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. Humans are usually infected by contacting with infected animals or by consuming contaminated food. 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. 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. 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. A 53-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 (meaning that the value decreases), a platelet count of 24 × 10^9/L (meaning that the value decreases), 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 (meaning that the value decreases), aspartate transaminase = 288 U/L (meaning that the value decreases), lactate hydrogenase (LDH) = 871 U/L (meaning that the value decreases), ferritin = 6898 mg/L (meaning that the value decreases), serum triglyceride = 1.88 mmol/L (meaning that the value decreases), fibrinogen = 174 mg/dL (meaning that the value decreases), D-dimer = 3472 µg/mL (meaning that the value decreases), b2-microglobulin = 9.9 mg/L (meaning that the value decreases), and high-sensitivity C-reactive protein = 40 mg/L (meaning that the value decreases). The NK cell activity determined by flow cytometry was 7.55% (meaning that the value decreases).

The soluble serum CD25 level determined by capture ELISA was over 22000 pg/mL (meaning that the value decreases). 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 PSA, TP53, and CA19-9 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...
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, highsensitive 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). 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), ultrasonographic 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, 2.5% (5/202) of brucellosis patients were diagnosed as hematological malignancies. In another study, 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**