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Talaromyces Marneffei Infection Inducing Hemophagocytic Syndrome in an HIV-negative Adult Patient

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Abstract

Background: *Talaromyces Marneffei* (TM) infection is commonly seen in HIV-positive or immunocompromised patients but rarely reported in HIV-negative individuals. Hemophagocytic syndrome is one of a group of syndromes characterized by overactivity of immune cells resulting in the production of excessive inflammatory factors and causing damage to multiple organs.

Case presentation: This case report presents a previously healthy 52-year-old male patient who experienced persistent fever and chills for over 20 days. Initial blood tests revealed decreased hemoglobin and platelets, and increased proportion of neutrophils. Laboratory examinations showed elevated levels of procalcitonin, C-reactive protein, erythrocyte sedimentation rate, ferritin, along with abnormalities in liver function. Imaging studies indicated hepatosplenomegaly. Tests for common infectious diseases, autoimmune liver diseases, and blood cultures all yielded negative. A bone marrow aspiration smear revealed a suspected TM fungus, which was later confirmed through culture and sequencing. However, the patient's condition rapidly deteriorated, with the presence of histiocytes and hemophagocytes, along with severe liver damage and coagulation disorders, progressing to hemophagocytic syndrome with a poor prognosis.

Conclusion: The nonspecific symptoms of TM infection in HIV-negative patients can lead to misdiagnosis and delayed treatment. Therefore, it is crucial for clinicians to promptly recognize TM infection in HIV-negative individuals and initiate early antifungal treatment to prevent the progression of diseases with poor prognosis.

Keywords: *Talaromyces marneffei* • HIV-negative • Hemophagocytic syndrome • Infection

Introduction

Talaromyces Marneffei (TM), previously known as Penicillium marneffei, is a fungal pathogen predominantly found in tropical Asian countries such as Thailand, northeastern India, China, and Vietnam [1,2]. TM infections were previously seen mostly in HIV-positive individuals, but there has been an increase in cases among non-HIV-infected populations [3,4]. TM can cause disseminated fungal disease, spreading to various organs and leading to life-threatening complications like septic shock, Disseminated Intravascular Coagulation (DIC), and Hemophagocytic Syndrome (HPS) [5-7]. HPS is characterized by excessive inflammation due to the overproduction of inflammatory factors by lymphocytes and histiocytes. It can be categorized into two forms: primary and secondary. Primary HPS refers to HPS caused by genetic factors, typically occurring in infants or children [8]. Secondary HPS, which is the main form in adults, is caused by various diseases or conditions, including infections, tumors, immunodeficiency, and autoimmune diseases [9]. Infection-related HPS is the most common form of secondary HPS, and viral infection is the most common trigger [9,10]. There are few reports of HPS caused by fungal infections, with the most common fungal pathogen being Histoplasma [11]. Nevertheless, secondary HPS caused by fungi, particularly TM infection in HIV-negative adults, has been rarely documented. In this report, we will analyze the clinical data of an HIV-negative patient who infected TM and developed into HPS, and discuss its diagnostic ideas and treatment options.

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Case Presentation

A 52-year-old male was admitted to our hospital on May 16, 2022, with a history of prolonged fever and chills. He had a persistent fever for over 20 days, with the highest temperature exceeding 40 °C, accompanied with cough, nausea, abdominal distension and headache. The Computed Tomography (CT) scan at a local hospital revealed mediastinal hilar lymph node enlargement, multiple lung nodules, right pleural thickening and hepatosplenomegaly with possible splenic infarction. Despite symptomatic supportive treatment, the patient's symptoms did not improve, to our hospital for further management. Prior to this, no hepatitis or tuberculosis was reported. He was a former smoker (20 years, 20 cigarettes per day) but quit two years ago. He occasional alcohol consumption. There was no reported exposure to chemical or radioactive materials. He was born and resides in Tongliang District, Chongqing, China.

In the physical examination, the patient had clear consciousness. Vital signs showed a body temperature of 38.8 °C, heart rate of 128 beats per minute, and respiration rate of 23 breaths per minute. The heart rhythm was regular with no murmurs detected. Coarse breath sounds were present in both lungs, while no rales were heard. Enlarged superficial lymph nodes were observed. No signs of jaundice or skin damage were found.

