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EVALUATION OF HEMATOLOGICAL CHANGES IN PATIENTS WITH BRUCELLOSIS

BRUSELLOZ HASTALARINDA HEMATOLOJİK DEĞİŞİKLİKLER

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Abstract

Objective: Brucellosis is a zoonotic infectious disease of domestic and wild animals caused by *Brucella* strains and is transmitted to humans by various routes. Brucellosis is an important problem leading to economic losses due to high morbidity rates. Although the disease has been eradicated in most developed countries it remains a public problem especially in the Mediterranean countries of the Middle East and Africa. The objective of this study was to investigate hematological changes in patients with brucellosis from Kahramanmaraş in light of the literature.
Methods: A total of 197 patients diagnosed with brucellosis and followed-up in the infectious diseases clinics of Kahramanmaraş Sütçü İmam University Hospital between 1 January 2012 and 31 December 2017 were retrospectively evaluated for hematological changes. Demographic and epidemiologic data of the patients including age, gender, profession, the habit of consuming fresh cheese, and contact with animals were recorded. Hematological changes were considered as leukopenia (leukocyte count 4.000/µL), anemia (hemoglobin concentration <12 g/dL in women and <13 g/dL in men), and thrombocytopenia (platelet count <150.000/µL).
Results: Sixty eight percent of the patients developed hematological changes. No significant difference was found between the patients with and without hematological changes in terms of age and sex. The most common hematological changes was anemia in 36.5% of the patients followed by thrombocytopenia by (11.7%), leukopenia (10.2%) and leucocytosis (9.6%).
Conclusion: Hematological changes are among the most common changes of brucellosis. Diagnostic tests for brucellosis should be kept in mind in cases of hematological anomalies including anemia, leukopenia, thrombocytopenia and pancytopenia in endemic regions.

Keywords: *Anemia, Brucella, brucellosis*

Öz

Amaç: Bruselloz, *Brucella* türlerinin neden olduğu zoonotik bir enfeksiyon hastalığıdır. Bruselloz yüksek morbidite oranları nedeniyle ekonomik kayıplara yol açan önemli bir problemdir. Hastalığın yayılımı çoğu gelişmiş ülkede engellenmiş olmakla birlikte özellikle Ortadoğu ve Afrika'daki Akdeniz ülkelerinde bir halk sağlığı problemi olarak devam etmektedir. Bu çalışmanın amacı, Kahramanmaraş ilinde brusellozlu hastalarda hematolojik değişiklikleri literatür eşliğinde araştırmaktır.
Yöntem: 1 Ocak 2012 ile 31 Aralık 2017 tarihleri arasında bruselloz tanısı konulan ve Kahramanmaraş Sütçü İmam Üniversite hastanesinin enfeksiyon hastalıkları kliniğinde takip edilen 197 hasta, hematolojik komplikasyonlar açısından geriye dönük olarak değerlendirilmiştir. Yaş, cinsiyet, meslek, taze peynir tüketimi alışkanlığı ve hayvanlarla temas gibi hastaların demografik ve epidemiyolojik verileri kaydedilmiştir. Hematolojik komplikasyonlar lökopeni (<4 000/µL), anemi (hemoglobin derişiminin kadınlarda <12 g/dL, erkeklerde <13 g/dL olması) ve trombositopeni (<150 000 µL) olarak kabul edilmiştir.
Bulgular: Hastaların %68'inde hematolojik değişiklikler gelişmiştir. Hematolojik komplikasyon bulunan hastalar arasında yaş ve cinsiyet açısından anlamlı fark yoktur. En yaygın hematolojik komplikasyon ortalama 12,3±2,1 hemoglobin derişimi ile hastaların %36,5'inde anemi olup, bunu %11,7 ile trombositopeni, %10,2 ile lokopeni ve %9,6 ile lokositoz izlemiştir.
Sonuç: Hematolojik değişiklikler brusellozda en yaygın komplikasyonlar arasındadır. Endemik bölgelerde anemi, lökopeni, trombositopeni ve pansitopeni dahil olmak üzere hematolojik laboratuvar anormallik durumlarında bruselloz için tanısal testler akılda tutulmalıdır.

