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Original Article *Özgün Araştırma*

COMPARISON OF CLINICAL, LABORATORY FINDINGS AND COMPLICATIONS IN BACTERIEMIC AND NON-BACTERIEMIC BRUCELLOSIS: A SINGLE CENTER EXPERIENCE

Bakteriyemik ve Bakteriyemik Olmayan Brusellozda Klinik, Laboratuvar Bulguları ve Komplikasyonların Karşılaştırılması: Tek Merkez Deneyimi

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ABSTRACT

Objective: Brucellosis is a systemic zoonosis that affects various organs or body systems and can mimic many diseases. Symptoms can range from acute febrile illness to chronic clinical manifestations with severe complications. In our study, we investigated the relationship between bacteremia and clinical and laboratory findings, and complications in patients with brucellosis.

Material and Methods: Two hundred and twenty-three patients diagnosed with brucellosis between 2005 and 2020 in the department of infectious diseases and clinical microbiology of a tertiary care university hospital were included in the study. Rose Bengal test, *Brucella* standard tube agglutination test and culture (blood and/or bone marrow culture) were used for the diagnosis of brucellosis. The patients were divided into two groups according to their bacteremia status. Patients with positive culture were identified as bacteremia, and patients with negative culture were identified as non-bacteriemic.

Results: A total of 223 patients were included in the study, of which 142 (63.7%) were male. While weight loss, fever and hematological complications were higher in bacteremia cases ($p=0.001$, $p<0.001$, $p=0.022$, respectively), lumbar pain and skeletal system complications were higher in non-bacteremia cases ($p=0.013$, $p<0.001$, respectively).

Conclusion: In areas where *Brucella* is endemic, brucellosis should be ruled out in the presence of signs indicating malignancy such as fever, weight loss, and cytopenia.

Keywords: *Brucellosis, bacteremia, complications*

ÖZ

Amaç: Bruselloz, çeşitli organları veya sistemleri etkileyen ve birçok hastalığı taklit edebilen sistemik bir zoonozdur. Semptomlar, akut ateşli hastalıktan ciddi komplikasyonları olan kronik klinik belirtilere kadar değişebilir. Çalışmamızda brusellozlu hastalarda bakteriyemi ile klinik ve laboratuvar bulguları arasındaki ilişkiyi ve komplikasyonları araştırdık.

Gereç ve Yöntemler: 2005-2020 yılları arasında üçüncü basamak bir üniversite hastanesinde enfeksiyon hastalıkları ve klinik mikrobiyoloji anabilim dalında bruselloz tanısı alan 223 hasta çalışmaya dahil edildi. Bruselloz tanısı için Rose Bengal testi, *Brucella* standart tüp aglütinasyon testi ve kültür (kan ve/veya kemik iliği kültürü) kullanıldı. Hastalar bakteriyemi durumlarına göre iki gruba ayrıldı. Kan kültürü pozitif olan hastalar bakteriyemik, negatif kan kültürü olan hastalar bakteriyemik olmayan olarak tanımlandı.

Bulgular: Çalışmaya dahil edilen 223 hastanın 142'si (%63.7) erkekti. Bakteriyemik olgularda kilo kaybı, ateş ve hematolojik komplikasyonlar (sırasıyla $p=0.001$, $p<0.001$, $p=0.022$), bakteriyemik olmayan olgularda bel ağrısı ve iskelet sistemi komplikasyonları daha yüksekti (sırasıyla $p=0.013$, $p<0.001$).

Sonuç: Özellikle Brucella'nın endemik olduğu bölgelerde ateş, kilo kaybı ve sitopeni gibi maligniteye işaret eden bulguların varlığında bruselloz ekarte edilmelidir.