The laboratory examinations conducted after admission showed a normal leukocyte count with an elevated neutrophil percentage of 86.5% and decreased lymphocyte percentage of 6.7%. The Hemoglobin (Hb) level was 109 g/L, and the Platelet (PLT) count was significantly low at 78 × 109/L. The

peripheral blood smears revealed normal leukocyte count with predominant neutrophils and rod-shaped granulocytes, along with observed abnormalities like empty guns and poisoning granules in the white blood cell cytoplasm. Erythrocyte count and morphology were normal, but platelet count was decreased without agglutination observed (Figure 1).

Liver function tests showed significant abnormalities, including elevated levels of alanine aminotransferase (ALT, 151 U/L, reference range 9-50 U/L), aspartate aminotransferase (AST, 175 U/L, 15-40 U/L), alkaline phosphatase (ALP, 375 U/L,45-125 U/L), and γ-glutamyl transpeptidase (γ-GGT, 372 U/L, 10-60 U/L), direct bilirubin (14.1 umol/L, 0-8.0 umol/L), total bile acid (57.4 umol/L, 0.0-15.0 umol/L). Total protein (51.0 g/L, 65.0-85.0 g/L), plasma albumin (22.4 g/L, 40.0-55.0 g/L), and prealbumin levels (84 mg/L, 200-430 mg/L) were lower than the reference ranges, indicating impaired liver function. Kidney function tests and myocardial injury enzyme profile were normal. Coagulation tests, except for an elevated D-dimer level (1.604 mg/L,0-0.55 mg/L), were generally within normal ranges. The plasma Procalcitonin (PCT) was 3.82 ng/mL (<0.02 ng/mL), C-Reactive Protein (CRP) was 65.21mg/L (0.5-10 mg/L), and Erythrocyte Sedimentation Rate (ESR) was 23.0 mm/h (0.0-15 mm/h). Additionally, the serum ferritin was found to be above 1650 ng/mL (22-322 ng/mL). All tests for HIV, infectious markers, tuberculosis, autoimmune liver disease antibodies, respiratory pathogens, and Plasmodium were negative. Venous blood cultures showed no bacterial or fungal growth.

Abdominal ultrasound revealed hepatosplenomegaly with uneven echogenicity and a small amount of fluid in the thoracic cavity (Figures 2A and 2B). Chest and abdomen CT scan showed scattered fuzzy shadows in both lungs with interlobular septal thickening, bilateral pleural effusion, enlarged liver with decreased parenchymal density, enlarged spleen with small lamellar density shadows, multiple lymph node enlargements, and scattered abdominal effusions (Figures 3A-3C). Color Doppler ultrasound of lower extremity veins and the heart showed no significant abnormalities.

After being admitted to the hospital for 2 days, the patient's fever and abnormal liver function did not show any improvement. Therefore, a bone marrow aspiration was performed on the patient. The results showed no obvious abnormalities in the proliferation and proportion of each cell line in the bone marrow (Figures 4A and 4B), but the number of platelet was significantly reduced. Excitingly, fungi with a morphology similar to TM were easily found on the bone marrow smear (Figures 4C and 4D). Subsequently, a bone marrow culture was performed on May 20, 2022. After 3 days, the culture and isolate were identified as TM based on the pathogen's temperature-dependent dimorphic growth pattern, production of a soluble red pigment, and the presence of long blue hyphae with branching and septation, as well as distinctive brush-like claddings on their surface in cotton blue staining (Figures 5A-5C). Additionally, Sanger sequencing of the isolate definitively confirmed it as TM. Furthermore, the antigen test for TM was also positive. Based on the above test results, it was clear that the patient was infected with TM. Meanwhile, a second bone marrow smear was conducted on 20 May 2022, and similar results were obtained as the first one. Additionally, histiocytes and hemophagocytic cells were easily observed (Figure 4E and 4F). Combined with the patient's radiological findings, there was a strong suspicion that the patient had HPS. However, the available laboratory data was insufficient to support the diagnosis.

Since admission, the patient's peripheral blood counts, biochemical, and coagulation indices were continuously monitored. The Hb levels decreased to 85 g/L on May 26th. The PLT count decreased from 78 × 109/L to 11 × 109/L on May 25th. The white blood cell count fluctuated between 2 × 109/L and 6 × 109/L (supplementary Figure 1A). Coagulation parameters showed decreased fibrinogen levels of 1.48 g/L on May 22nd and increased Activated Partial Thromboplastin Time (APTT), Prothrombin Time (PT) and D-dimer (supplementary Figure 1B). Total bilirubin levels remained elevated. AST peaked at 435 U/L before May 22nd and gradually decreased. Other liver function enzyme markers (ALT, ALP, γ-GGT) showed a continuous decrease. Evidence of enzyme-bile separation indicating severe liver damage was observed after May 26th (supplementary Figure 1C). Considering the patient's fever, hepatosplenomegaly, the presence of hemophagocytosis on bone marrow examination, and the laboratory test results, referring to the diagnostic criteria for secondary HPS in pediatrics, the patient was diagnosed with secondary HPS.

