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Hematological Complications in 787 Cases of Acute Brucellosis in Eastern Turkey

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Aim: In this paper, we present the hematological findings of 787 cases diagnosed with acute brucellosis.

Materials and Methods: Records of the cases seen between 1994 and 2006 were retrospectively investigated regarding hematological changes.

Results: Three hundred sixty-five (46%) patients were male and 422 (54%) were female. Mean age was 32 (range: 11-78 years). Mean hematological values were as follows: Hb 12 g/dl (4-19), Htc 36% (12-56), leukocyte 6.9 × 10^9/L (0.5-25) and platelets 213 × 10^9/L (9-617). According to differential counts, 34% and 14% of patients had mononuclear cell and neutrophil dominance, respectively. Fifty-six percent of patients were found to have anemia, alone or in combination with leukopenia or thrombocytopenia. Fourteen percent of patients had thrombocytopenia, 12% leukopenia, 5% pancytopenia, 4% leukopenia + thrombocytopenia, 0.5% acute hemolysis, and 0.1% disseminated intravascular coagulation. Restoration of thrombocytopenia and leukopenia and improvement in clinical situation were seen within one week and recovery of anemia occurred within 3-4 weeks.

Conclusions: Hematological complications such as anemia and leukopenia are more frequently seen in acute brucellosis cases. However, acute brucellosis should also be considered in the differential diagnosis in the presence of other hematological abnormalities such as severe thrombocytopenia, pancytopenia, acute hemolytic anemia, and disseminated intravascular coagulation.

Key Words: Acute brucellosis, hematological complications

Türkiye'nin Doğusundan 787 Akut Bruselloz Olgusunda Hematolojik Komplikasyonlar

Amaç: Bu çalışmada, akut bruselloz tanısı alan 787 olgunun hematolojik bulgularını sunduk.

Yöntem ve Gereç: 1994-2006 yılları arasında akut bruselloz olgularının kayıtları retrospektif olarak hematolojik komplikasyonlar açısından incelendi.

Bulgular: Hastaların, 365'i (% 46) erkek ve 422'si (% 54) kadın hasta idi. Yaş ortalaması 32 (11-78) idi. Ortalama hematolojik değerler: Hb 12 g/dl (4-19), hematokrit % 36 (12-56), lökosit 6.9 × 10^9/l (0.5-25) ve trombosit 213 × 10^9/l (9-617) olarak belirlendi. Hastaların % 34'ünde mononükleer hücre ve % 14'ünde nötrofil hakimiyeti gözlendi. Olguların % 56'sında anemi tek başına ya da lökopeni veya trombositopeni ile birlikte bulunmaktaydı. Hastaların % 14'ünde trombositopeni, % 12'sinde lökopeni, % 5'inde pansitopeni, % 4'ünde lökopeni + trombositopeni, % 0.5'inde akut hemoliz ve % 0.1'inde yaygın damar içi pıhtılaşma gözlendi. Antibiyotik tedavisinin başlamasını takiben klinik bulguların, trombositopeni ve lökopeninin düzelmesi bir hafta içinde oluşurken, aneminin düzelmesi 3-4 hafta içinde gerçekleşti.

Sonuç: Akut bruselloz olgularında anemi ve lökopeni sık gelişen hematolojik komplikasyonlardır. Bununla birlikte derin trombositopeni, pansitopeni, akut hemoliz ve yaygın damariçi pıhtılaşması gibi durumlarında da ayırıcı tanıda akut bruselloz akılda bulundurulmalıdır.

Anahtar Sözcükler: Akut bruselloz, hematolojik komplikasyonlar

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Introduction

Brucellosis constitutes a major health and economic problem in many parts of the world, including countries of the Mediterranean and the Middle East. Human brucellosis can be an acute or a chronic febrile illness and presents with a variety of manifestations after an incubation period, which can vary from 1 to 6 weeks or several months (1-14). Brucellosis may be difficult to distinguish clinically from a number of other infections

such as typhoid fever, tuberculosis, infective endocarditis, and acute rheumatic fever.

A presumptive diagnosis of acute brucellosis can be made in patients with clinical symptoms consistent with brucellosis by Rose Bengal test positivity. The definitive diagnosis of brucellosis is made when the organism is isolated from blood, bone marrow or other body fluids or tissues and/or by demonstrating significant brucella titers (>1:160 in one serum sample or four-fold increase in two separate samples taken at least 2 weeks apart) in standard tube agglutination test (15). The symptoms of acute illness are fever, chills, headache, muscle and joint pains, malaise, fatigue, nausea, night sweats and loss of appetite persisting 3 to 6 weeks. Brucellosis shows multi-system involvement, and gastrointestinal, cardiovascular, hematopoietic, nervous, skeletal, pulmonary, cutaneous and ocular manifestations have been reported (13,14,15).