Anahtar Kelimeler: *Anemi, Brucella, bruselloz*

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Introduction

Brucellosis is a disease, which has been found to be caused by *Brucella* strains a century ago. It is a zoonotic infectious disease of domestic and wild animals, which is transmitted to humans by several routes.[1] *Brucella* spp. are gram-negative, non-motile and non-spore-forming small coccobacilli.[2] *Brucella spp.* is highly sensitive to heat, ionized radiation, and disinfecting agents.[1,3] Six species have been identified including *B. abortus, B. melitensis, B. suis*, and *B. canis* that cause brucellosis in humans as well as *B. ovis* and *B. neotomae*. These six species have been proposed to be classified under one (*B. maris*) or two (*B. pinnipediae and B. cetaceae*).[4,5] The most commonly isolated *Brucella* species in Turkey is *B. melitensis.*[6]

Though spreaded worldwide, it is more commonly seen in the Mediterranean countries of Middle East and Africa.[3,6] Brucellosis is an important problem leading to economic losses with low mortality, but high morbidity rates.[7] England, Netherlands, Germany, Austria, Denmark, Finland, Sweden, Norway, and Luxembourg have officially completed the *Brucella* eradication. France, the largest agriculture country of Europe, and other European countries including Greece, Iceland, Portugal, and Spain are continuing the eradication program successfully.[8] The eradication program in Turkey, which had started 30 years ago once failed and was renewed in 2009.[6,8]

Brucellosis is transmitted to humans by direct or indirect contact with an infected animal.[3] Primarily it is transmitted through consumption of unboiled, unpasteurized dairy products such as milk, cheese and butter. Transmission may occur through contact of disintegrated skin through infected excreta, direct inoculation to conjunctiva, aerosol inhalation by laboratory staff, and contact with sea mammals.[6] Brucellosis is a disease, which may involve systems and multiple organs, and may be recognized by means of different clinical manifestations.[7] *Brucella spp.* may cause lymphoreticular (bone marrow, liver, spleen, lymph nodes) involvement.[7,9] This often results in hematological changes.[9]

In this study, we aimed to investigate hematological changes that developed in patients with brucellosis who were followed-up in our hospital, situated in a region where brucellosis is common, in comparison with the literature.

Methods

Epidemiological features, clinical data, and laboratory values of patients diagnosed with brucellosis who were followed-up in the infectious diseases outpatient clinics and inpatient wards of Kahramanmaraş Sütçü İmam University Hospital between 1 January 2012 and 31 December 2017 were investigated from the patient files and evaluated in terms of hematological changes. Patients' demographic and epidemiologic data such as age, gender, profession, consumption of fresh cheese, and contact with animals were recorded. The diagnosis of brucellosis was based on detection of a titer ≥1/160 in the standard tube agglutination test (STA), or isolation of *Brucella spp.* in any culture. Patients' C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were recorded as inflammatory markers. In order to define hematological changes; while a leococyte count of >10 000/μL was considered as leucocytosis; a leucocyte count of <4 000/μL, a hemoglobin value <12g/dL in women and <13 g/dL in men, and a platelet count <150 000/μL was considered as leukopenia, anemia and thrombocytopenia, respectively. CRP was studied with turbidimetric method and values of >6 mg/dL are considered as pathologic.

Statistical Analysis

Statistical analysis of the data was performed using SPSS 15.0 package software. Shapiro Wilk test was used to assess whether the parameters fit normal distribution. Chi-square test was used in statistical analysis of paired variables. Descriptive statistics for the continuous and orderable variables were expressed as mean, standard deviation, and median (minimum-maximum), while categorical variables were given as percentages. *p* values <0.05 were considered statistically significant.