Anahtar Kelimeler: *Bruselloz, bakteriyemi, komplikasyonlar*

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INTRODUCTION

Brucellosis is a zoonosis. The infection is frequently transmitted in contact with an infected animal directly or contact with the animal's products indirectly. It can cause infections in all age groups and genders. It is an important infectious disease in the world, specifically in the Mediterranean region of Europe, North and East Africa, in the Middle East, south and central Asia, and in Central and South America (1). It is a systemic infection and can mimic other diseases by involving various organs and systems in the body. Symptoms are nonspecific, ranging from acute febrile illness to different clinical manifestations that can lead to chronic, serious complications (2). Complications are common in brucellosis and may be seen with delayed diagnosis. The most frequently affected systems are osteoarticular, gastrointestinal, hematological, genitourinary, cardiovascular, respiratory, and central nervous systems (3). Isolation of the organism from blood and/or body fluids or positive serology accompanied by clinical symptoms is essential for the diagnosis (4). The positive culture rate in brucellosis is between 15% and 80%. Culture positivity rate is higher in acute brucellosis and lower in local disease and chronic stages (5). In this study we aimed to investigate the relationship between the bacteremia and the clinical and laboratory findings, and complications in patients with brucellosis.

MATERIALS AND METHODS

Following the approval by the local ethics committee of Karadeniz Technical University, a total of 223 cases of brucellosis diagnosed in the department of infectious diseases and clinical microbiology between 2005 and 2020 were included in this study (date: 17/06/2020; number: 24237859-333). Patient information was accessed from the patient electronic chart reviews. The diagnosis was made with the isolation of *Brucella spp*. from blood, bone marrow or body fluids, and/or compatible clinical symptoms such as fever, arthralgia, malaise with the positivity of rose Bengal test and standard tube agglutination (STA) test. Significant titers were determined to be ≥1/160 in the STA.

The criteria for anemia was Hb<12 gr/dl in women, and <13.5 gr/dl in men, neutropenia <1500/μL, leukopenia <4000/μL, leukocytosis >10000/μL, thrombocytopenia as $<150x10^9$/μL, and thrombocytosis as $>450x10^9$/μL. Organ-based complications of brucellosis were defined in the case of specific organ or system involvement. Osteoarticular complication was considered if there were any signs of inflammation in any joint and/or radiological alterations such as sacroileitis, spondylodiscitis, and peripheral arthritis. Neurobrucellosis was defined as the manifestations including meningitis, encephalitis, brain abscess, myelitis, radiculitis, and/or neuritis. Hematologic complication was defined as hematologic abnormalities in laboratory, including anemia, leukopenia, leukocytosis, thrombocytopenia, and thrombocytosis. Genitourinary complication was considered if there were any signs of scrotal pain and swelling and/or renal, testicular abscesses, prostatitis or orchitis.

Each patient was categorized according to their bacteremia status. Patients with positive blood and/or bone marrow culture were identified as bacteriemic, and patients with negative blood culture were identified as nonbacteriemic. The two groups were compared in terms of clinical and laboratory findings and complications.

Statistical methods:

Statistical analyses were performed on SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Normal distribution of data was assessed using the Kolmogorov-Smirnov test. Continuous data were presented as mean ± standard deviation. Categorical data were presented as numbers and percentages. The Chi-square test was used for comparing categorical variables. P<0.05 was regarded as statistically significant.

RESULTS

Two hundred and twenty-three cases (n=223) were evaluated. The mean age of the patients was 46.05±17.0 years. One hundred and forty two (63.7%) patients were male. Bacteriemic cases were 50.7% (n=113) and

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nonbacteriemic cases were 49.3% (n=110). There was no significant difference between the groups in terms of age and gender.

As presented symptoms, weight loss was higher in bacteriemic cases (p=0.001), and lumbar pain was higher in nonbacteriemic cases (p=0.013). Fever was more common in bacteriemic cases than nonbacteriemic cases (p<0.001). Demographics, signs and symptoms of patients are shown in Table 1.

Table 1. Demographics, signs, and symptoms of patients.