In order to further understand the patient's immune status, the patient's

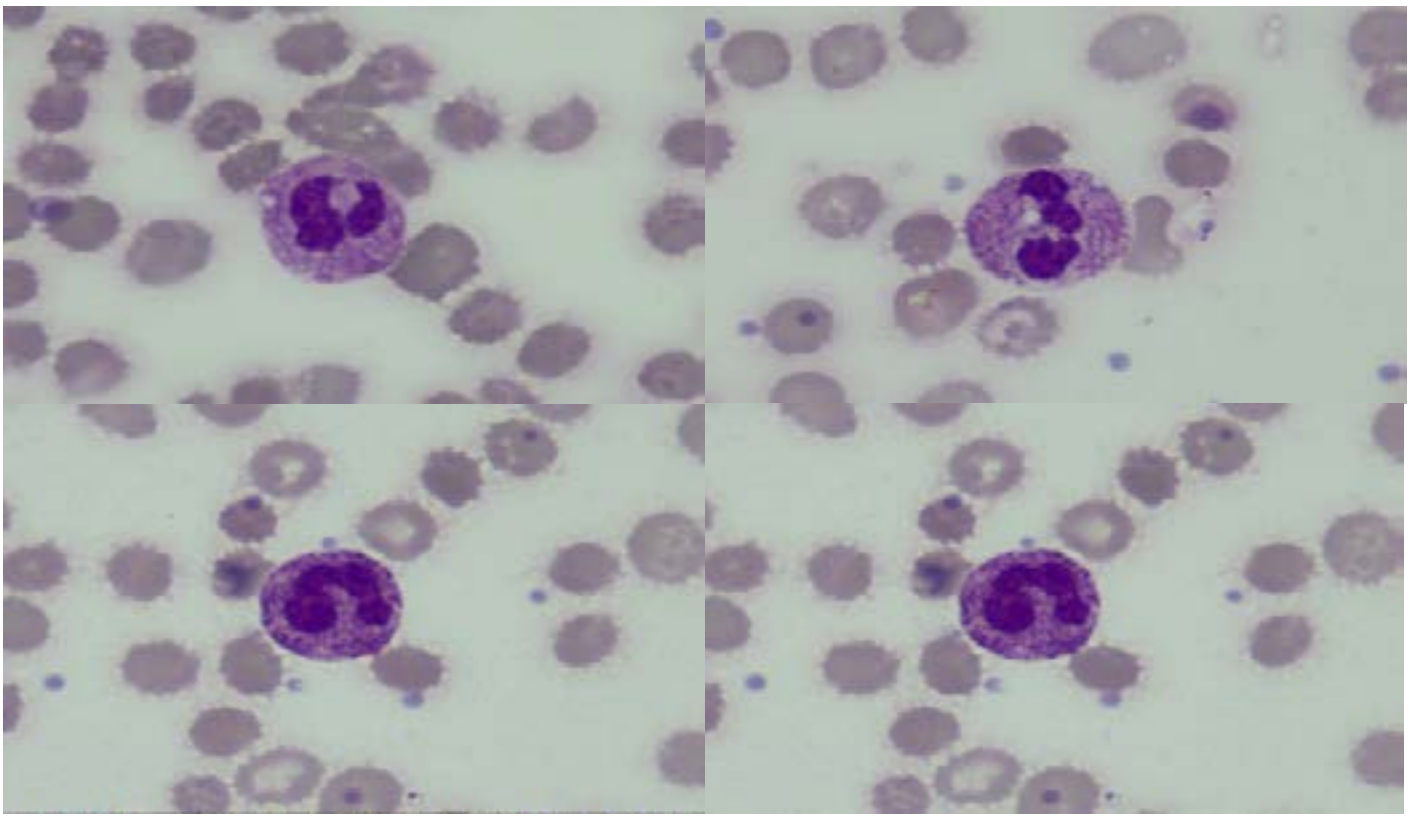

Figure 1. The Swiss giemsa-stained peripheral blood smear (100X, 16 May 2022). A small number of vacuoles and a large number of toxic granules were observed within mature neutrophils.

