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Case report

Secondary hemophagocytic syndrome in an acquired immunodeficiency syndrome and *Alpha*-thalassemia patient infected with *Talaromyces marneffei*: A case report and literature review

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disease characterized by a hyperinflammatory syndrome and impairment of multiple organ systems. Talaromycosis marneffei (TSM) is an opportunistic infection mostly found in immunosuppressed populations, such as those with acquired immunodeficiency syndrome (AIDS), and is prevalent in southern China. However, HLH secondary to TSM is extremely rare and has only been reported in isolated cases. A 30-year-old patient with recurrent high fever and progressive cytopenia was diagnosed with HLH secondary to disseminated TSM with AIDS and *Alpha*-thalassemia. The patient remained in sustained remission without recurrence after effective treatment with antifungals and glucocorticoids.

Introduction

Talaromycosis marneffei (TSM) is an acquired immunodeficiency syndrome (AIDS) - defining illness and opportunistic infection caused by *Talaromyces marneffei* (*T. marneffei*), predominantly found in southern China [1,2]. Thalassemia, a common disease in southern China, is a genetically heterogeneous disorder with varying clinical phenotypes, ranging from asymptomatic to severe, with some patients requiring lifelong transfusion support [3]. Hemophagocytic lymphohistiocytosis (HLH) is a highly aggressive disease characterized by hyperinflammatory syndrome and impairment of multiple organ systems [4,5]. Infections and malignancies are the primary etiologies of HLH, with viral infections being the most common trigger for infection-associated HLH , followed by bacterial, fungal, and parasitic infections [6]. However, HLH secondary to *T. marneffei* infection is exceedingly rare, and has only been reported as isolated cases in the literature [7–9]. We describe an exceptional case of a patient with human immunodeficiency virus (HIV) infection and *Alpha*-thalassemia who developed HLH secondary to TSM, but achieved successful remission after treatment.

Case presentation

A 30-year-old male patient with a three-day fever was admitted to the hospital. Blood routine examination revealed leukopenia (white blood cell count (WBC): 3.4×10^9/L), mild anemia (hemoglobin (HB): 121 g/L), and thrombocytopenia (platelet count (PLT): 54×10^9/L). C-reactive protein (CRP) was elevated at 68.03 mg/L and chest computed tomography scan (CT) suggested lung infections. The patient denied history of hypertension, diabetes, hepatitis, tuberculosis, AIDS, or other diseases but had habits of smoking and alcohol consumption. He originated from Guangxi province. There was no medical history of blood transfusion or familial hereditary diseases. Physical examination showed an enlarged spleen measuring 2 fingers' breadth below the costal margin. Considering the symptom of fever, high CRP, and manifestation of inflammatory exudation in chest CT, the patient was initially diagnosed with pulmonary infection, for which intravenous infusion of piperacillin-tazobactam 4.5 g was administered once every 8 h. Further examination over the next three days revealed the following results: WBC 2.3×10^9/L, HB 119 g/L, mean corpuscular volume 73 fL, mean corpuscular hemoglobin 24 pg, PLT 14×10^9/L, reticulocyte: 0.7%; erythrocyte sedimentation rate: 23 mm/h; biochemistry: glutamic pyruvic transaminase 46 U/L, glutamic-oxalacetic transaminase 74 U/L,