Variables	Bacteriemic (n=113)	Nonbacter Bacteriemic (n=110)	p
Age (mean±standard deviation)	44.6±16.8	47.6±17.1	0.186
Gender: n (%)			
Female	41 (36.3)	40 (36.4)	0.990
Male	72 (63.7)	70 (63.6)	
Symptoms*: n (%)			
Malaise	106 (93.8)	96 (87.3)	0.150
Lack of appetite	94 (83.2)	83 (75.5)	0.207
Fever	93 (82.3)	85 (77.3)	0.442
Sweating	89 (78.8)	73 (66.4)	0.054
Arthralgia	80 (70.8)	84 (76.4)	0.346
Weight loss	58 (51.3)	33 (30.3)	**0.001**
Lumbar pain	50 (44.2)	67 (60.9)	**0.013**
Nausea	35 (31.0)	23 (20.9)	0.119
Myalgia	41 (36.3)	39 (35.5)	1.000
Signs: n (%)			
Fever	76 (67.3)	45 (40.9)	**<0.001**
Hepatomegaly	29 (25.7)	20 (18.2)	0.235
Hepatosplenomegaly	23 (20.4)	14 (12.7)	0.177
Splenomegaly	18 (15.9)	8 (7.3)	0.071

*Multiple symptoms were present frequently

Anemia, leukopenia, thrombocytopenia, pancytopenia were detected more frequently among patients with bacteremia (p=0.020, p=0.001, p=0.002, and p=0.15, respectively). Of the 113 patients in bacteriemic group 8.8% (n=10) had leukocytosis. In nonbacteriemic group, there were 18.2% (n=20) patients who had leukocytosis (p=0.065). Elevated transaminase levels was detected more frequently among patients with bacteremia (p=0.002). Laboratory features of the patients are shown in Table 2 and 3.

There were 84.9% (n=96) complications in the bacteriemic cases and 80.9% (n=89) complications in nonbacteriemic cases. Hematological complications were higher in bacteriemic and complications related to the skeletal system were higher in nonbacteriemic cases (p=0.022, p<0.001, respectively). Complication distribution is shown in Table 4.

DISCUSSION

In the current study, we have compared the clinical and laboratory findings, and complications in patients with bacteriemic and non-bacteriemic brucellosis. Hematological complications were higher in bacteriemic cases (87.5% vs 73.0%, p=0.022). It was observed that the bacteriemic cases tended to have cytopenias (anemia, leukopenia, thrombocytopenia, and pancytopenia p=0.020, p=0.001, p=0.002, and p=0.15, respectively). On the other hand non-bacteriemic group had more leukocytosis than bacteriemic group but it was not statistically significant (p=0.065). Skeletal system complication was %36.3 (n=81) in all cases and non bacteriemic group had more skeletal complication than bacteriemic group (p<0.001).

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Table 2. Laboratory features of all patients.

Variables (mean±standard deviation)	Bacteriemic (n=113)	Nonbacteriemic (n=110)	p
WBC (x10³/μL)	6.46±2.68	7.69±2.79	**0.001**
Hb (g/dl)	12.4±1.7	12.9±1.6	**0.015**
PLT (x10³/μL)	242.12±120.28	290.94±105.69	**0.001**
NLR	2.1±1.6	2.6±2	**0.007**
CRP	5.4±5	4.1±4.3	**0.005**
PCT	0.2±0.3	0.1±0	**0.001**
ESH	35.8±24.2	35.7±29.6	0.470
ALT (U/L)	64.1±76.4	56.7±156.6	**<0.001**
AST (U/L)	63.9±62	48.3±88	**<0.001**

WBC: White blood cell, Hb: Hemoglobin, PLT: Platelet, NLR: Neutrophil / Lymphocyte ratio, CRP: C reactive protein, PCT: Procalcitonin, ESH: Erythrocyte sedimentation rate, ALT: Alanine transaminase, AST: Aspartate transaminase)

Table.3. Detailed hematologic features of patients.

