Hematological Manifestations in Brucellosis Cases in Turkey

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Abstract

The hematological findings of 233 patients with brucellosis are presented and the possible pathologies discussed. Anemia was present in 128 patients (55%), leukopenia in 49 (21%) and thrombocytopenia in 59 (26%). Bone marrow aspirates of 18 patients (8%) with pancytopenia were examined. The bone marrow was hypercellular in 15 and normocellular in 3 patients. Granulomatous lesions were detected in 12 cases (67%), and slight to moderate cytophagocytosis of erythrocytes, granulocytes and platelets existed in all patients. Blood cell counts reverted to normal within 2-3 weeks of initiating chemotherapy with recovery from the disease.

KEYWORDS: brucellosis, hematology, pancytopenia, disseminated intravascular coagulation

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Brief Note

Hematological Manifestations in Brucellosis Cases in Turkey

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The hematological findings of 233 patients with brucellosis are presented and the possible pathologies discussed. Anemia was present in 128 patients (55%), leukopenia in 49 (21%) and thrombocytopenia in 59 (26%). Bone marrow aspirates of 18 patients (8%) with pancytopenia were examined. The bone marrow was hypercellular in 15 and normocellular in 3 patients. Granulomatous lesions were detected in 12 cases (67%), and slight to moderate cytophagocytosis of erythrocytes, granulocytes and platelets existed in all patients. Blood cell counts reverted to normal within 2–3 weeks of initiating chemotherapy with recovery from the disease.

Keywords: brucellosis, hematology, pancytopenia, disseminated intravascular coagulation

Brucellosis constitutes a major health problem in many parts of the world, particularly in the Mediterranean and the Middle East. Human and animal infection with *Brucella melitensis* is a common disease, especially in the eastern and southeastern regions of Turkey. The disease is caused by the ingestion of fresh unpasteurized milk or milk products obtained from infected goats, sheep or cows, or contact with such infected animals (1, 2).

Brucellosis is a multisystem disease with a broad spectrum of clinical manifestations. Hematological abnormalities, ranging from a fulminating state of disseminated intravascular coagulopathy to subtle hemostatic alterations have been reported in Brucella infection (1–5). Involvement of the bone marrow and spleen may result in a myelophthisic pattern on peripheral blood smears (2). In the presence of pancytopenia, hepatomegaly, lymphadenopathy, and fever, brucellosis may mimic other clinical conditions leading to reticulosis or histiocytosis including some other infections such as infectious mononucleosis, leishmaniasis, tuberculosis, and typhoid fever. Consequently, in any patient exhibiting the aforementioned symptoms, these infectious diseases must first be ruled out (6–9).

Two hundred thirty-three patients with brucellosis, seen over a period of approximately three years from June 1994 to March 1997 at the Yuzuncu Yil University Hospital, in Van, Turkey, were studied for hematological changes during their active infection. Of the 233 patients, 108 (46%) were male, and 125 (54%) were female. Mean ages were 29.1 years, and 35.2 years, respectively. The spectrum of clinical manifestations of the patients varied from slight fever and mild malaise to severe prostration and toxicity. The main symptoms were fever (83%), malaise/myalgia (79%), arthralgia (77%), anorexia (62%), weight loss (54%), arthritis (33%), hepatomegaly (34%), splenomegaly (22%) and lymphadenopathy (11%). Brucella agglutination titers were positive at 1:160 or more in all cases. Blood and bone marrow cultures were positive in 124 patients (53%). *Brucella melitensis* was identified in all patients. Special stains and cultures of the bone marrows for acid-fast bacilli and fungi gave negative results.

The initial hematological findings of the 233 patients are summarized in Table 1. Anemia (defined as Hb less than 135 g/l in males and less than 115 g/l in females) was found in a total of 128 patients (55%). It was solely present in 75 patients (32%), and co-present with leukopenia in 21 patients (9%), with thrombocytopenia in 14 (6%) and with pancytopenia in 18 (8%). Of the 128 patients, 52 (41%) had an iron deficiency, and 3 (2%) had acute hemolysis due to bacteremia.

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Table I  Initial hematological findings in 233 patients with brucellosis

| Hematological findings (mean; range) | Number of patients (%)
<table>
<thead>
<tr>
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<tr>
<td>Total cases of anemia (Hb levels 10.2; 5.1-13.4 mg/dl)</td>
<td>128 (55)</td>
</tr>
<tr>
<td>Anemia without other findings</td>
<td>75 (32)</td>
</tr>
<tr>
<td>Iron deficiency in anemic patients (MCV 71; 55-79)</td>
<td>52 (41)</td>
</tr>
<tr>
<td>Acute hemolysis in anemic patients</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Anemia + Leukopenia</td>
<td>21 (9)</td>
</tr>
<tr>
<td>Anemia + Thrombocytopenia</td>
<td>14 (6)</td>
</tr>
<tr>
<td>Leukopenia (3.6; 1.8-4.5 × 10^9/mm^3)</td>
<td>49 (21)</td>
</tr>
<tr>
<td>Leukocytosis (11.8; 10-18.4 × 10^9/mm^3)</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Polymorphonuclear predominance in blood smears</td>
<td>42 (18)</td>
</tr>
<tr>
<td>Lymphomonocytosis in blood smears</td>
<td>93 (40)</td>
</tr>
<tr>
<td>Total cases of thrombocytopenia (81; 23-150 × 10^9/mm^3)</td>
<td>59 (26)</td>
</tr>
<tr>
<td>Thrombocytopenia without other findings</td>
<td>18 (8)</td>
</tr>
<tr>
<td>Thrombocytopenia + Leukopenia</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>18 (8)</td>
</tr>
<tr>
<td>Disseminated intravascular coagulopathy</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (ESR) (20-50 mm/h)</td>
<td>84 (36)</td>
</tr>
<tr>
<td>ESR higher than 50 mm/h</td>
<td>58 (25)</td>
</tr>
</tbody>
</table>

Pancytopenia was considered to be present if Hb was <135 g/l in men and <115 g/l in women, Total WBC <4.5 × 10^9/mm^3, and platelets <150 × 10^9/mm^3.

