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Original Research / Özgün Araştırma

Assessment of Hematological Parameters in the Diagnosis Brucella Epididymorchitis: Comparison of Brucella Epididymorchitis and Non-Brucella Epididymorchitis

Brucella Epididimorşiti Tanısında Hematolojik Parametrelerin Değerlendirilmesi: Brucella Epididimorşiti İle Non-Brucella Epididimorşitlerin Karşılaştırılması

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Özet

Amaç: Brucella epididimorşit (BEO) ile brusella dışı epididimorşitin (NBEO) ayırıcı tanısını kolaylaştırabilecek ve erken tanıyı kolaylaştırabilecek parametreleri araştırmak.

Gereç ve Yöntemler: Brusellozun yaygın olduğu Türkiye'nin doğusunda üçüncü basamak bir merkeze başvuran 23 BEO hastası ve 80 NBEO hastasının verileri retrospektif olarak incelendi. Yaş, hemogram parametreleri (beyaz kan hücresi (WBC), nötrofil, lenfosit, monosit, eozinofil, bazofil, trombosit, nötrofil-lenfosit oranı (NLR), monosit-lenfosit oranı (MLR), trombosit-lenfosit oranı (PLR), ortalama trombosit hacmi (MPV), kırmızı kan hücresi dağılım genişliği (RDW)), biyokimyasal parametreler (aspartat transaminaz ve alanin aminotransferaz), inflamatuar belirteçler (C-reaktif protein, eritrosit sedimantasyon hızı ve prokalsitonin), idrar kültürü ve skrotal doppler ultrason bulguları retrospektif olarak incelendi. BEO ve NBEO gruplarının sonuçları karşılaştırıldı.

Bulgular: BEO ve NBEO gruplarının karşılaştırılmasında, iki grup arasında WBC sayısı, nötrofil sayısı, monosit sayısı, NLR, MLR, MPV ve prokalsitonin seviyeleri açısından anlamlı fark vardı (sırasıyla p = 0,035, p = 0,007, p = 0,003, p = 0,005, p = 0,01, p < 0,001, p < 0,001).

Sonuçlar: NLR, BEO'nun erken tanısında kullanım için umut verici olabilir. MPV de değerlendirilebilecek bir diğer parameter olarak

Abstract

Objective: To analyze the parameters that can facilitate the differential diagnosis of brucella epididymorchitis (BEO) and non-brucella epididymorchitis (NBEO) and to facilitate early diagnosis.

Material And Methods: The data of 23 BEO patients and 80 NBEO patients, who applied in a tertiary center in eastern Turkey, where brucellosis is common, were retrospectively analyzed. Age, hemogram parameters (white blood cell (WBC)), neutrophil, lymphocyte, monocyte, eosinophil, basophil, platelet, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), red blood cell distribution width (RDW), biochemical parameters (aspartate transaminase and alanine aminotransferase), inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, and procalcitonin), urine culture, and scrotal doppler ultrasound findings were analyzed retrospectively and were compared between BEO and NBEO groups.

Results: In the comparison of the BEO and NBEO groups, there was a significant difference between the two groups in WBC count, neutrophil count, monocytes count, NLR, MLR, MPV, and procalcitonin levels (p = 0.035, p = 0.007, p = 0.003, p = 0.005, p = 0.01, p < 0.001, p < 0.001, respectively).

Conclusions: The NLR may be promising

This study was reviewed and approved by the Van Training and Research Hospital medical ethics committee on March 21, 2019 (approval number: 2019/06). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

dikkat çekmektedir.

Anahtar Kelimeler: brusellozis, genitoüriner, enfeksiyon, epididimorşit

for use in the early diagnosis of BEO. The MPV also drew attention as parameters that can be evaluated

Keywords: brucellosis, genitourinary, infections, epididymorchitis

INTRODUCTION

Brucellosis is an endemic zoonotic disease caused by gram-negative coccobacillus Brucella (1). It is one of the most common zoonoses, with over 500,000 cases each year (2). Although the incidence of brucellosis is low in developed countries, it occurs sporadically in occupationally exposed groups, such as farmers, veterinarians, laboratories, and abattoir workers (3). In Türkiye, the eastern and southeastern regions are especially affected (1).