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uric acid 440μmol/L, creatinine 63umol/L, lactic dehydrogenase (LDH) 601 U/L, triglyceride 3.01 mmol/L, albumin 30.6 g/L; CRP: 125.06 mg/L; negative for Epstein-Barr virus DNA, cytomegalovirus DNA in Polymerase Chain Reaction test and influenza virus antibody in colloidal gold test. The results of Widal test, antinuclear antibody and tuberculosis infection rate t cell spot test were all negative. No significant abnormalities were observed in tumor markers, thyroid function, stool routine or urine routine. Abdominal ultrasound revealed splenomegaly (145 ×52 mm) and multiple enlarged lymph nodes (maximum 24 ×10 mm) in the posterior peritoneum. However, the recurrent high fever (maximum: 39.7 ℃) remained uncontrolled, and there was a progressive cytopenia (minimum: PLT 14 $\times 10^9$/L, HB 80 g/L), suggesting that there might be other potentially and serious causes hidden behind pneumonia. Under this consideration, blood culture was obtained and the antibiotic regimen was escalated to meropenem 1 g intravenous drip every 8 h and peroral linezolid 0.6 g every 12 h on the third day after admission. Subsequently, a bone marrow puncture and culture were performed. Concurrently, other laboratory findings revealed elevated levels of procalcitonin (2.61 ng/mL), ferritin (>4000 ng/mL), solute interleukin-2 (IL-2) receptor (2991 U/mL), and glactomannan test result showed an elevation of 309 pg/mL. Considering the patient had microcytic hypochromic anemia , Thalassemia gene screening was done and the results showed heterozygosity for -α3.7 gene deletion (-α3.7 / $\alpha\alpha$). The result of Hepatitis B surface antigen test was negative, while the initial screening test for HIV showed a positive outcome. Subsequent diagnosis also confirmed the presence of HIV with a viral load of 5.32×10^5 IU/mL. T cell subsets analysis revealed CD4 cells count at 16/μl, and CD4 / CD8 ratio of 0.05. The results of blood culture and bone marrow examination were successively obtained 6 days after admission. The bone marrow morphology revealed the following: (1) presence of microorganisms in smears (Fig. 1); (2) increased number of megakaryocytes with poor plate production function; (3) small amount of hemophagocytic cells observed (Figure B); and (4) fungal nature similar to *T. marneffei* shown in bone marrow samples (Figure C, D), while filamentous fungi with biphasic bacterial characteristics at 25 °C and 37 °C were detected in blood cultures (Figure E, F). Consequently, the antibiotics were switched to a daily dose of 40 mg amphotericin B (initial dosage 5 mg) intravenous drip. Meanwhile, given the evident indicators such as cytopenia, hypertriglyceridemia, elevated ferritin and IL-2 receptor levels, splenomegaly, the patient was diagnosed with hyperinflammatory syndrome, and dexamethasone was promptly administered at a daily dose of 15 mg. Three days later, the patient's body temperature returned to normal (< 37.2 ℃) . After 10 days, there was a rebound in platelet count. However, abnormal renal function and electrolyte disturbance manifested with creatinine level at 98umol/L and potassium level at 2.41 mmol/L. Thus, the patient was commenced on oral itraconazole at a dosage of 200 mg every 12 h until discharge. The final diagnoses were: 1. Disseminated Talaromyces marneffei; 2. Hemophagocytic syndrome; 3. AIDS; 4. *Alpha*-thalassemia. Subsequently, the patient underwent follow-up care at the department of infectious diseases and received a three-month course of itraconazole capsules along with continuous anti-HIV virus therapy with Elvitegravir 1 tablet per day orally (a compound mixture, which including Elvitegravir 150 mg, Cobicistat 150 mg, Emtricitabine 200 mg and Tenofovir Alafenamide Fumarate 10 mg per tablet). The patient presently remains in a state of sustained remission.

Discussion

Thalassemia is a hereditary disorder characterized by the production of an unbalanced globin chain, which results in ineffective erythropoiesis, increased hemolysis, and deranged iron homoeostasis [3]. The –α3.7 deletion represents the most common mutation in *Alpha*-thalassemia, causing clinically significant microcytosis and mild anemia [10]. Considering the presence of small cell hypochromic anemia and the patient's origin from the Guangxi province, a region with a high prevalence of thalassemia, genetic analysis was performed. The result revealed -α3.7 gene deletion heterozygous, which may be related to the initial mild anemia, but subsequent significant reduction in hemoglobin levels should consider other causes (HLH).

T. marneffei is an opportunistic pathogen that primarily affects individuals with compromised immune states, and can cause systemic fungal diseases. In China, approximately 99% of *T. marneffei* infections have been reported in southern regions, with Guangxi accounting for 43% and Guangdong Province accounting for 41%. Among these, 88% were discovered in the HIV/AIDS population [1]. A previous study demonstrated that infection with *T. marneffei* increased the in-hospital mortality risk by 1.8–4.5 times among HIV/AIDS patients [11], highlighting its clinical significance. The manifestations of TSM are diverse and atypical and include fever, weight loss, fatigue, hepatosplenomegaly, lymphadenopathy, and respiratory and

