

“Typhoidal Cells” Appear in a Woman with Hemophagocytic Syndrome Secondary To Brucellosis: A Case Report

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ABSTRACT

We report a case of hemophagocytic syndrome (HPS) secondary to brucellosis, in which typhoidal cells were found in bone marrow, suggesting typhoidal cells present not only in *Salmonella typhi* infections but also in other bacterial infections. Typhoidal cells in bone marrow can be used to quickly identify the presence of bacterial infection pending the results of bone marrow and/or blood cultures.

Key words: brucellosis; hemophagocytic syndrome; typhoidal cells

INTRODUCTION

Brucellosis is a zoonotic disease caused by *Brucella melitensis* infection. The clinical manifestations of *Brucella melitensis* infection are non-specific, mainly including fever, fatigue, hyperhidrosis, arthralgia, liver enlargement, spleen enlargement, lymph node enlargement, and cytopenia. Secondary hemophagocytic syndrome (HPS) is an unusual manifestation following *Brucella melitensis* infection ^[1].

CASE DESCRIPTION

The patient, a 29-year-old female of Han nationality, had suffered from fever without obvious cause for 2 months. The fever was intermittent, with the body temperature increased only in the afternoon and night and fluctuating between 38°C and 40.7°C. The patient sought medical care at several medical institutions and

had been treated with acetaminophen, Lianhua Qingwen capsules, and levofloxacin but with poor response.

The patient showed fever again, with the highest temperature reaching 39°C, along with other symptoms including chills, fatigue, dizziness, headache, and joint pain. She visited Qingdao Municipal Hospital for treatment. Blood tests revealed a leucocyte count of $2.46 \times 10^9/L$ with 24.8% neutrophils, 65.0% lymphocytes, 0.40% basophils and 9.80% monocytes, a haemoglobin concentration of 99 g/L, and a platelet count of $60 \times 10^9/L$. The analysis of lymphocyte subsets showed that T lymphocytes accounted for 91.93%, natural killer cells for 2.14%, and B lymphocytes for 5.71%. Hypersensitive c-reactive protein was 5.99 mg/L, triglyceride was 0.84 mmol/L, fibrinogen was 2.30 g/L, and soluble CD25 was 4469.16 U/mL. Examinations for Epstein-Barr virus, mycobacterium tuberculosis, cytomegalovirus, herpes simplex virus, rubella virus, Legionella pneumophila, Mycoplasma pneumoniae, adenovirus, antinuclear antibodies, and thyroid function were negative or normal. No obvious abnormality was found in chest computed tomography examination. Ultrasonography revealed splenomegaly and deposits in the bladder. On the third day of admission, bone marrow smears revealed hemophagocytic cells (**Fig. 1A**) and “typhoidal cells” (**Fig. 1B**) containing 0.5% and 0.1% of the nuclear cells, respectively.

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The patient's blood was cultured in an automatic blood culture machine for 4 days and 8 hours, and the instrument reported positive results. The cultures were stained with Gram and Swiss giemsa, and gram-negative coccobacteria (**Fig. 2A**) and purple coccobacteria (**Fig. 2B**) were found.

The blood culture was transferred to 5% sheep blood plate, and round milky-white colonies appeared 3 days after culture (**Fig. 3**). The bacterium was identified as *Brucella melitensis*. The standard tube agglutination test for brucella spp antigens yielded a ratio of 1:200. A more detailed patient history was taken and showed that she had a habit of drinking unpasteurized goat milk. Therefore, the case was diagnosed as brucellosis.

After diagnosis of brucellosis, the woman was transferred to an infectious disease hospital and was administered oral rifampicin (0.6g, q.d.) and doxycycline (0.1g, b.i.d) for 30 days. Her clinical condition improved gradually and the patient was discharged after 30 days of treatment in hospital. The patient continued to take rifampicin (0.6g, q.d.) and doxycycline (0.1g, b.i.d) for 8 weeks after discharge, and was as-

ymptomatic at 6-month follow-up.

DISCUSSION

HPS, also known as hemophagocytic lymphohistiocytosis (HLH), is a severe inflammatory response syndrome caused by inherited or acquired immune regulatory dysfunction. HPS can be classified as "primary" or "secondary" according to the presence or absence of definite HPS associated genetic abnormalities. Secondary HPS is a severe inflammatory response syndrome caused by tumors, rheumatic immune disease, infections, and other etiologies. Infection is the most common cause of secondary HPS, including bacterial, fungal, viral and protozoal infections, among which viruses, especially Epstein-Barr virus (EBV), are the most common cause of infection-associated HPS^[2-5]. The diagnostic criteria of HPS were established by the Histiocyte Society^[6].

In the present case report, the diagnosis of HPS was made based on the presence of fever, splenomegaly, pancytopenia, raised soluble CD25, and bone marrow hemophagocytosis. The patient had a positive

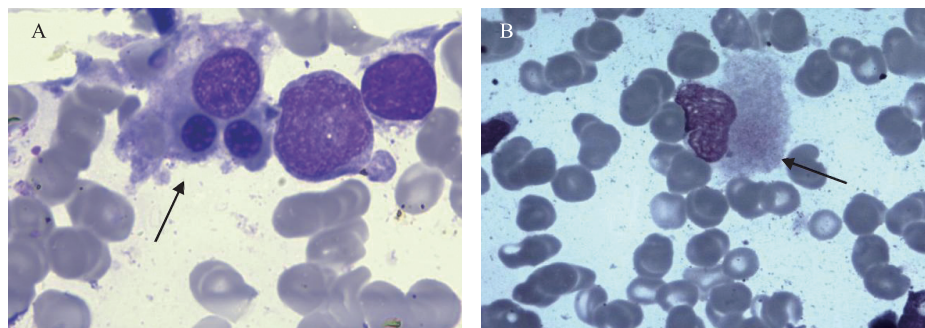


Figure 1. Photomicrograph images of bone marrow smears in a 29-year-old patient with hemophagocytic syndrome. (A) Hemophagocytosis (arrow) by a macrophage (Swiss Giemsa stain, 100×). (B) Typhoidal cells (arrow) (Swiss Giemsa stain, 100×)

