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*Case Report*

# A case of hemophagocytic syndrome caused by mycobacterium abscess and literature review

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**Abstract:** A 61-year-old male patient was diagnosed with haemophagocytic syndrome (HLH). The presence of pathogenic bacteria was found in a lymph node tissue culture and blood culture, and the bacteria DNA sequencing confirmed the presence of mycobacterium abscess. The patient received a modified HLH94 regimen combined with clarithromycin, amikacin, cefoxitin, moxifloxacin, tegacycline and other antibiotics, and achieved a temporary effect. Because we could not control the infection, the patient eventually gave up the treatment. Mycobacterium abscess infection is a very rare cause of secondary HLH. HLH can get better only when we control the infection effectively.

**Keywords:** Hemophagocytic syndrome, mycobacterium abscess

## Introduction

Haemophagocytic syndrome (HLH) is a rare, life-threatening condition characterized by over-stimulation of the immune system [1]. The most common causes of HLH in adults are lymphoma and Epstein barr virus, followed by bacteria and fungi. At present, HLH has increasingly been caused by severe tuberculosis [2, 3]. But HLH associated with non-tuberculous mycobacterial (NTM) infection is still very rare. Clinicians have also had sporadic reports of HLH caused by NTM such as mycobacterium intracellulare [4]. Therefore, we report a rare case of HLH caused by NTM-mycobacterium abscess, and review the literature on the relationship between NTM and HLH.

## Case description

A 61-year-old male patient had a fever with chills and pain in the mouth and throat after drinking unclean water. His temperature was about 38°C on January 20, 2017. He went to a local hospital for a penicillin infusion, but there was no significant curative effect. Multiple herpes accompanied by painful red and white ulcers in the mouth appeared above his lip.

On February 20, 2017, the patient was admitted to the First Affiliated Hospital of Zhejiang University for treatment. After admission, a blood routine examination showed the following: white blood cell $0.9\times10^9$/L, neutrophil $0.6\times10^9$/L, hemoglobin 83 g/L, platelet $41\times10^9$/L. Serum ferritin was 1815.7 ng/ml. A bone marrow smear showed hemophagocytosis (**Figure 1A**) with phagocytic reticular cells accounting for 1.5%. The patient received anti-infective treatment including ribavirin, tikolanen and mikofen. The herpes around the mouth and lips gradually subsided, but he had an obvious fever up to 39.6°C. A positron emission tomography-computed tomography (PET-CT) scan indicated the following: 2-Fluoro-2-deoxy-D-glucose (FDG) metabolism in bone marrow unevenly increased; liver and spleen enlargement with a slight increase of FDG metabolism; right supraclavicular and mediastinal lymph node enlargement with different degrees of FDG metabolism increase (**Figure 2**). On March 6, 2017, the right neck lymph node biopsy was performed. The pathological result showed that the lymphoid tissue hyperplasia was accompanied by massive necrosis and the acid-fast stain was positive, which was considered as

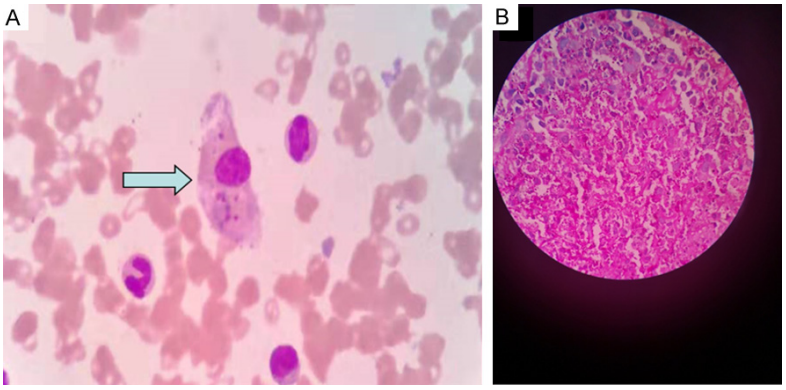


**Figure 1.** A. Bone marrow smear showed a haemophagocyte engulfing platelet and erythrocytes (Wright-Giemsa stain, 1000×) (arrow); B. Lymphatic histopathology: there were large amounts of homogeneous pigmented fine particles in the necrotic tissues and cytoplasm, PAS stain (+), 1000×.

tuberculosis infection. After the operation, the patient was given 80 mg/d of methylprednisolone by intravenous injection, and his temperature dropped to normal. On March 20, 2017, the dose of methylprednisolone by intravenous injection was gradually reduced to 20 mg/d.

