CASE REPORT

A Case Report of Brucellosis and the Differential Diagnosis of Lymphoma and Tuberculosis

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ABSTRACT

*In this paper, we present a male patient from Xinjiang with fever of unknown origin and significant weight loss for more than 1 month. He was admitted to hospital with negative Rose Bengal test (RBT) and decreased leucocyte count. Ultrasound revealed splenomegaly and abdominal computed tomography,which showed multiple hypodense splenic nodules. The patient was suspected of lymphoma or tuberculosis. Pathological biopsy suggested brucellosis infection following splenectomy. Anti-*Brucella *treatment was effective and his temperature gradually returned to normal. During the follow-up, the patient's RBT result turned to positive and he was instructed to continue the anti-*Brucella *drug regimen. His temperature, weight, white blood cell count, other laboratory examinations, and imaging findings all returned to normal during the 6-month follow-up after the treatment.*

Keywords: Brucellosis, fever of unknown origin, hypodense nodules, lymphoma,tuberculosis.

INTRODUCTION

Fever of unknown origin (FUO) is commonly seen in the clinic, for which infectious diseases are the leading cause. Fever caused by brucellosis infection has attracted lots of attention and should not be ignored. Here we report a patient with prolonged fever, whose serological test and bacteriological culture for brucellosis were both negative. Surprisingly, his pathological biopsy of spleen was consistent with the characteristics of brucellosis infection. Subsequent serological test was repeated during his follow-up, and brucellosis infection was ultimately confirmed.

CASE REPORT

A 36-year-old male living in Kashi, the Xinjiang Uygur Autonomous Region, complained of fever with highest temperature up to 40°C and 12 kg weight loss over a 1-month period before his admission to the First Affiliated Hospital of Xinjiang Medical University. Rose Bengal test (RBT), *Brucella* titre and blood culture were all negative. Abdominal ultrasound suggested splenomegaly and dilated splenic vein. Abdominal computed tomography (CT) scan and contrast-enhanced scan showed multiple hypodense nodules of unknown cause in the spleen (Fig. 1A). Positron emission tomography-CT scan suggested lymphoma for his spleen enlargement, hypersplenism and nodules with concentrated radioactivity. The patient was then admitted to West China Hospital, Chengdu City, Sichuan Province, PR China, for further treatment.

On admission, his temperature was 39.1°C and the spleen was not palpable. Urine and stool exams were normal. Routine blood tests revealed reticulocytes of 0.1280×10^{12}/L and white blood cells of 2.46×10^{9}/L. Biochemical blood tests showed alanine aminotransferase 57 IU/L, aspartate aminotransferase 46 IU/L, lactate dehydrogenase 349 IU/L and hydroxybutyrate dehydrogenase 283 IU/L. Other laboratory examinations indicated ferritin 698.40 ng/ml, CA15-3 29.82 U/ml, CA19-9 24.73 U/ml, CA-125 40.01 U/ml, autoimmune antibodies negative, IgG 23g/L, IgA 3210 mg/L, erythrocyte sedimentation rate (ESR) 31.0 mm/h, C reaction protein (CRP) 5.24 mg/L, procalcitonin 0.10 ng/ml, 1-3-β-D glucan 376.90 pg/ml, and Epstein–Barr

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(EB) virus DNA 1.81×10^2 copies/ml. Other virus antibodies, parasite antibodies and bone marrow culture were all negative. Bone marrow examination showed absence of parasites. Abdominal ultrasound indicated splenomegaly and uneven echogenecity. The patient received anti-EB viral and anti-fungal treatment on admission; however, his temperature did not return to normal. Taking his clinical manifestations and tests into consideration, the patient was strongly suspected to have lymphoma or tuberculosis. He was initially diagnosed with FUO, multiple space-occupying lesions in the spleen and leucopenia.

The patient lived in a region where tuberculosis is endemic. Considering his long disease duration with fever, increased ESR (31.0 mm/h) and CRP (38.1 mg/L), and presence of multiple hypodense splenic nodules, tuberculosis was suspected. However, test of tuberculosis antibody, T-SPOT.TB test and tubercle bacillus qPCR analysis were all negative; making the diagnosis of tuberculosis less likely.

The patient was strongly suspected to have lymphoma. The reasons are as follows: he had experienced prolonged fever accompanied by significant weight loss, leucopenia (2.46×10^9/L), positive EB virus DNA(1.81×10^2 copies/ml) and elevated ferritin (698.40 ng/ml, two times higher than the normal limit). Imaging findings indicated hypersplenism, splenomegaly and multiple hypodense nodules of unknown nature in the spleen. Neither bone marrow flow cytometry nor blood flow cytometry found any cell with abnormal phenotypes. Bone marrow smear also did not suggest any abnormal cell. Bone pathological biopsy revealed haematopoietic cell proliferation in the marrow with no other special abnormality. Splenectomy was performed for a definitive diagnosis. The spleen biopsy showed red pulp enlargement with scattered granulomas. Special staining did not find any acid-fast bacilli or fungi. Immunohistochemisty suggested positive CD163, CD20, CD3ε and MPO, and negative CD30. Therefore, the patient was excluded from lymphoma in pathology. Considering his history of living in the endemic area and the clinical manifestations, the pathological changes were largely consistent with *Brucella* infection of the spleen (Fig. 1B). The treatment was initiated with 2×100 mg/day doxycycline and 600 mg/day rifampin and proved to be effective. Finally, his fever gradually subsided. After discharge, the patient had a repeated RBT during his follow-up, which turned to positive. As such, he was diagnosed as brucellosis and continuous anti-brucellosis treatment was given. The temperature, weight, white blood cell count, radiologic exams, and other laboratory investigations all remained normal for more than half a year.

