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Acute Lymphoblastic Leukemia Associated with Brucellosis in Two Patients with Fever and Pancytopenia

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Brucellosis is a disease involving the lymphoproliferative system, which may lead to changes in the hematological parameters; however, pancytopenia is a rare finding. However, malignant diseases in association with brucellosis are rarely the cause of pancytopenia. Herein, two cases with fever and pancytopenia, diagnosed as simultaneous acute lymphoblastic leukemia and brucellosis are presented. Anti-leukemic therapy and brucellosis treatment were administered simultaneously, and normal blood parameters obtained. The first patient is in complete remission; the other recovered from the brucellosis, but later died due to a leukemic relapse.

Key Words: Acute lymphoblastic leukemia, brucellosis, pancytopenia

INTRODUCTION

Brucellosis is an infectious disease involving the lymphoproliferative system. Changes in the hematological parameters are observed in most patients, but pancytopenia is rare.[1,2] Hemophagocytosis, hypersplenism or granulomatous changes in the bone marrow may be responsible for pancytopenia occurring during brucellosis.[1,2] Additionally, bone marrow involvement due to the simultaneous presentation of malignant diseases with brucellosis rarely lead to pancytopenia. Herein, two cases with fever and pancytopenia, diagnosed as simultaneous acute lymphoblastic leukemia (ALL) and brucellosis are presented with the associated literature data.

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CASE REPORT

Case I

A 39-year-old female presented with a one month history of weakness, headache, nausea, vomiting and fever. A physical examination revealed significant pallor, fever (axillary's measurement: 39℃) and tachycardia (pulse rate: 100/min). A high erythrocyte sedimentation rate (120 mm/hr), pancytopenia in complete blood count (Hb: 6.0 g/dL, platelet: 34×10^9/L, WBC: 1.1×10^9/ L with 80% lymphocyte, 10% atypical mononuclear cells, 10% neutrophil) was detected in a laboratory examination. The serum biochemistry parameters were within normal ranges; BUN: 24 mg/dL, creatinine: 1.2 mg/dL, urate: 6.6 mg/dL, alanine transaminase: 22 U/L, aspartate transaminase: 31 U/L and lactic dehydrogenase: 185 U/L. Bone marrow aspiration and trephine biopsy histologically consisted of ALL (90% of the nucleated cells of bone marrow were lymphoblasts which were T cell immuno-histochemical markers) (Fig. 1, 2). A chemotherapy regimen, consisting of adriamycine (50 mg/week/total two doses), vincristine (2 mg/week/total two doses) and prednisone (100 mg/day/p.o./for 14 days), was started. Brucella melitensis was detected in a bone marrow culture, so a brucellosis treatment (streptomycin 1 g/day/intramuscularly, doxycycline 100 mg/bid/p.o.) was added. Her temperature returned to normal within three weeks, and the complete blood count and bone marrow findings

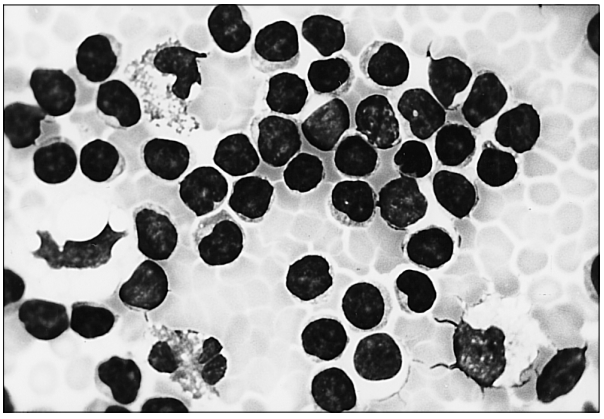

Fig. 1. The predominating cells are lymphoblasts; these cells possess round, oval or indented nuclei containing coarse granular chromatin (My-Grunwald-Giemsa × 1000).