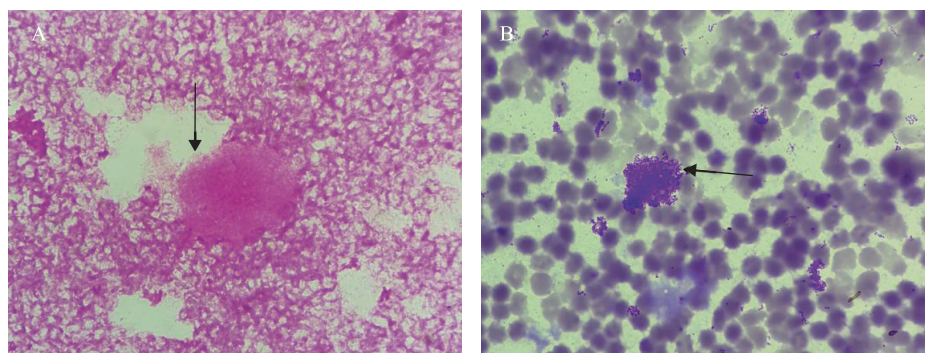


Figure 2. Photographs of blood culture in a 29-year-old patient with hemophagocytic syndrome revealed *Brucella melitensis* infection. (A) Gram-negative coccobacteria (arrow) was identified (Gram stain, 100×). (B) Purple coccobacteria (arrow) was identified (Swiss Giemsa stain, 100×).

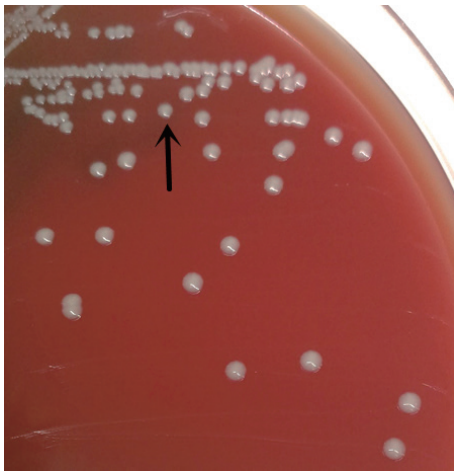


Figure 3. *Brucella melitensis* colonies (arrow) appeared 3 days after culture on 5% sheep blood plate

brucella agglutination test and was diagnosed with brucellosis-induced HPS.

Brucellosis-induced HPS has been described in literature^[7-13]. It is difficult to diagnose *Brucella melitensis* infection because *Brucella melitensis* grows slowly in blood culture — the colonies will not be visible until at least three days later. In addition, the clinical symptoms of *Brucella melitensis* infection are non-specific, and the clinical manifestations (e.g., fever, hepatomegaly, splenomegaly, and cytopenia) of brucellosis and HPS often overlap^[1]. Thus, the diagnosis of HPS is often missed in brucellosis patients. Huang *et al.* retrospectively analyzed the clinical data of 192 patients with hemophagocytic syndrome and found only two patients had *Brucella melitensis* infection-related HPS^[14]. When the peripheral blood of patients with brucellosis shows three or two lines of significant decline, the possibility of complicated HPS should be considered, and bone marrow puncture can be further performed to search for phagocytosis.

The inflammation caused by *Salmonella typhi* is an acute hypertrophic inflammation characterized by macrophage proliferation. When macrophages proliferate actively, *Salmonella typhi* is phagocytic in the cytoplasm of the macrophages, which are called typhoidal cells. Typhoidal cells are usually found in patients with typhoid fever. However, this case report showed that typhoidal cells were present not only in patients with *Salmonella typhi* infection but also in patients with *Brucella melitensis* infection, as already reported by Sun *et al.*^[15].

Therefore, once the bacteria invades the bone marrow, the phagocytes in the bone marrow will engulf

the bacteria, forming the so-called “typhoidal cells”, which can be used to quickly identify the presence of bacterial infection, pending the results of bone marrow and/or blood cultures. However, “typhoidal cells” have not been reported in bacterial infections other than *Brucella melitensis* and *Salmonella typhi*, which may be explained by the low rate of bone marrow puncture during bacterial infection and the small number of “typhoidal cells” in bone marrow.

To sum up, morphological examination of bone marrow cells is valuable in the diagnosis and treatment of infectious diseases, during which the presence of “typhoidal cells” can be highly informative.

Conflict of interests

The authors declare no conflict of interest.

Patient consent

Written informed consent was obtained from the reported patient.

Authors' contributions

Song WQ wrote the manuscript, Zheng X collected data, Li HN processed data, Li L and Yuan JS analyzed data, and Wang SG revised the manuscript. All authors approve the final version.

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病例报告

“伤寒细胞”见于布鲁氏菌病继发噬血细胞综合征：一例报道

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摘要

我们报告一例继发于布鲁氏菌病的噬血细胞综合征（hemophagocytic syndrome, HPS），在骨髓中发现了“伤寒细胞”，表明伤寒细胞不仅存在于伤寒沙门氏菌感染中，也存在于其他细菌感染中。在骨髓和/或血液培养结果出来之前，骨髓中的伤寒细胞可用于快速识别细菌感染的存在。

关键词：布鲁氏菌病；噬血细胞综合征；伤寒细胞

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