Case Report

Acute Brucellosis with Typical Hemophagocytic Lymphohistiocytosis Accompanying Elevated Tumor Markers

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Abstract

We reported a typical brucellosis, which was diagnosed as hemophagocytic lymphohistiocytosis (HLH). Although some tumor markers (CEA, CYFRA21-1, NSE, CA19-9) in the patient's serum were elevated, carcinomas were excluded by a variety of inspections including bone marrow aspirations, ultrasound examinations, and whole-body PET-CT scans. It was concluded that serum tumor markers are considered medically necessary as a screening test for brucellosis with HLH, however, detailed inspections were needed to make a final diagnosis. Moreover, combination of epidemiology investigations and laboratory inspections were helpful to determine the etiology of HLH and initiate the corresponding treatments.

Keywords: Brucella, hemophagocytic lymphohistiocytosis, tumor markers

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Introduction

Brucellosis is a serious and globally distributed zoonotic disease caused by *Brucella* spp,. Four species, *B. Melitensis*, *B. Suis*, *B. Abortus*, and *B. Canis* are currently known to be pathogenic to humans.[1] Humans are usually infected by contacting with infected animals or by consuming contaminated food.[2] In China, 160214 brucellosis cases were reported between 2005 and 2010.

Human brucellosis has a wide spectrum of clinical manifestation, including fever, osteoarticular involvement, sweating; and hepatic, cardiac, central nervous system, or ocular involvement.[3] However, the disease also produces a variety of non-specific hematological abnormalities. The most frequently associated complications were mild anemia, leukopenia, pancytopenia, and thrombocytopenia, however hemophagocytic lymphohistiocytosis (HLH) is rarely reported.[4,5] Here we reported a brucella-infected patient with typical HLH complications accompanying elevated tumor markers.

Case report

Written informed consent was obtained from the patient. A53-year-old man was admitted to Hematopoietic Stem Cell Transplantation Center of our hospital with pancytopenia, abdominal pain, and prolonged fever for seven days. The patient lived in Hebei Province in north China. Before his sudden onset, he had ever closely contacted with goats. Because of no responses to treatment in local hospital, he was transferred to our center. Physical examinations revealed the abdominal pain and high body temperature (39.1ºC), however the absence of diarrhea, cough, expectoration, frequent micturition, hematuria, and pain in urination were reported. Laboratory test results showed a white blood cell count of 3.39×10^9 cells/L (↓ means that the value decreases), a platelet count of 24×10^9/L (↓), and a hemoglobin level of 123 g/L. The differential leukocyte count on the peripheral smear was 65.5% neutrophils, 31.7% lymphocytes, and 2.8% monocytes (↓). The reticulocyte count was 2.8%. Biochemical analysis revealed that alanine transaminase=168 U/L (↑ means that the value decreases), aspartate transaminase = 288 U/L (↑), lactate hydrogenase (LDH) = 871 U/L (↑), ferritin = 6898 mg/L (↑), serum triglyceride = 1.88 mmol/L (↑), fibrinogen = 174 mg/dL (↓), D-dimer = 3472 ng/mL (↑), b2-microglobulin = 9.9 mg/L (↑), and high-sensitivity C-reactive protein = 40 mg/L (↑). The NK cell activity determined by flow cytometry was 7.55% (↓). The soluble serum CD25 level determined by capture ELISA was over 22000 pg/mL (↑). The tumor marker levels of CEA (4.34 ng/mL), CYFRA21-1 (3.64 ng/mL), NSE (23.03 ng/mL), and CA19-9 (35.45 U/mL) were elevated, but FPSA, TPSA, AFP, and CA72-4 were within the normal levels. Serological analysis performed for Cytomegalovirus, Epstein-Barr virus, HIV, HAV, HBV, HCV, Tuberculosis, and Treponema Pallidum were all negative. Pneumonia was excluded by CT examinations and radiations on chest. Bone marrow aspiration showed hemophagocytosis (Figure 1), and leukemia was excluded. The ultrasonic examination revealed splenomegaly (4.1 cm × 11.6 cm) and an enlargement of lymph nodes in the neck, axilla, inguen, and abdomen, but no tumors were detected. Further, whole-body PET-CT scan also excluded the possibility of tumors in the patient.

In order to control the possible infection, the broad-spectrum anti-bacteria drug Tienam (0.5 g/6 hr iv) was initiated on the administration day. After five days of continuous treatment, the body temperature decreased to 38ºC and the abdominal pain was markedly relieved. The blood count showed that white blood cells and

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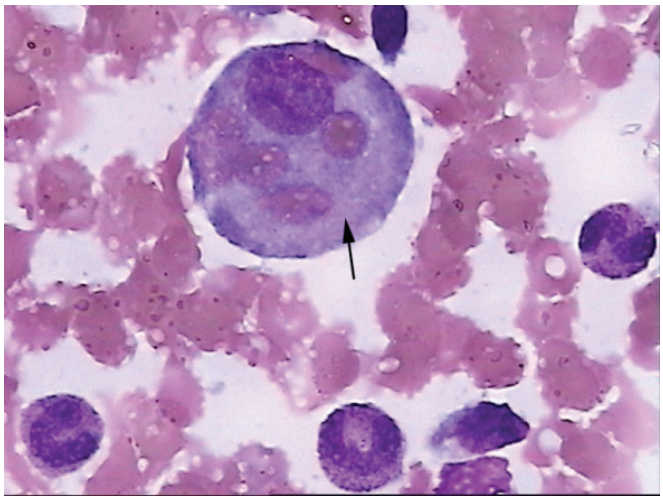