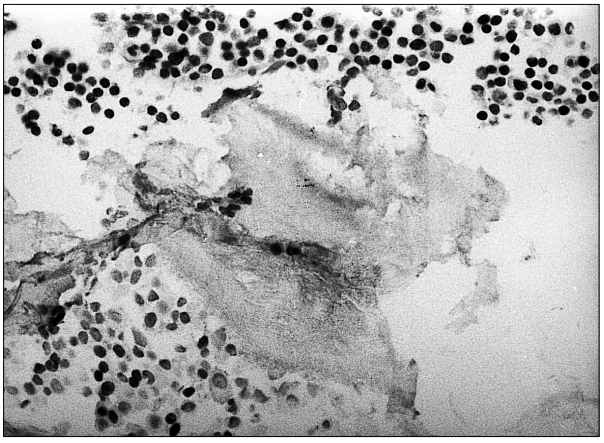

Fig. 2. Intensive lymphoblastic cells in the paratrabecular area (Hematoxylin-eosin × 400).

also returned to normal (Hb: 12 g/dL, platelet: 180 $\times 10^9$/L, WBC: 4.5×10^9/L, with 70% neutrophil, 25% lymphocyte and 5% monocyte, a bone marrow aspirate was normocellular and the blasts content was less than 1% of the nucleated cells). The patient received brucellosis treatment for six weeks. Repeat blood and bone marrow cultures and an agglutination test were negative. The patient is in complete remission from ALL, and the follow up continuing.

Case II

A 40-year-old female presented with a 20 day history of fever, weakness, headache and weight loss and a one week history of jaundice. On admission she was febrile (axillary's measurement: 38.5℃), pancytopenic (Hb: 7g/dL, platelet: 20×10^9/L, WBC: 0.5×10^9/L, with 90% lymphocyte and 10% neutrophil) and demonstrated acute hepatitis (AST: 250 U/L, ALT: 320 U/L, direct bilirubin: 12 mg/dL, indirect bilirubin: 8 mg/dL, LDH: 450 U/L). A bone marrow aspiration histologically consisted of ALL (90% of the nucleated cells of bone marrow were lymphoblasts, which were T cell immuno-histochemical stained). The blood and bone marrow cultures were positive for *Brucella melitensis*. Because the liver function tests were abnormal, i.v. ciprofloxacin was started at 100 mg twice a day. In addition to this treatment prednisone (100 mg/day/p.o.) and vincristine (2 mg/ day/once in a week for three doses) were used for ALL. Her temperature was normal on the 14th day, and the clinical and laboratory findings were nearly normal (Hb: 11 g/dL, platelet count: 90×10^9/L, WBC: 3.2×10^9/L, with 75% neutrophil, 23% lymphocyte, 2% monocyte, AST: 72 U/L, ALT: 83 U/L, direct bilirubin: 2.1 mg/dL, indirect bilirubin: 1.2 mg/dL, LDH: 450 U/L). The leukemic infiltration disappeared in a bone marrow biopsy (blasts < 1%) and a liver biopsy revealed findings of granulomatous hepatitis (Fig. 3). Twenty days later she presented again with fever, jaundice and pancytopenia. A bone marrow biopsy showed 90% lymphoblasts. The blood and bone marrow cultures were negative for brucella, and a brucella agglutination test was negative. The ALL Hoelzer remission induction protocol was administered to the patient, and complete

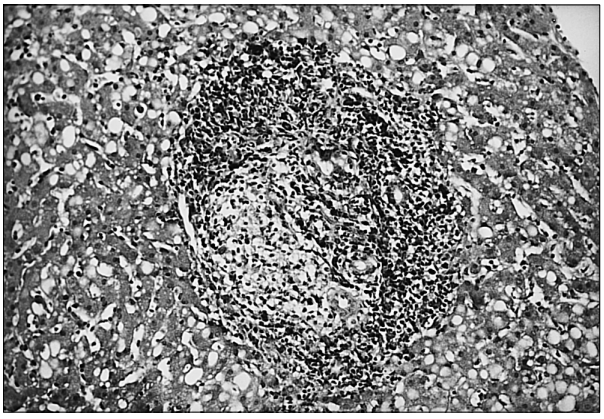

Fig. 3. Granulomatous structure, consisting of epitheloid histiocytes in the liver section (Hematoxylin-eosin × 200).

remission obtained. Two months later, a relapse occurred during the administration of consolidation treatment. Although re-induction treatment was given, she died due to resistant leukemia.