Leukopenia (total WBC <4.5 × 10^9/mm^3) occurred in 49 patients (21%), of whom 42% were also neutropenic, 63% were lymphopenic and 8% were relatively lymphocytotic. Thrombocytopenia (platelets <150 × 10^9/mm^3) was seen in a total of 59 cases (26%); solely in 18 (8%), in combination with anemia in 14 (6%), with leukopenia in 9 (4%), and with pancytopenia in 18 (8%) cases.

Three patients had clinically detectable bleeding. The bleeding episodes comprised epistaxis in one patient, gross hematuria in one, and cutaneous petechiae and melena in another who had disseminated intravascular coagulopathy. Their PT and PTT were normal and the direct Coombs’ test was negative in all three patients. Bone marrow aspirates were obtained from the 18 patients with pancytopenia. The bone marrow was hypercellular in 15 of these patients and normocellular in three. Granulomatous lesions were detected in the bone marrow of the 12 cases (67%), and slight to moderate cytopenocytosis of erythrocytes, granulocytes and platelets was present in all of them. Restoration of normal peripheral blood cell counts occurred within two to three weeks after initiation of chemotherapy, in conjunction with full recovery from the disease.

The erythrocyte sedimentation rate (ESR) was elevated in 142 patients (61%). In 84 of these patients, ESR was between 20-50 mm/h, and in 58 it was greater than 50 mm/h. Blood smears of these patients indicated that 42% had normal ranges while 18% showed polymorphonuclear dominance and 40% showed lymphomonocytosis.

Although brucellosis has been controlled or eradicated in many developed countries, it still remains a health problem in developing countries. The majority of these patients with a prolonged fever 1-3 weeks in duration admitted to our hospital were found to have brucellosis. The hematological abnormalities detected in our patients and the related signs were further analyzed. Mild to moderate splenomegaly was found in 22% of brucellosis patients and in 80% of those patients with pancytopenia, as compared with other studies in which splenomegaly has been noted in 21 to 55% of patients with brucellosis and in 86-88% of those patients with pancytopenia and Brucella melitensis infection (10-12).

Anemia has been reported more often with Brucella melitensis than with other Brucella species. We found anemia in 128 of the 233 cases (55%), which is comparable to the rates of 57 to 83% reported in other recent studies of adults (1, 6, 9, 12). Current thinking holds that anemia in a patient with brucellosis results from alterations in iron metabolism which occur after infection, hypersplenism, bleeding, bone marrow suppression or autoimmune hemolysis. Hemolytic anemia has rarely been reported in patients with brucellosis, and hypersplenism accompanied by a vigorous reticulocytic response appears to be the most likely mechanism for excessive hemolysis (1, 3).

Previous literature has characterized brucellosis as a disease whose primary manifestations are normal or reduced leukocyte counts with relative or absolute lymphocytosis. Leukopenia has been found to occur in 21 to 68% of the reported cases (1, 6, 9, 12). In this study, 21% of the patients had leukopenia while relative lymphocytosis was present in only 8% and absolute lymphocytosis in only 2% of the cases. These observations are in accord with the findings of patients with brucellosis as reported by Garcia P et al. (9). Other studies have reported incidence of thrombocytopenia in...
the range of 20–33% (1, 6, 12). In this study, thrombocytopenia incidence was 26%, which is comparable with other studies.

Brucellosis is a disorder in which hyperplasia of the reticuloendothelial cells occurs and pancytopenia may be a result of hypersplenism with excessive destruction of formed blood elements. Pancytopenia may be attributed to hypersplenism, or to hemophagocytosis and/or bone marrow depression due to associated septicemia. Other studies have reported incidence of pancytopenia in the range of 3–21% (1, 2, 6, 7). In this study, the incidence was 8%.

Brucella-associated histiocytic hemophagocytosis is reversible and the hematological abnormalities revert to normal values following antibrucellar therapy. The role of the bone marrow aplasia has rarely been reported in patients with brucellosis. The frequency of splenomegaly with a tendency to narrow hyperplasia suggests that hypersplenism is of major pathogenetic importance (2, 7, 8).

The ESR may be elevated, but it is usually not elevated and is only of prognostic rather than of diagnostic significance if the value was elevated prior to onset of the disease (13). Hemorrhagic manifestations have been observed in patients with brucellosis, and the incidence varies from 3 to 26% of the cases reported (14). The bleeding episodes among our patients were less frequent than in other reports (2%) and all were mild.

The presence of bone marrow granulomas has been demonstrated in brucellosis. In one series, non-caseating granulomas were observed in the bone marrow biopsies of 68% of total cases (2). In other diseases or infections, such as sarcoidosis, tuberculosis, listeriosis, histoplasmosis, cryptococcosis, malaria, toxoplasmosis and leishmaniasis, granulomatous lesions may be seen and all these diseases are entirely different from the standpoint of treatment (15). Hence, the bone marrow cultures in such cases are of great importance in a differential diagnosis.

In conclusion, brucellosis is a common disease in our region. Occasionally, diagnosis may be delayed, particularly if uncommon features such as pancytopenia are present. This particular manifestation might mimic other clinical conditions leading to histiocytosis and/or bone marrow infiltration or failure. Hence, brucellosis must be considered in the differential diagnosis of all those conditions leading to pancytopenia in areas endemic for brucellosis.

References


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