Figure 1. Bone marrow smear showing hemophagocytosis. Erythrocytes were engulfed by a macrophage (Wright stain, 400×).

platelets increased to 4.03 × 10^9 cells/L and 33 × 10^9 /L, respectively. Biochemical abnormalities were also improved: alanine transaminase = 113 U/L, aspartate transaminase = 180 U/L, high-sensitive C-reactive protein = 18 mg/L, and ferritin = 4955 mg/L. On day 6, the patient requested to discharge from our hospital and continued the anti-infection treatment in a local hospital. Later, blood cultures identified the pathogen as *B. Melitensis* by Vitek two identification systems. Therefore, the patient was informed to initiate anti-brucella treatment in a local hospital. He was fully recovered after specific anti-bacteria drug treatment. The patient was normal within 10 months of follow-up.

Discussion

HLH is a potentially fatal hyperinflammatory syndrome, which is characterized by histiocyte proliferation and hemophagocytosis. HLH may be inherited (primary, familial), and often presents during infancy. This disease may also be acquired due to infection, malignancy, and rheumatologic conditions occurring at any age. The mechanism of HLH is unclear yet. However, HLH is diagnosed using clinical criteria developed by the HLH study group of the Histiocyte Society (at least 5 of 8 criteria fulfilled).[6,7] According to the criteria, the patient reported here was diagnosed as HLH based on a prolonged high fever, splenomegaly, hypertriglyceridemia/hypofibrinogenemia, hemophagocytosis in bone marrow, low NK-cell activity, high ferritin, and high soluble CD25 in serum, which fulfilled seven criteria. Although the patient had elevated tumor markers (CEA, CYFRA21-1, NSE, CA19-9), ultrasonic examination (abdomen, pelvic cavity, superficial organ) and whole-body PET-CT scan excluded the presence of tumors. The final blood culture confirmed the pathogen as *B. Melitensis*, which was consistent with the fact that the patient had ever closely contacted with goats. To the best of our knowledge, this is the first brucellosis with typical HLH complications accompanying elevated tumor markers.

For brucellosis patients with elevated tumor markers, careful screening is needed to avoid misdiagnosis as carcinomas. In a previous multicenter retrospective study,[8] 2.5% (5/202) of brucellosis patients were diagnosed as hematological malignancies. In another study,[9] a patient with brucella prostatitis was ever misdiagnosed as prostate carcinoma. Therefore, to those brucellosis patients, serum tumor markers are medically necessary for cancer screening, but detailed imaging examinations, especially whole-body PET-CT scan, were needed to make a final diagnosis.

HLH is a life-threatening immunodeficiency, which is associated with a wide variety of underlying disorders. As seen in this patient, due to lack of pathogen evidences at the beginning, the broad- spectrum anti-bacteria drug Tienam was used, but it was less effective than the traditional aggressive combination of two antibiotics (such as rifampicin or streptomycin plus doxycycline). Therefore, early identification of its etiology based on epidemiology investigations and laboratory inspections is very important to initiate the corresponding treatments.

Conflict of interest

No conflict of interest to declare.

References

1. Seleem MN, Boyle SM, Sriranganathan N. Brucellosis: a re-emerging zoonosis. *Vet Microbiol.* 2010; **140:** 392 – 398.
2. Lucero NE, Ayala SM, Escobar GI, Jacob NR. Brucella isolated in humans and animals in Latin America from 1968 to 2006. *Epidemiol Infect.* 2008; **136:** 496 – 503.
3. Franco MP, Mulder M, Gilman RH, Smits HL. Human brucellosis. *Lancet Infect Dis.* 2007; **7:** 775 – 786.
4. Pappas G, Kitsanou M, Christou L, Tsianos E. Immune thrombocytopenia attributed to brucellosis and other mechanisms of Brucella-induced thrombocytopenia. *Am J Hematol.* 2004; **75:** 139 – 141.
5. Akbayram S, Dogan M, Akgun C, Peker E, Parlak M, Caksen H, Oner AF. An analysis of children with brucellosis associated with pancytopenia. *Pediatr Hematol Oncol.* 2011; **28:** 203 – 208.
6. David A, Iaria C, Giordano S, Iaria M, Cascio A. Secondary hemophagocytic lymphohistiocytosis: forget me not! *Transpl Infect Dis.* 2012; **14:** E121 – E123.
7. Cascio A, Pernice LM, Barberi G, Delfino D, Biondo C, Beninati C, et al. Secondary hemophagocytic lymphohistiocytosis in zoonoses. A systematic review. *Eur Rev Med Pharmacol Sci.* 2012; **16:** 1324 – 1337.
8. Sari I, Altuntas F, Hacioglu S, Kocyigit I, Sevinc A, Sacar S, et al. A multicenter retrospective study defining the clinical and hematological manifestations of brucellosis and pancytopenia in a large series: hematological malignancies, the unusual cause of pancytopenia in patients with brucellosis. *Am J Hematol.* 2008; **83:** 334 – 339.
9. Aksoy F, Aksoy HZ, Sözen EE, Yilmaz G, Köksal I. A case of Brucella prostatitis misdiagnosed as prostate carcinoma. *Mikrobiyol Bul.* 2009; **43:** 493 – 497.