL, %89,3 nötrofil, CRP 168 mg/L, sedimentasyon 82 mm/saat (0-20) olan hastanın kan ve boğaz kültüründe üreme olmamıştı. Karaciğer fonksiyon testleri, böbrek fonksiyon testleri, tam idrar tahlili, toraks ve abdomen tomografisi normal sınırlardaydı. Servikal lenfadenopatiler nedeni ile istenilen boyun bilgisayarlı tomografisinde (BT) de bilateral zon 2 ve zon 3'de patolojik boyutta izlenen, en büyüğünün çapı yaklaşık 2,5 cm olan multiple lenf nodları ve supraklaviküler bölge zon 4 ve zon 5'de multiple lenf nodları olduğu görüldü. Hastanın Ebstein Barr virüs, Parvo virüs, Sitomegalovirüs, Toxoplazma, Brucella, Sifiliz, Bartonella, tüberküloz, hepatit B ve C, İnsan Bağışıklık Yetmezliği Virüsü (HIV) açısından tetkikleri istendi. Lenfoproliferatif hastalık Malignite düşünülerek eksizyonel lenf nodu biyopsisi yapıldı. Antibiyoterapisi sefiksim 400 1x1 olarak değiştirilen hasta 1 hafta sonra kontrole geldiğinde muayene sırasında karaciğer ve dalakta büyüme tespit edilmesi üzerine hepatobiliyer USG istendi, USG'de hepatosplenomegali olduğu görüldü. Tetkiklerinde CRP: 247 mg/L, prokalsitonin: 0,62 µg/L (0-0,08), alanin aminotransferaz (ALT):72 U/L (0-41), aspartat aminotransferaz (AST): 64 U/L (0-40) idi. Histopatolojik incelemede hematoksilen eozin boyama ile nekrotik alanlar, histiyositler, nötrofillerin yer aldığı granülomatöz lenfadenit tespit edildi (Şekil 1). Whartin Starry boyası ile yapılan incelemede B. hensalae ile uyumlu, kümeler halinde çomak biçiminde bakteriler görüldü (Şekil 2).



Şekil 1. Servikal lenfadenopatiden yapılan eksizyonel biyopsi materyalinin hematoksilen eozin boyaması ile görülen granülomatöz lenfadenit.



Şekil 2. Servikal lenfadenopatiden yapılan eksizyonel biyopsi materyalinin Whartin Starry boyaması ile görülen Bartonella henselae ile uyumlu basiller.

Hastanın B. Hensalae immunglobulin M (Ig M) antikoru 1/320 titrede, immunglobulin G (Ig G) antikoru >1/512 titrede pozitif geldi. (Ig M için pozitiflik sınırı 1/20, Ig G için pozitiflik sınırı >1/64). Hastaya semptomatik tedavinin yanında ilk gün 500 mg, takip eden günlerde 250 mg olmak toplam 5 gün boyunca azitromisin tedavisi verildi. Tedavi sonrası bakılan tetkiklerinde lökosit: 10,300 10*3/mL, %56,5 nötrofil, ALT: 32 U/L, AST: 24 U/L, CRP: 3,3 mg/L, sedimentasyon: 10 mm/saat, prokalsitonin 0,02 µg/L idi.

Tartışma

Kedi tırmığı hastalığı sıklıkla çocukları etkilemek ile birlikte vakamızda olduğu gibi erişkinlerde de görülebilir. Ülkemizde sporadik olarak tespit edilmektedir (9). Yılmaz

ve arkadaşlarının sağlıklı 800 kan donörü üzerinde yaptıkları bir çalışmada Bartonella henselae antikoru 48 hastada (%6) pozitif tespit edilmiştir (10). Bu hastalığın sanıldığı kadar nadir olmadığını, tipik formun kendisini sınırlayan, benign seyir gösterdiğinden tanı almayan vakalar olduğunu düşündürmüştür. İnsanlara bulaş kediler yolu ile olmaktadır. B.henselae, kedilerde eritrositlerin içine yerleşerek nükslerle seyreden kronik asemptomatik bakteriyemi oluşturmaktadır. Kedi piresi (Ctenocephalides felis) bakteriyemi sırasında enfekte kediyi emdikten sonra dışkısında bol miktarda bakteri bulunur ve dışkıdaki bakteri uzun süre canlılığını korur. Kedinin kaşınma ve yalama sureti ile tırnaklarına, dişlerine ve tükürüğüne aldığı bakteri ısırma, tırmalama, bütünlüğü bozulmuş deriyi yalama sureti ile insanlara bulaşır. Ayrıca kedi piresinin direkt insana sıçraması ve ısırması yolu ile de bulaşma olabilmektedir (11). Vakamızda hastamızın diz bölgesinde bulunan açık yara kedi tarafından yalanmıştı.