Transmission of the agent to humans occurs through aerosols contaminated with the conjunctival sac by consuming unpasteurized dairy products, direct contact with animals, or animal secretions through cuts and abrasions on the skin. Clinical signs usually include a high fever, night sweats, joint pain, and splenomegaly (4). Epididymoorchitis is the most common type of genitourinary complication. It causes granulomatous-type orchitis and can be seen in 2%–20% of infected men (1). Scrotal pain, swelling and fever are the most common findings in Brucella epididymorchitis (BEO) (5). These symptoms are not specific to BEO and are also seen in other epididymoorchitis. Therefore, the differential diagnosis of BEO becomes even more important. At the same time, the treatments of BEO and non-Brucella epididymorchitis (NBEO) are different from each other. Combinations of doxycycline, rifampicin, and streptomycin are generally used for BEO, and the treatment takes longer (6, 7). In addition, it is very important to separate BEO from emergency urological conditions that cause acute scrotum to prevent unnecessary operations and organ loss (8).

In brucellosis, which is characterized by an increase in acute phase reactants, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), it has been predicted that it may change indirect inflammatory parameters, such as white blood cell (WBC) count, platelet count, mean platelet volume (MPV), red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), and platelet lymphocyte ratio (PLR) (9).

This study aimed to reach parameters that can be beneficial in the diagnosis of BEO by evaluating hemogram parameters (WBC, neutrophil, lymphocyte, monocytes, eosinophil, basophil, platelet, MPV, RDW), NLR, MLR, PLR, aspartate transaminase (AST), alanine aminotransferase (ALT), inflammatory markers (CRP, ESR, and procalcitonin), pyuria and microorganism detection in the urine, and abscess formation on ultrasound (US).

MATERIALS AND METHODS

The data of 103 epididymoorchitis patients, including 23 BEO patients and 80 NBEO patients, who applied to the infectious diseases and urology clinics of Van Training and Research Hospital, a tertiary center in eastern Turkey, between July 2017 and December 2021, were retrospectively analyzed. Patients diagnosed with BEO were determined as the case group, and patients diagnosed with NBEO were determined as the control group. The laboratory data of patients with BEO and NBEO were compared.

Since the region where the Van Training and Research Hospital is located is an area where brucellosis is endemic, hemogram parameters (WBC, neutrophil, lymphocyte, monocytes, eosinophil, basophil, platelet, MPV, and RDW), NLR, MLR, PLR, biochemical parameters (AST and ALT), inflammatory markers (CRP, ESR, and procalcitonin), Rose Bengal test, serum tube agglutination test, blood culture,

and scrotal Doppler US performed by a specialist radiologist are routinely performed in all patients with epididymoorchitis clinic (scrotal swelling, pain, redness, fever, night sweats, and joint pains) who apply to urology or infectious diseases outpatient clinics.

A positive blood culture, positive Rose Bengal test result, or serum tube agglutination test above 1/160 as well as clinical and ultrasonographic findings of epididymoorchitis were determined as the main diagnostic criteria for BEO.

Blood culture samples sent in BACTEC 9240 and BacT/Alert FA Plus culture bottles were analyzed using automated culture systems. Due to the late growth of Brucella bacteria, these bottles were kept for 30 days. Afterwards, samples were taken from the bottles with growth, inoculated on blood agar, eosin-methylene blue (EMB) agar, and chocolaty agar media, and kept for up to 48 hours. The diagnosis was made by taking samples from growing media.