Variables	Bacteriemic: n (%)	Nonbacteriemic: n (%)	p
Anemia	71 (62.8)	52 (47.3)	**0.020**
Leukocytosis	10 (8.8)	20 (18.2)	0.065
Leukopenia	21 (18.6)	4 (3.6)	**0.001**
Thrombocytopenia	23 (20.4)	6 (5.5)	**0.002**
Thrombocytosis	3 (2.7)	5 (4.5)	0.495
Elevated transaminases	54 (47.8)	30 (27.3)	**0.002**
Pancytopenia	12 (10.6)	2 (1.8)	**0.015**

Table 4. Complication ratios of all patients.

Complications*	Bacteriemic: n (%)	Nonbacteriemic: n (%)	p
Hematological	84 (87.5)	65 (73)	**0.022**
Nervous system	10 (10.4)	10 (11.2)	1.000
Skeletal system	28 (29.2)	53 (59.6)	**<0.001**
Genitourinary system	6 (6.3)	5 (5.6)	1.000

* Percentage is given out of 155 cases that have complications. Multiple complications were simultaneously present in some cases

There are few studies comparing bacteriemic and non bacteriemic brucellosis. Fever (4,6-8), anemia (7), leukopenia (4), thrombocytopenia (9), elevated CRP levels (6,8), and elevated liver enzymes (4,6) were found to be higher in bacteriemic cases. Kadanali et al. also showed that the osteoarticular involvement was higher in nonbacteriemic patients (4). Among our patients, fever, weight loss, elevated CRP, procalcitonin and elevated liver enzymes levels were found to be significant parameters in patients with bacteremia. All these factors were predicting an inflammatory reaction. On the other side, lumbar pain and skeletal system involvement, which found to be higher in non bacteriemic cases, suggested that it is rather a chronic infection. These results are also consistent with previous similar studies (4,10).

Hematologic abnormalities in brucellosis were reported between 33.5% and 50.9% (11-13). Among these abnormalities cytopenias are more common. Multiple factors could be associated with cytopenias and bacteriemic status correlation. In bacteremia, the host immune mechanisms eliminate bacteria from the blood via innate immune and adaptive immune defense (14). Moreover, immunoreactive lymphokines, such as IF-γ, TNF-α, or antibody mediated peripheral immune destruction of granulocytes might cause neutropenia or other cytopenias (15)**.** It is known that splenomegaly can also cause cytopenia. Among our patients, splenomegaly was encountered more in bacteriemic

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group than in non bacteriemic group [15.9% (n=18) vs 7.3% (n=8)], but not statistically significant.

Macrophage activation and reactive hemophagocytosis are the other possible causes that could explain cytopenias in brucellosis. However, in our study, very few patients had bone marrow biopsy. Since these data would provide insufficient information to the evaluation, no further interpretation could be made. We believe that cytopenias mainly result from high inflammatory states and immune responses during bacteriemic status, presenting with fever, elevated liver enzymes, high CRP, and procalcitonin levels.

This study's main strengths are: (1) the large number of cases, (2) the presence of blood culture test in each case. The retrospective nature is the handicap of our study. A prospective study might help to clarify pathogenesis of cytopenias in brucellosis. *Brucella* is a difficult and slow-growing bacterium. Some factors, such as use of antibiotics, may prevent the bacteria from being isolated from the blood. Therefore, bacteria could not be isolated from the blood of some bacteriemic patients. For this reason, it may not reflect the fact that all of the patients in whom bacteria cannot be isolated from the blood are described as 'non-bacteriemic'.

In conclusion, in the presence of signs indicating malignancy such as fever, weight loss and cytopenias, brucellosis should be ruled out especially in endemic areas.

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

Researchers' Contribution Rate Statement: Concept/ Design: FA, OB ,NNA;

Analysis/Interpretation: FA, OB, NNA; Data Collection:FA, NNA, MGU ; Writer:FA, OB, NNA ; Critical Review:FA, OB, GY, SK ; Approver : FA, OB, NNA, MGU, GY, SK, IK

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