On March 20, 2017, the patient came to our hospital. After admission, he stopped taking methylprednisolone injection, but he quickly developed a fever with a maximum temperature of 40°C accompanied by obvious chills before fever. The fever was difficult to effectively control with non-steroidal antipyretic drugs. Then he received cefoxitin injection 2.0 q8h anti-infection plus a HRZE regimen (isoniazid+rifampicin+pyrazinamide+ethambutol) anti-tuberculosis therapy. At this time, his blood routine examination revealed: white blood cell $3.6\times10^9$/L, neutrophil $3.20\times10^9$/L, hemoglobin 74 g/L, platelet $61\times10^9$/L. The coagulation routine showed: prothrombin time (PT) 13.0 seconds, activated partial thromboplastin time (APTT) 42.5 seconds, fibrinogen 74 mg/dl, d-dimer 1360.0 mu/L. Blood biochemistry revealed: creatinine 72.5 mol/L, albumin 29.0 g/L, glutamate transaminase 18 U/L, glutamate transaminase 17 U/L, lactate dehydrogenase 211 U/L, triglyceride 1.68 mmol/L, c-reaction protein (CRP) 0.47 mg/L. Serum ferritin was 6264.5 μg/L. Serum soluble interleukin-2 receptor was 828 U/ml (normal range: 223-710). Hepatitis B virus (HBV) surface antigen (+), HBV E antibody (+), HBV core antibody (+), HBV deoxyribonucleic acid (DNA) $<1\times10^3$ IU/ml, T-SPOT (-). The patient still had a fever after the above treatment. On March 23, 2017, the cefoxitin injection was stopped, and linezolid injection 600 mg q12h was given intravenously to resist Gram-positive bacteria. The patient had a fever, enlarged spleen, significant decrease in peripheral blood cells, decrease in serum fibrinogen, abnormal increase in serum ferritin, increase in serum soluble interleukin-2 receptor, and hemophagocytosis in bone marrow smear. These symptoms were in line with seven articles of HLH diagnostic criteria, so the diagnosis of HLH was clear.

On March 24, 2017, the patient received ultrasonic imaging of his right cervical lymph node, which showed an enlarged lymph node with rich blood supply. A lymph node biopsy was performed, and the lymphoid tissue was cultured and pathologically examined. His lymphatic histopathology showed: scattered plasma cells and scattered histiocytes were observed in the proliferative lymphoid tissues, and clastic necrosis was observed in the focal area; there were large amounts of homogeneous pigmented fine particles in the necrotic tissues and cytoplasm, which seemed to be pathogenic microorganisms (**Figure 1B**); there was no granuloma or caseous necrosis. Special stain results: acid-fast (-), periodic acid-schiff (PAS) (+), pamethenamine (PAM) (+), reggie (+). Immunohistochemical results: CD138 (+), CD56 (+), CD38 (+), TIA-1 (+), Perforin (+). Lymphoid tissue culture took about 90 hours to detect pathogen growth, and acid-fast stain was positive (**Figure 3**).

On March 27, 2017, a blood routine examination revealed: white blood cell $1.1\times10^9$/L, neutrophil $0.7\times10^9$/L, hemoglobin 70 g/L, platelet $15\times10^9$/L; procalcitonin 0.14 ng/ml. The coagulation routine showed: PT12.7 seconds, APTT38.0 seconds, fibrinogen 308 mg/dl, d-dimer 16830.0 mug/L. Blood biochemistry: urea nitrogen 3.91 mmol/L, creatinine 75.6 mol/L, albumin 26.8 g/L, alanine transaminase 42 U/L, lactate dehydrogenase 404 U/L, CRP 82.72 mg/L. Serum ferritin was 8154.9 μg/L An enhanced chest computed tomography (CT) scan showed: multiple diffuse balloon shadows in both lungs, a little interstitial changes in both lungs, mediastinal lymph node enlargement.