Hastalığın %90 olarak görülen tipik formunda inokülasyon bölgesinde primer deri lezyonu ortaya çıkar. Bu lezyon genellikle 1-3 hafta içerisinde gerilemekle birlikte aylarca kalabilir. Lezyonu takiben 1-7 hafta içerisinde inokülasyon bölgesinin drene olduğu alanda lenfadenopati ortaya çıkar. Lenfadenopati sıklıkla aksiller, epitroklear, servikal, preaurikular, supraklavikülar, submandibular ve inguinal bölgededir. Lenfadenopati 1-5 ay sürebilir. Hastalık kendisini sınırlar. %10 oranında görülen atipik formda ise uzun süreli ateş, atipik pnömoni, oküler tutulum, nörolojik tutulum ve vakamızda olduğu gibi organomegali ile seyreden hepatosplenik tutulum görülebilir. Ateş, halsizlik, yorgunluk, iştahsızlık, kilo kaybı gibi maligniteyi akla getirecek bulgular tabloya eşlik edebilir. Atipik form sıklıkla immünsuprese konakta görülmekle birlikte vakamızda olduğu gibi immunkompetan konakta da görülebilir (5,12). Yaygın hastalığı olanlarda iyileşme ilgili sisteme bağlı morbiditeler ile birlikte bir yıla kadar uzayabilir. Çoğu hasta enfeksiyona karşı ömür boyu bağışıklık geliştirir (13). Tanıda anamnez, fizik muayene, seroloji ve histopatoloji kullanılır. Moleküler yöntemler ve kültür pratikte kullanılmamaktadır. Kan tahlillerinde lökositoz, CRP, sedimentasyon, prokalsitonin, ferritin yüksekliği, karaciğer tutulumuna bağlı karaciğer enzim yüksekliği tespit edilebilir. Histolojik incelemede görülen granülomatöz lenfadenit hastalık için tipiktir ancak spesifik değildir. Whartin Starry boyası ile B. henselae ile uyumlu basiller gösterilebilir ancak duyarlılığı %100 değildir. Bu nedenle tanıda kedi ile temas öyküsü, fizik muayene bulguları, antikor tespiti ve histopatoloji birlikte anlamlı ve tanı koydurucudur (14). Hafif vakalarda antibiyoterapi gerekli değildir. Antipiretik ve antiinflamatuar ajanlar, inokülasyon bölgesine sıcak kompresler gibi destekleyici tedavi yeterlidir. Orta-ağır dereceli prezentasyonda doksisiklin, rifampisin, trimetoprim-sulfametoksazol, siprofloksasin gibi antibiyotikler kullanılabilmekle birlikte ilk tercih azitromisindir. Total lenf düğümü büyüklüğünde ciddi gerileme yalnızca azitromisin kullanan hastalarda tespit edilmiştir. Azitromisin erişkin dozu birinci gün 500 mg, sonraki günler 250 mg olmak üzere toplam beş günlük kullanım şeklindedir. Vakamızda semptomatik tedavinin yanına eklenen azitromisin antibiyoterapisi ile dramatik klinik ve laboratuar yanıt alınmıştır (8,13,15).

Sonuç olarak çocuk ve erişkin tüm yaş gruplarını etkileyebilen, yalnızca immunsuprese hastalarda değil immunkompetan hastalarda da atipik seyredebilen ve atipik formu malignite dahil olmak üzere birçok hastalığı taklit edebilen kedi tırmığı hastalığı akut, subakut ve kronik lenfadenopati ile başvuran hastalarda akla getirilmeli ve bu gibi hastalar hayvan teması açısından mutlaka sorgulanmalıdır.

Yazarlık katkısı: Fikir/Hipotez: EY, ARG, SY. Tasarım: EY, ARG, SY. Veri toplama/Veri işleme: EY, ARG, SY. Veri analizi: EY, ARG, SY. Makalenin hazırlanması: EY, ARG. Makalenin kontrolü: EY.

Etik Kurul Onayı: Gerekli değildir.

Hasta Onayı: Olgu sunumu için hastadan izin alınmıştır.

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