Results

Among 346 patients diagnosed with brucellosis, 197 patient with complete epidemiological, clinical and laboratory data were included in this study. The standard tube agglutination tests of all patients were positive with values ≥1/160. Of the patients, 42.1% (n=83) were male, and 57.9% (n=114) were female with a mean age of 49.61±19.07 years. As for the season of presentation, 51.3% (n=101), 22.3% (n=44), 19.7% (n=39), and 13.7% (n= 27) of patients presented in summer, spring, autumn, and winter, respectively. Of the patients diagnosed with brucellosis, 71.6% (n=141) were living in rural areas, and 28.4% (n=56) in urban areas. The most common possible transmission was consumption of fresh cheese (77%) (n=153), followed by animal feeding (68.5%) (n=135), and consumption of raw meat (43.6%) (n= 86).

The changes in hematological parameters developed in 52 % (n=104) of the patients. Of the patients who developed hematological changes, 42.3% (n=44) were male, and 57.6% (n=60) were female with a mean age of 47.5±17.7 years. No significant difference was found between the patients with change of hematological parametersin terms of age and gender. The most common hematological finding was anemia (36.5%) (n=72) with a mean hemoglobin value of 12.3±2.1 (7.3-16.0). This was followed by thrombocytopenia (11.7%) (n=23), leukopenia (10.2%) (n=20), and leucocytosis (9.6%) (n=19). The median values of plateletes and white blood cells were 260.200 (min=5.000, max=580.000) and 6.600 (min=530, max=16.060), respectively. Of the 72 anemic patients, 62.5% were female. Anemia was identified in 39.5% (n=45) of female and 32.5% (n=27) of male patients with brucellosis. Patients were divided into three groups with respect to hemoglobin concentration: <8 g/dL, 8-10 g/dL, and >10. There were two (one male, one female), 12 (1 male, 11 female), and 59 (26 male, 33 female) patients in the groups, respectively. The incidence of anemia was higher in female than in male patients. The prevalence of anemia was found to be 42.4% (n=25) in premenopausal female patients and 36.4% (n=20) in postmenopausal female patients with brucellosis. No significant difference was found between the premenopausal and postmenopausal female patients in terms of incidence of anemia (p=0.512) (Table 1). When laboratory values of the patients who developed hematological changes were evaluated; the mean CRP was found as 43.7±26.5 (range: 12.5-112), and the mean ESR was found as 39.1±26.4 (range: 2-138).

Table 1. Comparison of female patients in reproductive age/menopausal period in terms of anemia

	Patinets with anemia	Patients without anemia	Total
Reproductive age			
n	25	34	59
%	42.4	57.6	100
Menopausal period			
n	20	35	55
%	36.4	63.6	100
Total			
n	45	69	114
%	39.5	60.5	100

Pearson Chi-Square $\chi 2 = 0.430$; $p = 0.512$

Discussion

Brucellosis is a common systemic disease, which is seen all the year round in Turkey and is more common during calving period of small cattles and in cheesemaking period (spring and summer).[10,11] In studies conducted in Turkey, 46-50% of the patients present in summer months.[10,11] Seasonal distribution of the cases in our study was consistent with the literature.

Veterinarians and laboratory personnel constitute the occupational risk groups for brucellosis in developed countries whereas in developing countries; persons dealing with animal husbandry, those living in rural areas, and individuals consuming unpasteurized milk and cheese are more commonly diagnosed with brucellosis.[7,12] In the study by Demir et al., 76.8% of the patients were living in rural areas.[11] This ratio was 80% in the study by Gursoy et al.[13] In the present study, 71.6% (n=141) were living in rural areas, 68.5% (n=135) were dealing with animal husbandry, and 77.7% (n=153) had a history of unpasteurized dairy products consumption.

Patients can be classified as acute, subacute, and chronic based on disease onset. Lack of these data in our study may be considered as a limitation. Our results were consistent with the literature in terms of profession, living in rural areas, and consumption of raw milk habits. One patient used to consume raw meat. Ulug et al. reported raw meat as a risk factor for brucellosis in their study which is conducted in Turkey.