In the serum tube agglutination test, an equal amount of Brucella agglutination antigen was added to the patient's serum and diluted with physiological saline in the tubes. An evaluation was made after 48 hours of incubation at 37 °C. If agglutination was observed in a single sample at dilutions of 1/160 and above in the serum samples taken from the patients, the result of the test was considered positive.

The Rose Bengal test was carried out in an acidic environment using the Brucella antigen prepared from the Brucella bacteria and stained with Rose Bengal dye using special techniques. The test was considered positive as a result of the presence of Rose Bengal staining.

At the time of first admission of the patients diagnosed with BEO and the control group, the following sample parameters were recorded: white blood cells (ul), neutrophils (ul) lymphocytes (ul), monocytes (ul), eosinophils (ul), basophils (ul), platelets (ul), NLR, MLR, PLR, MPV (fL), red blood cell distribution width (%), AST, ALT, C-reactive protein (mg/dl), ESR (mm/h), Procalcitonin (ng/ml), pyuria (%), abscess formation, and microorganisms isolated in urine. These parameters were statistically compared between the two groups.

This study was reviewed and approved by the medical ethics committee of Van Training and Research Hospital on 21 March 2019 (approval number: 2019/06).

Statistical Analysis

The normal distribution of continuous variables was evaluated using visual and analytical methods. In the descriptive findings, categorical variables are given as numbers (percent), and continuous variables are presented with median (minimum–maximum) or mean ± standard deviation for normal non-scattering data. Categorical variables were analyzed using the appropriate chi-squared test, chosen between Pearson and exact tests. For the continuous variables, the statistical difference among groups was determined using Mann-Whitney U tests. The data that follows a normal distribution was analyzed using an independent t-test, while the data that does not follow a normal distribution was evaluated using the Mann-Whitney U test. Statistical significance was accepted as p and lt: 0.05. The statistical analysis of the research data was performed using R version 4.2.1.

RESULTS

Out of 103 patients, 23 (22.33%) were diagnosed with BEO, while 80 (77.67%) were in the NBEO group. The median age of the patients was 40 (20–80) in the BEO group and 42.5 (6–89) in the NBEO group. There was no statistically significant difference between the ages of the two groups.

The WBC count was 8100/μL in the BEO group and 10100/μL in the NBEO group. The WBC count was significantly higher in the NBEO group ($p = 0.035$).

While the number of neutrophils was 4400/μL in the BEO group, it was found to be 6500/μL in the NBEO group. The neutrophil count was significantly higher in the NBEO group ($p = 0.007$).

The monocyte count was 500/μL in the BEO group and 700/μL in the NBEO group. The number of monocytes was significantly higher in the NBEO group ($p = 0.003$).

The NLR was 1.68 in the BEO group and 3.21 in the NBEO group. The NLR was statistically significantly higher in the NBEO group ($p = 0.005$).

The MLR was 0.25 in the BEO group and 0.44 in the NBEO group. It was significantly higher in the NBEO group ($p = 0.01$).

The MPV was 9.2 fL in the BEO group and 10.1 fL in the NBEO group. It was statistically significantly higher than in the NBEO group ($p = <0.001$).

Procalcitonin was 0.02 ng/ml in the BEO group and 0.06 ng/ml in the NBEO group. It was significantly higher in the NBEO group ($p < 0.001$).

There was no statistically significant difference between the two groups in terms of lymphocyte count, eosinophil count, basophil count, platelet count, PLR, RDW, AST, ALT, CRP, ESR, pyuria rates, abscess formation, and microorganism isolation rate (Table 1).