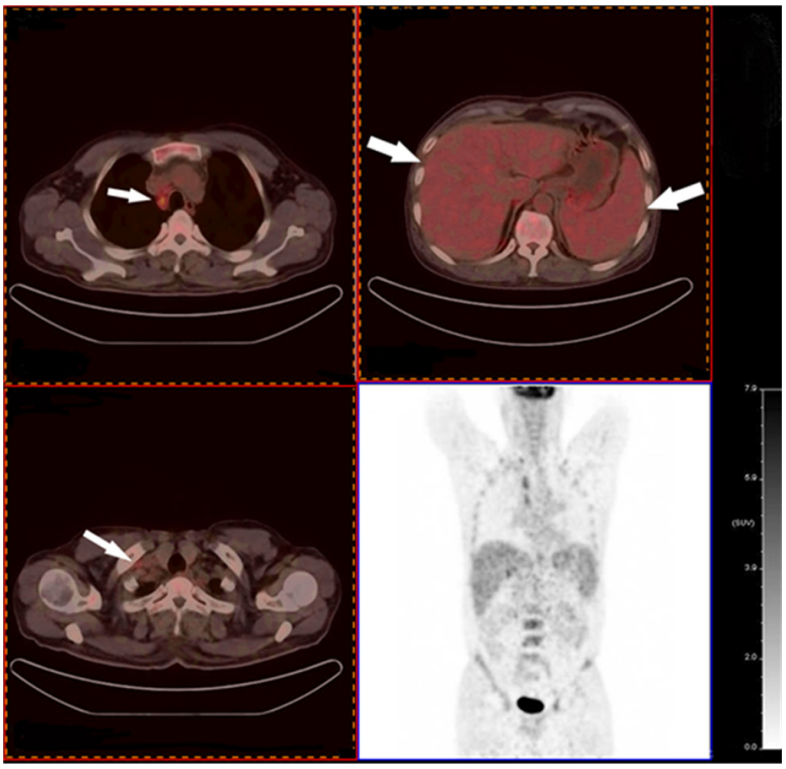

**Figure 2.** PET/CT: liver and spleen enlargement with slightly increased FDG metabolism, right supraclavicular and mediastinal lymph node enlargement with varying degrees of increased FDG metabolism (arrow).

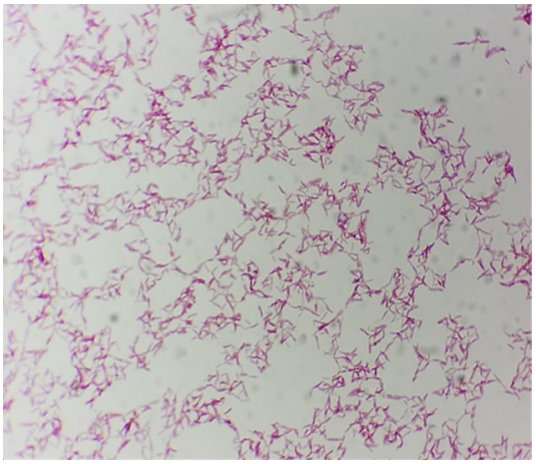

**Figure 3.** The culture of right supraclavicular lymph node puncture indicated that acid-fast stain was positive, 1000×.

An abdominal CT scan revealed splenomegaly. The Epstein barr virus and cytomegalo virus DNA were negative. The patient was treated with the modified HLH94 regimen of immunochemotherapy (etoposide 50 mg d1, d4+ methylprednisolone injection 100 mg d1-3+80 mg d4-14+60 mg d15-18+30 mg d19-21). The patient had no fever for 3 days after immunochemotherapy. Then, he stopped with linezolid injection and was given cefoperazone/sulbactam 2.0 q8h anti-infection therapy. Entecavir inhibited HBV. At the same time, he was given symptomatic treatment with infusion of fresh plasma and gamma globulin. BLAST analysis of the sequence through the National Center for Biotechnology Information server revealed a similarity of 100% with the 16S rDNA sequence of mycobacterium abscess (GenBank No.CP016193.1).

Mycobacterium abscess was found in blood culture specimens of the patient on March 30, 2017. The regimen of HRZE anti-tuberculosis was discontinued. The regimen of 0.4 qd of butylaminacanil injection+0.4 qd of moxifloxacin injection+0.5 bid of clarithromycin tablet was used to fight mycobacterium abscessus. However, the patient developed a fever up to 39°C again.

On April 5, 2017, the drug-sensitive results of lymph node tissues suggested that the strain showed extensive drug resistance and was only sensitive to the mediation of cefoxitin. Therefore, the patient received 100 mg q12h of tetracycline injection (200 mg first dose) + 3.0 q6h of cefexitin injection + 0.4 qd of baifule tablet to resist mycobacterium abscesses. After that, the patient's temperature slowly returned to normal. The genes associated with HLH were negative. Therefore, the patient was diagnosed with secondary HLH caused by mycobacterium abscess.