There is no difference of gender in distribution of cases reported from Turkey.[13-15] In a study by Abdi-Liae in the Middle East, male patients outnumbered females.[16] There are studies in Turkey reporting more female patients because of women's dealing with animal care, milking, and cheesemaking.[17,18] In the study period, we encountered a total of 114 female patients - a predominance compared to the male patients, and a higher proportion of female gender compared to other studies[14,15].

The best-known clinical involvement of brucellosis is in the locomotor system followed by gastrointestinal and hematological systems.[18-20] Studies in the literature have often reported hematological changes of brucellosis.[21] The most common laboratory disorders have been reported also in the hematological system.[14] In a study of 233 patients by Akdeniz et al. leucopenia, anemia, thrombocytopenia, and pancytopenia were seen in 21%, 44%, 26%, and 8% patients, respectively.[22] In a study of 38 cases by Crosby et al., the same abnormalities were detected in 45%, 74%, 39.5%, and 21%, respectively.[23] In our study, while hematological deteriorations such as thrombocytopenia and leukopenia were observed, severe leucopenia cases were rare. Consistently with the literature, anemia was the most common changes in our study. Of our anemic patients, 60% (n=27) were in the reproductive ages, and anemia, which is encountered in 15-47 years of age in Turkey, may not be associated with brucellosis.[24,25]

The studies before 2000 have reported the incidence of anemia between 55-74%, while the studies published after 2000 have reported this incidence as 14.2-43% (Table 2).[7,10,22,23,26-29] This decrease might be due to awareness training, increasing number of healthcare facilities, and close obstetric follow-up.[25] Our study seems to be consistent with the literature data published after 2000.

Table 2. Incidence of anemia in the studies conducted before and after 2000

Year	Authors	Country	Rate of anemia	Number of cases
2003	Namıduru[26]	Turkey	36.8	120
1998	Akdeniz[22]	Turkey	55	233
2010	Uluğ[10]	Turkey	43	78
2007	Gül[27]*	Turkey	14.2	140
2010	Buzgan[7]	Turkey	40.3	1028
2005	Yüce[28]	Turkey	29.1	55
2010	Demir[29]	Turkey	26.5	83
1995	Aygen[20]	Turkey	62.8	183
1984	Crosby[23]	Peru	74	38

*Since the research was carried out in a military hospital, all patients were male.

Hemophagocytosis, hypersplenism, and granulomas in bone marrow are thought to play major roles in the development of hematological changes in patients with brucellosis.[30] Rarely bleeding has been associated with intravascular hemolysis and autoimmune mechanisms.[23,32] Bleeding and purpura may be seen secondary to severe thrombocytopenia and coagulopathies in brucellosis cases.[3] In our study, thrombocytopenia was severe in one of the 23 patients with thrombocytopenia. The changes in hematological parameters may mimic primary hematological disorders, malignancies, thus lead to delayed diagnosis of brucellosis.[32] In our study, the patients had presented to other healthcare centers before getting the diagnosis of brucellosis in our hospital.

In conclusion, hematological manifestations are among the most common laboratory findings in brucellosis. Since brucellosis symptoms are nonspecific, a detailed history should be taken. It should be kept in mind that brucellosis may be confused with other diseases and malignancies. The hematologic laboratory abnormalities (leukopenia, anemia, thrombocytopenia or pancytopenia) observed in an endemic region should prompt the physician to order diagnostic tests for brucellosis.

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Conflict of Interest
No conflict of interest was declared by the authors.

Compliance of Ethical Statement
Ethical Approval
Ethical approval for the study was granted by the Clinical Research Ethics Committee of Kahramanmaraş Sütçü İmam University Faculty of Medicine (Decision Number: 322, Decision Date: 25.07.2018). No patient consent was obtained since the study was conducted retrospectively.

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Author Contributions

ARŞ: Critical revision; data analysis and interpretation; data collection; literature search, resources, materials; manuscript drafting/writing/editing; study design and conception; supervision, SA: Critical revision; study design, SN: Critical revision; data collection; data analysis and interpretation, AE: Data analysis and interpretation; supervision.

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