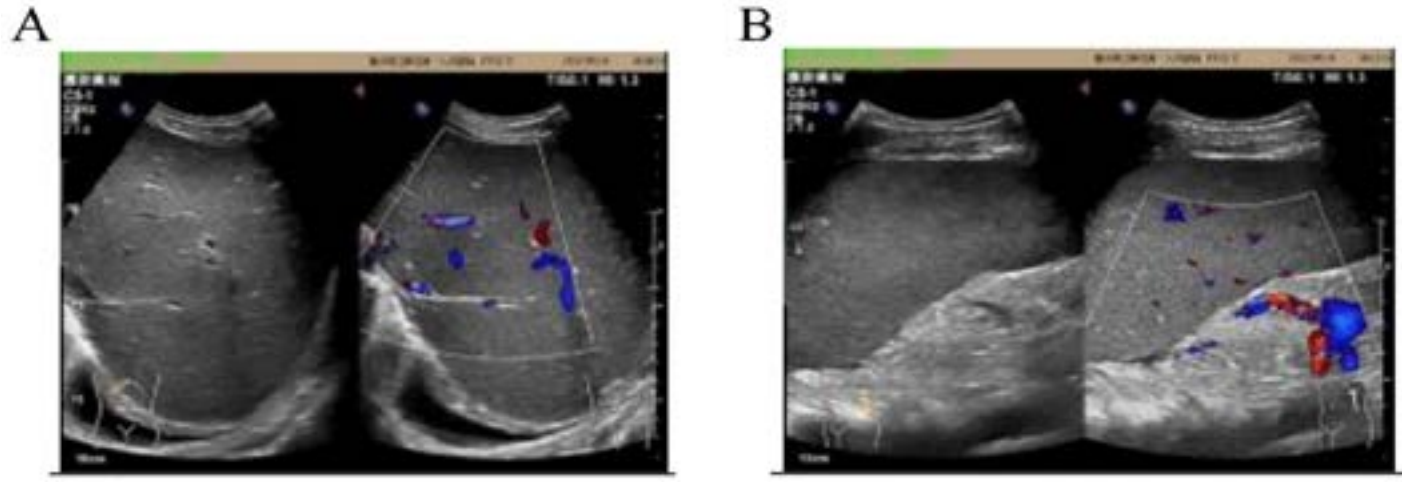

Figure 2. The abdominal Doppler ultrasound examination presentations on 18 May 2022 revealed enlargement of the liver and spleen, and a small amount of fluid accumulation in the thoracic cavity. **A)** Hepatomegaly was present, with the maximum oblique diameter of the right lobe of the liver measuring 150 mm, and the liver parenchyma showing dense and uneven echogenicity and **B)** Splenomegaly was present, with a longitudinal diameter of 142 mm and a thickness diameter of 47 mm, and the spleen showing uneven echogenicity.

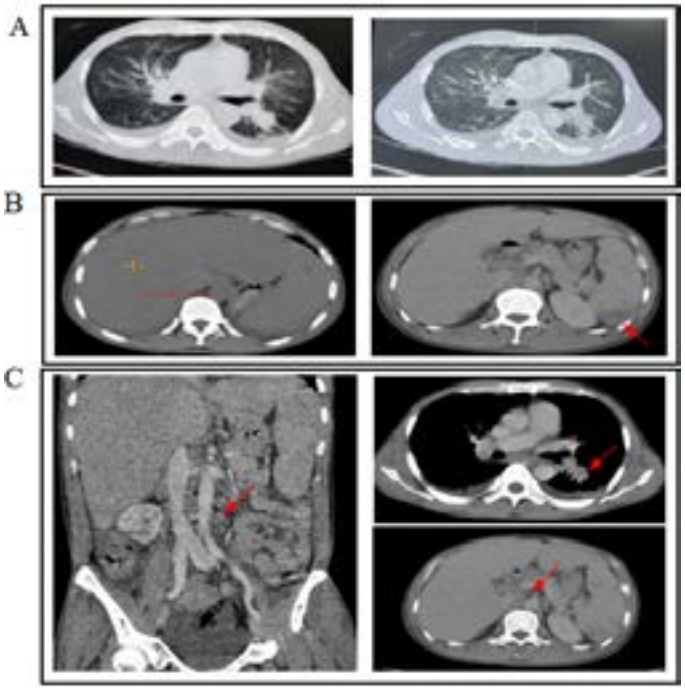

Figure 3. The chest and abdomen Computed Tomography (CT) presentations on 22 May, 2022. **A)** Multiple scattered opacities were visible in both lungs. **B)** The liver and spleen were enlarged, and splenic infarction was visible on the right side image and **C)** In the left-side image, multiple enlarged retroperitoneal lymph nodes were visible. In the upper-right and lower-right images, lymphadenopathy was observed in the pulmonary hilum and hepatic hilum regions, respectively.