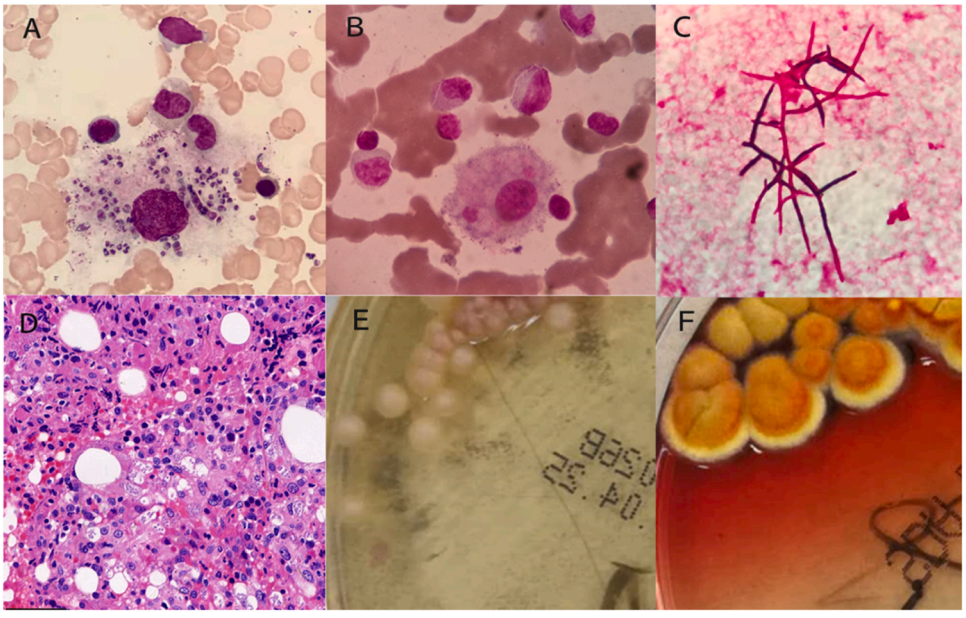

Fig. 1. Macrophages phagocytized fungal spores; Figure B: hemophagocytic cells; Figure C: filamentous fungi; Figure D: HE staining, many pink fungal spores in the middle of bone marrow stroma; Figure E: white yeast-like colonies grown at 37 °C; Figure F: red filamentous colonies at 25 °C.

gastrointestinal abnormalities [2]. Patients with HIV are more prone to disseminate TSM, affecting multiple organs, including the lymph nodes, liver, skin, and spleen, resulting in poor prognosis and higher mortality rates [12]. The patient in our case was positive for HIV infection and had low CD4 T lymphocyte counts. Thus, the patient acquired *T. marneffei* infection while being immunocompromised.

The isolation of *T. marneffei* through tissue or body fluid culture remains the gold standard for diagnosis, characterized by dimorphic fungi that grow as mycelium at 25 °C and yeast at 37 °C [12]. However, owing to the low positive rates in the early infection stages and prolonged culture times, metagenomic next-generation sequencing (NGS) may be a viable option for clinical practice [13]. In the present case, the patient declined NGS because of financial constraints. Nevertheless, *T. marneffei* was isolated from both the venous blood and bone marrow.

Anti-fungal treatments are essential and commonly used against *T. marneffei*, including amphotericin B (AmB) and azoles [14]. An open-label trial showed that compared to itraconazole, AmB had a superior effect in HIV-infected patients with *T. marneffei* concerning clinical response and fungicidal activity, albeit with a higher risk of side effects such as infusion-related reactions, renal failure, and electrolyte abnormalities [15]. In our case, the patient was intravenously injected AmB at a dose of 0.6 mg/kg/day as initial treatment, but he had a slightly elevated creatinine level (98umol/L) and severe hypokalemia (2.41 mmol/L) during treatment, thus he switched to oral itraconazole at a dose of 200 mg q12h until discharge.

The 3-year progression-free survival (PFS) rate and overall survival (OS) rates were 69.1% and 71.2% in patients co-infected with HIV and *T. marneffei* , respectively. Prognosis may be associated with prothrombin time and combination anti-fungal therapy with AMB and triazoles [16]. Among HIV patients with bloodstream infection caused by *T. marneffei*, those with CD8 count $< 200/\mu l$ had a 12.6-fold increased risk of poor prognosis, while those with whole blood BDG < 100 pg/mL had a 34.9-fold increased risk [17].

Hemophagocytic lymphohistiocytosis(HLH), characterized by hyperinflammatory syndrome due to excessive activation of cytotoxic T-lymphocytes, natural killer T-cells, and macrophages followed by cytokine storm and multiorgan injury [5], is a rare, rapidly progressive disease that can be classified as genetic (primary HLH) or acquired (secondary HLH). Infection and malignancy are the primary precipitating factors for secondary HLH. Infection-associated HLH commonly arises from viral infections such as the Epstein-Barr virus, but bacterial, fungal, or parasitic infections have also been identified in some cases [6]. The main infectious triggers of HLH in HIV/AIDS patients were bacteria (34%), cytomegalovirus (14%), and Cryptococcus neoformans (11%) [18]. As reported previously, HLH secondary to TSM is exceptionally rare. One case reported a child with recurrent fever, and lymphadenopathy was diagnosed as HLH secondary to *T. marneffei* infection; whole-exome sequencing revealed complex mutations associated with immunodeficiency [7]. Two other cases of HLH secondary to *T. marneffei* infection were HIV infection [8,9]. Therefore, awareness should be given to potential TSM in immunosuppressed crowds, regardless of HIV infection, to avoid fatal complications, such as HLH. HIV, in and of itself, can be a possible cause of HLH. But the patient's low CD4 cells count and CD4 / CD8 ratio indicated that he had been infected with HIV for a period of time and immune system had been suppressed, which led to susceptibility to other infection. But this time of hospitalization was an acute onset, manifested as fever and splenomegaly. Besides, both of blood culture and bone marrow culture suggested *T. marneffei* infection. During hospitalization, progressive cytopenia occurred. Therefore, we consider that the long-term immunosuppressive state caused by AIDS made him easily infected with *T. marneffei*, and the acute onset infection led to an inflammatory storm of HLH. After the treatment of anti-fungal drugs and glucocorticoid, the patient 's symptoms were controlled and the blood cells were improved, which also confirmed the speculation.