On April 26, 2017, the patient had a fever again, with the highest temperature being 38.2°C, accompanied by chills. The blood routine examination showed: white blood cell $4.3\times10^9$/L, neutrophil $4.1\times10^9$/L, hemoglobin 82 g/L, and platelet $2\times10^9$/L. Blood biochemistry results

were: urea nitrogen 12.38 mmol/L, creatinine 131.6 mol/L, albumin 18.1 g/L, glutamate transaminase 28 U/L, lactate dehydrogenase 521 U/L. A coagulation routine revealed: PT15 seconds, APTT 62.5 seconds, fibrinogen 142 mg/dl, d-dimer 2340.0 mg/ L, serum ferritin 1954.7 ug/L. At this point, the patient gave up the treatment.

## Discussion

The clinical manifestations of HLH are mainly characterized by fever, hepatosplenomegaly, pancytopenia, low fibrinogenemia, high triglyceridemia and macrophage phagocytosis with a very high fatality rate [1]. Once HLH is considered clinically, doctors should actively look for the etiology. According to statistics, the most common causes of HLH in adults are lymphoma and Epstein barr virus followed by bacteria and fungi, and severe tuberculosis can also cause HLH [2, 3]. Zhang et al. reported 8 cases of tuberculosis-associated with HLH [5]. Other scholars have reported a case of tuberculosis-associated HLH in an umbilical cord blood transplant recipient [6]. We once reported a case of severe tuberculosis causing HLH, and the patient got better after active anti- tuberculosis treatment [7]. HLH may have a chance to be controlled only if the etiology is treated. However, NTM induced HLH is very rare, and only more than 10 cases have been reported in the literature.

The patient had recurrent fever, splenomegaly, pancytopenia, low fibrinogenemia, increased ferritin, and macrophage phagocytosis, so the diagnosis of HLH was clear. In addition, malignant lymphoma, Epstein barr virus infection and congenital HLH were excluded. Fortunately, we obtained the pathogen through a lymph node tissue culture and blood culture. We confirmed the mycobacterium abscess, which was a type of NTM, by bacterial DNA sequencing. Therefore, this patient was diagnosed with secondary HLH caused by mycobacterium abscess. Because mycobacterium abscess is widely found in contaminated water sources in nature [8], drinking unclean water is an important factor for patients to come into contact with mycobacterium abscess.

It is well documented that cultures can be positive for mycobacteria in cases where the acid-fast stain is negative. This holds true for tuberculosis as well as for NTM lung disease [9, 10]. Therefore, negative acid-fast staining of lymph node biopsy pathology in our hospital could not exclude tuberculosis or NTM infection completely. For the patient, the lymphoid tissue culture confirmed positive acid-fast staining of pathogen, and bacterial DNA sequencing confirmed mycobacterium abscess infection.

On one hand, with the development of new microbiological methods, more and more patients with NTM infection are being found [11]. M. avium complex and M.kansasii are the most common species in patients with immunosuppressive conditions [12]. On the other hand, NTM infection can trigger HLH, but the relationship remains unclear. It is generally believed that secondary HLH is often associated with intracellular bacteria that induce classical Th1 immune responses, which are needed for the control of tuberculosis infection [12]. This might be the main reason why NTM infections can cause HLH.

Clinically, the treatment of infection-related HLH is a challenge. Modified 94 or 04 regimen treatment for HLH should be given as soon as possible. Additionally, physicians should emphasize the importance of timely and efficient treatment of the primary infection. Similarly, for the treatment of HLH caused by mycobacterium abscess, both should be taken into consideration. In addition to using the modified HLH94 or 04 regimen, doctors need to treat mycobacterium abscess infection on time. The treatment of mycobacterium abscessus disease usually involves a combination of macrolide plus intravenous agents for at least 2 weeks to several months [11]. The first choice for initial intravenous administration is amikacin plus cefoxitin or imipenem [10]. Although treatment varied, the overall prognosis of NTM-related HLH is promising. Unfortunately, the modified HLH94 regimen combined with several antibiotics including clarithromycin, amikacin and cefoxitin had a short effect for the patient. He finally gave up the treatment, which may be related to the rapid growth of mycobacterium abscess and multi-drug resistance.

Mycobacterium abscess infection is a very rare cause of secondary HLH. Although the overall treatment effect of the patient was not good, we made brief curative effects through a modi-

fied HLH94 scheme combined with anti-infection. Due to the limited experience and lack of cases, we need to further explore the HLH caused by mycobacterium abscess.

## Disclosure of conflict of interest

None.

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