DISCUSSION

Brucella species are gram-negative, coccobacillary, non-motile and facultative aerobic, intracellular microorganisms. The main sources of Brucella are infected animals or their products, such as milk, cream, butter, fresh cheese, ice cream, urine, blood, carcasses and abortion products. Brucellosis is a systemic disease that may involve any organ or tissue. The most common symptoms of brucellosis are fever, sweats, malaise, anorexia, arthralgia and back pain.[3,4] The majority of these symptoms, including fever, sweats and malaise, were also observed in our patients.

Serological tests (Wright agglutination test above 1/160 titers) are helpful in the diagnosis, but the accurate diagnosis is based on the positivity of blood or bone marrow cultures. Anemia is the most frequently observed hematological abnormality in brucellosis, with leukopenia and thrombocytopenia less frequently observed.[1,2,5] Pancytopenia is reported in 5.8 to 14% of cases.[1,2,6] In brucellosis, patients with pancytopenia generally show hypercellularity on bone marrow examination.[7,8] Hemophagocytosis is thought to be primarily responsible for the pancytopenia, but granulomatous lesion formation in the bone marrow or hypersplenism may also play a role.[7,8] Bone marrow and other hematological abnormalities generally revert to normal within 2 - 3 weeks of therapy.[1,6] We saw hypercellularity and infiltration, with lymphoblastic cells, in bone marrow examinations of our cases. Neither hemophagocytosis nor granulomatous lesions were present. Leukemic infiltration of the bone marrow was thought to be responsible for the pancytopenia in these patients. Anti-leukemic therapy and brucellosis treatment were administered simultaneously, and normal blood parameters obtained within three weeks. One of the patients is in complete remission; the other recovered from the brucellosis, but later died because of an ALL relapse.

Hepatocellular carcinoma[9], multiple myeloma,[10] Hodgkin's disease,[11] sinus histiocytosis, with massive lymphadenopathy,[12] and hairy cell leukemia[13] in association with brucellosis have been reported in the literature. Immunity to brucellosis is especially dependent on CD 8 positive T cells and the T cell mediated activation of macrophages.[14,15] For this reason an organism is more susceptible to brucellosis when the cellular immunity is defective. The development of brucellosis may have resulted from a cellular immunity defect in our cases. The incidence of ALL is approximately 1/100,000, 25% of these are of T cell origin. A genetic predisposition, radiation, chemotherapy and viral infections (Epstein-Barr virus, HTLV-I virus) may play roles in the etio-pathogenesis. The relationship between brucellosis and acute lymphoblastic leukemia is extremely rare, even in the regions where brucellosis is endemic.[16] Brucella infection was not shown to play a role in leukemic development in humans. However, the increase in the absolute number of splenic cells in mice infected with the Rauscher leukemia virus and brucella was initially caused by the lymphoid tissue reaction to brucella rather than by the development of leukemia in mice.[17] It is difficult to distinguish the simultaneous occurrence of ALL and brucellosis from the facilitatory effects of other or coincidental events.

The true incidence of human brucellosis is unknown. The World Health Organization (WHO) points out that 500,000 cases of brucellosis are reported each year from around the world. Turkey is also an endemic country for brucellosis. In 1999, 11,462 cases were notified to the Ministry of Health, with an incidence rate of 17.4/100,000. In a multicenter seroprevalence study in Turkey, the seropositivity rate was found to be 1.8% in the healthy population and 6% in the high-risk occupational groups (veterinarians, workers in abattoirs and butchers, etc.).[18]

When we consider the hematological findings and treatment results in our patients, the differential diagnosis should include brucellosis in patients presenting with fever and pancytopenia, especially in regions where brucellosis is endemic. Pancytopenia, observed in association with brucellosis, may be caused by the infection itself or by

bone marrow infiltration of malignant disease. In addition, hematologic guidelines recommend a bone marrow trephine biopsy be performed in patients with unexplained cytopenia.[19,20] For this reason, a bone marrow aspiration or biopsy should be considered both for the determination of the cause of pancytopenia and to eliminate any other disease that may be a cause of pancytopenia, even if brucellosis is accurately diagnosed in these patients. In patients with brucellosis and acute leukemia we suggest that simultaneous treatment for infection and leukemia is the best choice to decrease the morbidity and mortality.

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