While mild hematological abnormalities such as anemia and leukopenia are common in the course of human brucellosis, severe thrombocytopenia, pancytopenia, severe bicytopenia, acute hemolysis and disseminated intravascular coagulation (DIC) are rarely seen.

In this paper, we present the hematological findings in 787 cases diagnosed with acute brucellosis.

Materials and Methods

Records of the 787 cases of brucellosis, hospitalized in our department over a 12-year period from 1994 to 2006, were retrospectively investigated regarding hematological parameters. Routine laboratory tests were done, including complete blood count, peripheral blood smear examination, erythrocyte sedimentation rate (ESR), liver and renal function profiles, and urine examination. As required, coagulation parameters such as prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen level were measured. In cases with bicytopenia, severe cytopenia and pancytopenia, bone marrow aspiration/biopsy was also performed. When results were abnormal or when needed, the complete blood cell count was repeated.

Brucellosis was diagnosed by presence of antibodies against brucella (titer of ≥1:160 by standard tube agglutination test; SAT) (Brucella abortus antisera, Cromatest, Linear Chemicals, Barcelona, Spain) and/or isolation of brucella organisms from blood or bone marrow (Bactec, Becton Dickinson, USA) and a clinical syndrome consistent with brucellosis. When SAT was negative, SAT test was repeated with Coombs' serum to detect anti-brucellar blocking antibodies (>1:160 in one serum sample or four-fold increase in two separate samples taken at least 2 weeks apart) (15). Anemia, thrombocytopenia and leukopenia were defined as hemoglobin (Hb) level <120 g/dl in females, <135 g/dl in males, a platelet count of $< 150 \times 10^9$/L and leukocyte count of $<4 \times 10^9$/L, respectively. Patients were treated with oral rifampicin and doxycycline for at least 6 weeks in combination with intramuscular streptomycin for the first 2 weeks in some cases. The patients were followed up for 3 to 6 months after completion of the therapy.

Results

Three hundred sixty-five (46%) patients were male and 422 (54%) were female. Mean age was 32 (range: 11-78 years). The main presenting symptoms were arthralgia (77%), fever (74%), night sweat (64%), malaise (65%), anorexia (44%), weight loss (36%), headache (21%) and abdominal pain (6%). The main signs are given in Table 1. Samples for blood culture were taken from 443 (59%) cases and bone marrow aspiration specimens from 80 cases. Brucella serological titers were diagnostic in 779 (99%) patients.

Table 1. Clinical and hematological findings observed in the 787 adult cases with brucellosis.

Findings	Case Number (n)	Rate (%)
Fever	136	17
Hepatomegaly	155	20
Splenomegaly	126	16
Lymphadenopathy	26	3
Hepatosplenomegaly	33	4
Anemia	337	43
Thrombocytopenia	111	14
Leukopenia	93	12
Anemia + leukopenia	57	7
Pancytopenia	41	5
Anemia + thrombocytopenia	47	6
Leukopenia + thrombocytopenia	34	4
Acute hemolysis	4	0.5
Disseminated intravascular coagulation	1	0.1

SAT was found positive (≥1:160) in 749 (95%) patients; SAT with Coombs' was positive in 30 (4%) patients in whom SAT was found to be negative. Our patients had titers ranging from 1:160 to 1:20480. In 8 (1%) patients with both SAT and SAT with Coombs' negativity, the laboratory diagnosis was made with culture positivity. Typing of brucella species was performed using conventional biochemical (oxidase, catalase, urease and nitrate) and serological (agglutination with monospecific antisera) tests (15). The organism was isolated from blood and/or bone marrow of 168 (21%) patients tested. In these patients, *B. melitensis* was identified from 125 (16%) blood samples and from 43 (5%) bone marrow specimens tested.

Mean hematological values were as follows: Hb 12 g/dl (4-19), hematocrit (Htc) 36% (12-56), leukocytes 6.9 × 10^9/L (0.5-25) and platelets 213 × 10^9/L (9-617). According to differential counts, while 52% of patients were found in normal range, 34% and 14% of patients had mononuclear cell and neutrophil dominance, respectively. Fifty-six percent of patients were found to have anemia, alone or in combination with leukopenia or thrombocytopenia. The initial hematological findings in the 787 patients are summarized in Table 1. The ESR was elevated in 306 (58%) patients (>20 mm/h). In 9 patients whose bone marrow biopsies were evaluated, there was hypercellular bone marrow in 4 patients, decrease in granulocytic series and hypocellularity in 3 patients, and normocellular bone marrow in 2 patients. On the other hand, there was increase in plasmocytes in 5 specimens and increase in eosinophils in 2 specimens. Restoration of thrombocytopenia and leukopenia to normal range occurred within one week after initiation of antimicrobial therapy. Recovery of anemia occurred within 3-4 weeks.