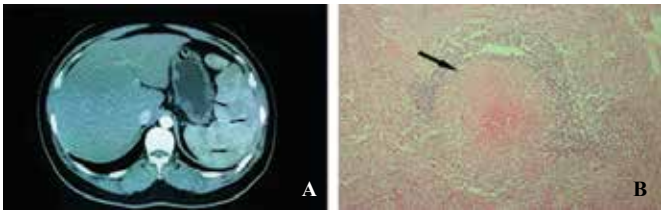

Fig. 1: (A) Abdominal CT scan showed splenomegaly and multiple hypodense splenic nodules (arrows). (B) Spleen biopsy showed granulomas (arrow), HE stain (100×).

DISCUSSION

Fever of unknown origin is mainly caused by infectious, neoplastic, non-infectious inflammatory and miscellaneous disorders. Infections such as those from virus, bacteria and parasites are the most commonly identified aetiologies of FUO, but brucellosis has become more common in the recent years. For patients from epidemic areas with FUO, brucellosis should also be considered.

Brucellosis, the most common global zoonotic disease, has an annual occurrence of more than 500 000 cases in the world (1). Xinjiang is one of the epidemic areas of brucellosis. Brucellosis is a systemic disease that can involve any organ or tissue especially the mononuclear phagocyte system, manifesting varied clinical signs and symptoms. Typical clinical symptoms and physical examinations during the acute and subacute phase of brucellosis revealed intermittent fever, hyperhidrosis, migratory joint pain, hepatosplenomegaly, and lymph node enlargement. The symptoms of chronic infection were not obvious. Patients may complain of fatigue, malaise, depression and joint damage. In most cases, except for the typical symptoms, wide clinical polymorphism is also presented leading to many misdiagnoses such as lymphoma and tuberculosis. All three diseases (brucellosis, lymphoma and tuberculosis) show prolonged fever, weight loss, splenomegaly and elevated ESR.

Considering the clinical manifestations of our patient who was from Xinjiang, a region where both brucellosis and tuberculosis were endemic, he was suspected of tuberculosis. Tests of tuberculosis antibody, T-SPOT and tubercle bacillus qPCR could effectively help to exclude tuberculosis.

Pathology biopsy is the golden standard to diagnose lymphoma. For our patient, both bone and spleen biopsies were performed and lymphoma was excluded.

However, our findings suggested that pathology biopsy combined with epidemiological history and clinical manifestations can strengthen the suspicion of brucellosis infection.

Various complications of brucellosis are classified as neurobrucellosis, endocarditis, orchitis, arthritis, bronchial pneumonia, etc. However, complications of spleen are rarely reported (2, 3). A few reports indicated splenic abscesses of brucellosis shown as hypodense lesions in the imaging findings (4). Multiple splenic hypodense nodules caused by brucellosis as seen in our case have rarely been reported in the literatures and should be differentiated from other diseases with the same radiological characteristics.

The laboratory diagnoses of brucellosis mainly include bacteriological tests, serological tests and molecular assays (5). At the early stage of the disease, the serological tests and bacteriological culture of our patient were both negative. Bacteriological culture is always considered as the gold standard for a definitive diagnosis. However, only a minority of the cases show positive results. Serological test is a type of antigen–antibody reaction widely used for its convenience, rapidity and accuracy. Approximately a week after the disease onset, the specific IgM antibodies appear, which reach their maximum 1 to 3 months later; the IgG antibodies, however, appear about 3 weeks after the onset of the disease and reach the peak level after 6 to 8 weeks (6).The RBT, one of the common serological tests, mainly measures the level of IgG1. False-negative result might be observed if the antibody titres are low during the early stage of the disease. We suppose that with the progression of disease, the IgG1 expression gradually increased, changing the RBT results from negative to positive. When a patient has low immunity or immune suppression, the body cannot effectively generate antibodies, and RBT can also appear false negative. In addition, prozones and RBT antigens of various sources can make positive serum appear negative. Occasionally, RBT-negative results are also presented in patients with the focal forms of brucellosis (7). Serological test should be repeated in different stages of the disease in order to improve brucellosis detection. Pathology biopsy of the lesions can help to exclude other diseases of FUO. Especially when both the bacteriological tests and serological tests are negative, pathology biopsy combined with epidemiological history and clinical manifestations may suggest brucellosis.

The recommended treatment for brucellosis is the combination of doxycycline (200 mg/day) with rifampin (600–900 mg/day) for 6 weeks. It is critical to prolong the antibiotic treatment in order to prevent relapse (8).

CONCLUSION

Brucellosis always leads to various organ and tissue involvement and has non-specific laboratory or radiological findings. It shares manifestations and signs with many other diseases leading to misdiagnoses. Brucellosis should be considered after excluding other diseases, especially for patients from epidemic areas presenting with unexplained organ involvements. Early brucellosis may be missed with conventional bacteriological culture and serological test while pathological biopsy provides evidence for its diagnosis. Repeated serological testing is warranted at different stages to improve the detection of brucellosis.

AUTHORS' NOTE

The authors declare that they have no conflicts of interest.

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