Table 1. Demographic data and laboratory results of patients

	BEO (n=23, 22.33%) (median (IQR))	**NBEO (n=80, 77.67%) (median (IQR))**	**p value**
Age (year)	40 (22-52)	42.5 (23-66)	0.433
WBC (µl)	8100 (6100 – 11000)	10100 (7925 –12900)	**0.035**
Neutrophil (µl)	4400 (3000 – 6900)	6500 (5200 – 8700)	**0.007**
Lymphocyte (µl)	2600 (1900-3500)	2200 (1420 – 3100)	0.175
Monocyte (µl)	500 (400 – 900)	700 (600 – 1200)	**0.003**
Eosinophil (µl)	80 (50 – 200)	90 (42.5 – 157.5)	0.911
Basophil (µl)	20 (20 – 40)	30 (10 – 40)	0.914
Platelet (µl)	238000 (207000 – 293000)	290500 (216500 – 333250)	0.114
NLR	1.68 (1.11 – 3.36)	3.21 (1.99 – 4.20)	**0.005**
MLR	0.25 (0.13 – 0.36)	0.44 (0.24 – 0.56)	**0.01**
PLR	108.75 (75.81 – 133.33)	128.41 (95.31 – 176.95)	0.051
MPV (fL)	9.2 (8.6 – 9.8)	10.1 (9.3 – 11.3)	**<0.001**
RDW (%)	13.5 (13.3 – 14.2)	13.25 (12.6 – 14.3)	0.163
AST (U/L)	27 (18 - 49)	28 (19.3 – 34.8)	0.981
ALT (U/L)	22 (18 – 59)	26.5 (19 – 35)	0.623
CRP (mg/dl)	14 (3 – 90)	13 (6.3 – 43.2)	0.877
ESR (mm/h)	10 (5 – 24)	8.5 (4 – 19.8)	0.297
Procalsitonin (ng/ml)	0.02 (0.01 – 0.03)	0.06 (0.03 – 0.1)	**<0.001**
Pyuria n (%)	3 (13.0 %)	24 (30.0 %)	0.103
Abscess formation n (%)	3 (13.0 %)	7 (8.8 %)	0.540
Microorganism isolated in urine sample n (%)	3 (13.0 %)	8 (10.0 %)	0.677

BEO: Brucella epididymorchitis, NBEO: Non-brucella epididymorchitis , WBC: White blood cell,NLR: Neutrophil/ Lymphocyte Ratio, MLR: Monocyte/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio, MPV: Mean Platelet Volume, RDW: Red blood cell distibution width, AST: Aspartate transaminase , ALT: Alanine aminotransferase, CRP: C – reactive protein, ESR: Erythrocyte sedimentation rate

DISCUSSION

Brucellosis can mimic many systemic diseases (10). This leads to a delay in diagnosis, misdiagnosis, and loss of time in treatment (11). BEO is a common complication of brucellosis. BEO does not come to mind as pre-diagnosis like systemic brucellosis. Therefore, there are delays in diagnosis and different complications develop. Since there are delays in the diagnosis, complications such as male infertility, necrotizing orchitis resulting in orchiectomy might develop. The diagnosis of BEO is made by laboratory tests (such as a serum tube agglutination test, Rose Bengal test, and blood culture), in addition to clinical findings. However, the increase in the number of additional tests brings into question the appropriate laboratory conditions and costs. Therefore, obtaining auxiliary parameters is very useful for easy diagnosis and cost reduction (12). Increases in CRP, ESR, WBC, AST, and ALT values can be seen in BEO cases (13). In some studies, an increase in acute-phase reactants was found to be an expected result in BEO cases (1). However, different results have been found regarding the levels of these parameters in different studies (1, 3, 5).

Due to the rarity of brucellosis in developed countries, as far as we know, there are not many studies in the literature, except for a few studies comparing BEO and NBEO in terms of inflammatory markers. (12-15).

In their study, Çift et al. found the mean age to be lower in the BEO group than in the NBEO group (12). The reason for this may be that agricultural workers, in whom brucellosis is common, comprise young people. In addition, considering that lower urinary system symptoms and recurrent urinary tract infections are facilitating factors in the formation of NBEO, it can be thought that this group may have an older population (16, 17). Contrary to this study, Papatsoris et al. and Aydın et al. found no difference in mean age in their studies, but they did not comment on this (15). The reason for this may be the consumption of raw milk and dairy products, which cause brucellosis, by people of all ages.