Discussion

The World Health Organization estimates the number of new cases of brucellosis at more than 500 000 per year in the world (13). Although brucellosis has been controlled in many developed countries, it remains an important health problem in developing countries (1). In the present study, brucella serological titers were diagnostic in 779 (99%) patients. On the other hand, blood or bone marrow cultures were positive in 21% of cases.

Patients with brucellosis usually present with fever, chills, malaise, weight loss, joint involvement, hepatosplenomegaly and lymphadenopathy (2). In this study, the main symptoms at presentation in 787 patients with brucellosis were arthralgia (77%), fever (74%), night sweat (64%), malaise (65%), anorexia (44%) and weight loss (36%). The main signs in these patients were hepatomegaly (20%), fever (17%) and splenomegaly (16%) (Table 1). Mean hematological values were as follows: Hb 12 g/dl, Htc 36%, leukocytes 6.9 × 10^9/L and platelets 213 × 10^9/L. According to differential counts, while 52% of patients were found in normal range, 34% and 14% of patients had mononuclear cell and neutrophil predominance, respectively. Fifty-six percent of patients were found to have anemia, alone or in combination with leukopenia or thrombocytopenia, and 5% of patients had pancytopenia (Table 1). Restoration of thrombocytopenia and leukopenia to normal range occurred within one week after initiation of antimicrobial therapy.

The incidence of anemia has been reported as 44 to 74% in adult series in brucellosis (3,4,13). In our patient group, incidence of anemia was 56%, while it was close to 54.6% in the study of Aygen et al. (13). Anemia in patients with brucellosis results from alteration in iron metabolism secondary to infection, hypersplenism, bleeding, bone marrow suppression or autoimmune hemolysis (5).

Because brucella endotoxin is less toxic than lipopolysaccharides of other Gram- negative bacteria, acute hemolysis and DIC seem to be rare (4). DIC was detected in one patient in the study of Al-Eissa et al. (5). In our study, acute hemolytic anemia was present in four patients and DIC in one patient (Table 1).

Earlier literature has emphasized the characteristic picture of a normal or reduced leukocyte count with relative or absolute lymphocytosis in patients with brucellosis (5). Leukopenia has been found to occur in 30-68% of the reported cases (5). In this study, 52% of the patients had a normal leukocyte count and 12% had leukopenia; mononuclear cell and neutrophilic predominance were present in 34% and 14% of the cases, respectively. Aygen et al. found the rate of leukopenia as 7.7% (13). The cause of leukopenia seems to be multifactorial.

Thrombocytopenia has been reported to occur in 1-8% of patients with brucellosis (4). Although the mechanism of the thrombocytopenia in brucellosis is not yet entirely known, it may be hypersplenism, bone marrow suppression due to septicemia, hemophagocytosis, granulomas and peripheral immune destruction of thrombocytes (3). While thrombocytopenia was detected in 5% of patients in the study of Al-Eissa et

al. (5), it was detected at a higher rate in our study (14%). Aygen et al. reported the thrombocytopenia rate as 13.7% (13).

The possible mechanisms suggested for pancytopenia in brucellosis include hypersplenism, granuloma formation in the bone marrow, phagocytosis of formed elements by reticuloendothelial cells or bone marrow depression due to the associated septicemia (5,8,10,11,14). Pancytopenia has been described as between 3 to 21% in patients with brucellosis in the published series (5,6). Sari et al. reported the pancytopenia rate as 14.9% (14). In our study, the incidence of pancytopenia was 5%. The role of bone marrow hypoplasia in the pathogenesis of pancytopenia has rarely been reported in patients with brucellosis (14). In our series, three patients had hypocellular bone marrow.

Splenomegaly is reported to occur in 15-60% of cases with brucellosis (6,7,9,12,13,16). In our study, the frequency of splenomegaly was 16%. The frequency of hepatomegaly (20%) in our study was similar to the finding of Aygen et al. (13). In the study of Taşbakan et al., hepatomegaly rate in their patients was higher, at 37.6% (16). It has been reported that in the patients with pancytopenia, hepatosplenomegaly rates are found to be higher (63.3%) (14). While the lymphadenopathy rate reported from Yemen was 26.6%, it was detected as 3% in our study. Similarly, it has been suggested that in patients with pancytopenia, lymphadenopathy is seen at higher (40%) rates (14). After appropriate antibiotic treatment, thrombocytopenia, leukopenia and the clinical situation improved within one week and recovery of anemia occurred within 3-4 weeks.

In conclusion, hematological abnormalities accompanying brucellosis are common. However, these abnormalities disappear following successful antimicrobial therapy of brucellosis. We want to emphasize here that in a patient with fever, arthralgia and hematological abnormalities such as anemia, leukopenia, thrombocytopenia or pancytopenia, brucellosis should be kept in mind, especially in geographical areas where the disease is still endemic, as in our region.

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