The main symptoms of HLH include persistent fever, hepatosplenomegaly, abnormal laboratory findings such as pancytopenia, hepatic dysfunction, elevated levels of ferritin, triglycerides, LDH, and soluble IL-2 receptor α-chain, as well as decreased fibrinogen levels [4]. However, these typical symptoms, such as fever, cytopenia, and splenomegaly, lack specificity and can easily lead clinicians to overlook HLH when masked by other conditions, such as T-cell large granular lymphocyte leukemia or HIV/AIDS. Therefore, it is crucial to raise awareness about this comorbidity. Clinicians should be aware of the possibility of HLH when patients present with rapid-onset pancytopenia, particularly acute platelet decline, significant increases in serum ferritin and soluble IL-2 receptor levels, low NK cell activity, and the presence of hemophagocytic cells in the bone marrow [19,20].

There are two widely accepted diagnostic methods for HLH: the HLH-2004 criteria and the HLH probability calculator (HScore) [21]. The former is mainly based on data applicable to clinicians, requiring either a molecular diagnosis consistent with HLH or fulfillment of at least five of the following eight criteria: 1. Fever$\geq$ 38.3 ℃; 2. Splenomegaly; 3. Cytopenia (affecting at least two of the three lineages in the peripheral blood: Hemoglobin < 9 g/dL, Platelets < 100 $\times 10^3$/ul, Neutrophils < 1000/uL; 4. Hypertriglyceridemia ($\geq$265 mg/dL) and/or hypofibrinogenemia ($\leq$150 mg/dL); 5. hemophagocytosis in the bone marrow, spleen, lymph nodes, or liver, and 6. Low or absent NK cell activity, and 7. Ferritin $\geq$ 500 ng/mL; 8. soluble IL-2 receptor $\geq$ 2400 U/mL. Conversely, the latter method involves a web-based online calculator known as HScore with a cutoff value of 169 that incorporates nine criteria assigned different numerical values: presence of immunosuppression, fever, organomegaly, elevated triglyceride levels, ferritin levels, aspartate aminotransferase/serum glutamic oxaloacetic transaminase levels, fibrinogen levels cytopenias presence, and hemophagocytosis observed in bone marrow samples[22]. In our case, the patient's presentation aligned with seven out of eight standards outlined in the HLH-2004 criteria, except for low or absent NK cell activity, which we were unable to assess because of current limitations.

To suppress the overactive cytokine storm in HLH, the recognized treatment methods primarily utilize epipodophyllotoxin derivatives (etoposide and teniposide) and steroids [4,5]. In infection-triggered HLH, immediate antimicrobial therapy is crucial, because specific antimicrobial agents alone can sometimes effectively treat this condition [23]. In the present case, dexamethasone was administered to suppress suspected excessive inflammation. Upon TSM diagnosis, antibiotics were promptly adjusted to Amb. Furthermore, if a male patient presents with an activated partial thromboplastin time greater than 36 s, LDH greater than 1000 U/L, and CRP greater than 100 mg/L, this combination is consistently associated with a poor prognosis for HLH [24]. Our patient has been undergoing follow-up at the outpatient department for infectious diseases for three years post-discharge, and currently, their condition remains effectively controlled without any signs of recurrence.

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Author statement

Wu qingqing (First author) participated in conceptualization, methodology, investigation, writing - original draft. Yu Yixiu, Feng Shenhong, Fang Bingqian, Zheng Renzhi and Sun Weidong were all involved in the care and data curation. Zhao jianzhi (corresponding author) was responsible for conceptualization, writing, review, and editing.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the

written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical approval

Approved.

CRediT authorship contribution statement

Sun Weidong: Data curation. **Zheng Renzhi:** Data curation. **Fang Bingqian:** Data curation. **Feng Shenhong:** Data curation. **Yu Yixiu:** Data curation. **Wu Qingqing:** Conceptualization, Methodology, Writing – original draft, Investigation. **Jianzhi Zhao:** Conceptualization, Data curation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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