Non-Brucella epididymoorchitis is an acute inflammation; therefore, a more pronounced WBC response can be expected. Our study supports this expectation as well as the studies by Papatsoris et al. and Çift et al. (16, 17). However, two studies by Aydin et al. and Korkmaz et al. did not report a difference in WBC count between the two groups (14).

In acute inflammation, leukocytosis is usually predominantly neutrophil. Since NBEO usually causes acute inflammation, a mostly neutrophil-dominated leukocytosis is expected (16, 17). Brucellosis is an inflammatory process that can often become chronic. In addition, since it is a facultative intracellular bacterium, the cellular immune response is dominant. Therefore, leukocytosis is expected with more lymphocyte dominance. Similar to other studies in the literature, our study also supports this finding (16, 17). With similar results obtained in different studies, the lymphocyte count may come to the fore as a preferable parameter in the differential diagnosis of BEO (16, 17).

Brucella is an intracellular microorganism; therefore, lymphocytosis is expected in brucellosis. With a decrease in neutrophils, the NLR becomes more meaningful than evaluating these two values separately. Therefore, we think that the NLR may be the most useful parameter in the early diagnosis of BEO and in the differential diagnosis from other causes of epididymoorchitis. The statistical significance of this rate in our study suggests that it can be used in early diagnosis. We think that the deficiency in the studies of Papatsoris et al. and Aydın et al. is that neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts were not compared separately (14,15).

It has been shown in the literature that some chronic infections, such as brucellosis, are associated with monocytosis (12). However, contrary to expectations, in our study, the number of monocytes was higher in the NBEO group. This was not unexpected, given that the WBC count was also higher in the NBEO group. In fact, when the percentages of monocytes were examined, both groups were similar. Moreover, in the two studies by Çift et al. and Korkmaz et al.,

no significant difference was found between the two groups' monocyte counts (12).

In terms of MLR, different results have been obtained in the literature on Brucella orchitis. Aydın et al. and Çift et al. found the MLR to be lower in the BEO group (12). However, the MLR was found to be higher in brucellosis patients in a study by Balın et al. (18). The reason why the MLR was lower in the BEO group may largely be due to the lymphocyte dominance in the BEO group in our study, as previously explained.

Mean platelet volume is an indicator of platelet activation (19). The excessive release of proinflammatory cytokines seen in brucellosis may affect platelet maturation, thus causing a decrease in platelet size (20). Our findings also support this view. A study conducted by Çift et al. with 72 patients revealed that the MPV value was lower in patients with brucellosis (12). Another study showed no difference between the groups in this regard (21).

Brucella species are intracellularly located, cause less cytokine release, and their endotoxins are less toxic than other gram-negative bacteria. Therefore, procalcitonin, which is a very sensitive infective parameter, can be expected to increase less in BEO than in NBEO (19). Although our study supports this interpretation, we found only one study in the literature evaluating procalcitonin for Brucella orchitis, and the authors did not report a significant difference in this parameter (12).

There were some limitations to this study. The first is the retrospective nature of the study and the small number of samples. It would be better to support the results we found in our study with various prospective studies with larger samples. The lack of long-term follow-up of changes in inflammatory parameters after treatment is another limitation.

CONCLUSIONS

The NLR is particularly promising in terms of an additional parameter to be used to prevent both cost increases and delays in the diagnosis of BEO. Mean platelet volume and procalcitonin may be other parameters to be evaluated in this regard. However, since Brucella is mostly seen in underdeveloped and developing countries, in this sense case reporting is insufficient. To conclude, multicenter and prospective studies can create stronger findings in this regard.

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethics Statement: This study was reviewed and approved by the Van Training and Research Hospital medical ethics committee on March 21, 2019 (approval number: 2019/06).

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