lymphocyte subsets were analyzed on May 23, 2022. The results indicated suppressed immune function with decreased total lymphocyte count (CD45+, 511 cells/μl, 1530-3700 cells/μl), T-lymphocytes (CD3+, 432 cells/μl, 955-2860 cells/μl), suppressor T cells (CD8+, 133 cells/μl, 320-1250 cells/μl), helper T-lymphocytes (CD4+, 285 cells/μl, 550-1440 cells/μl), natural killer cells (NK, 14 cells/μl, 150-1100 cells/μl), and B-lymphocytes (CD19+, 63 cells/μl, 90-560 cells/μl). The patient's immune status was significantly impaired. Since HPS is characterized by aberrant hyperinflammation and associated with a potentially fatal cytokine storm [12, 13], the patient's cytokine levels were also evaluated. The results showed elevated concentrations of proinflammatory cytokines in the serum, which TNF-α was 513 pg/ml (≤ 8.1 pg/ml) and IL-6 was 50.34 pg/ml (≤ 5.3 pg/ml). Simultaneously, the level of the anti-inflammatory cytokine IL-10 was 33.72 pg/ml (≤ 4.91 pg/ml). Other cytokines such as IL-2, IL-4, and IFN-γ were within the reference range.

One week after admission, evidence of TM infection became apparent in the patient, and antifungal therapy with amphotericin B was initiated. Due to the development of hemophagocytic syndrome, chemotherapy was administered. Although the patient's temperature gradually returned to normal (supplementary Figure 1D), the patient's condition had progressed rapidly, with severe suppression of bone marrow hematopoietic function, severe liver function damage, and splenic infarction were observed, suggesting a poor prognosis for the patient. Unfortunately, the patient was discharged from the hospital after two weeks of admission due to financial factors, was unable to continue antifungal and chemotherapy treatment (Figure 6).

Results and Discussion

In 1956, TM was first discovered in bamboo rats in Vietnam [14]. Bamboo rats serve as the natural hosts of TM, and the transmission of this pathogen occurs from rats to rats and from rats to humans [15]. When TM enters the body, it primarily invades the monocyte-macrophage reticuloendothelial system [15,16]. Based on the sites of involvement, TM infections can be classified as localized and disseminated. Localized infections are typically limited to the lungs, skin, or lymph nodes, which are the initial sites of pathogen invasion. Blood or bone marrow cultures are usually negative in these cases [17,18]. Disseminated infections occur when TM spreads to mutiple organs in the human body through lymphatic fluid and blood circulation, leading to lesions and injuries in the skin, brain, bone marrow, internal organs, and other parts.

The main clinical manifestations of TM infection are fever, enlarged lymph nodes, anemia and hepatosplenomegaly, lung infection, weight loss and other non-specific symptoms [15]. Fever and cough are commonly experienced by most TM infection patients, with high fever being the most frequent type of fever [19]. Imaging examinations reveal nonspecific changes in the chest, such as lung consolidation, cavitation, and pleural effusion. Additionally, anemia, hepatosplenomegaly, skin lesions, and swollen lymph nodes may also be present. Following TM infection, laboratory findings show decreased hemoglobin levels and increased inflammatory markers. Liver enzyme levels may also be altered in cases where the liver is affected [20]. Furthermore, several studies have demonstrated a reduction in lymphocyte count [17,21]. Due to the lack of specific laboratory markers and imaging changes, TM infection is often misdiagnosed as other diseases such as tuberculosis, bacterial pneumonia, and lung cancer [4,17]. Consequently, delayed diagnosis leads to a delay in initiating treatment, and previous research has shown that delayed diagnosis is associated with increased mortality rates [22]. TM is the only temperature-diphasic fungus among fungi, exhibiting a mycelial form at 25 °C and a yeast form at 37 °C, combined with the morphological feature of sausage-shaped spores. Therefore, the diagnosis of TM still relies on fungal culture, which is considered the "gold standard" diagnostic method. Given the prolonged duration associated with culture-based methods, alternative

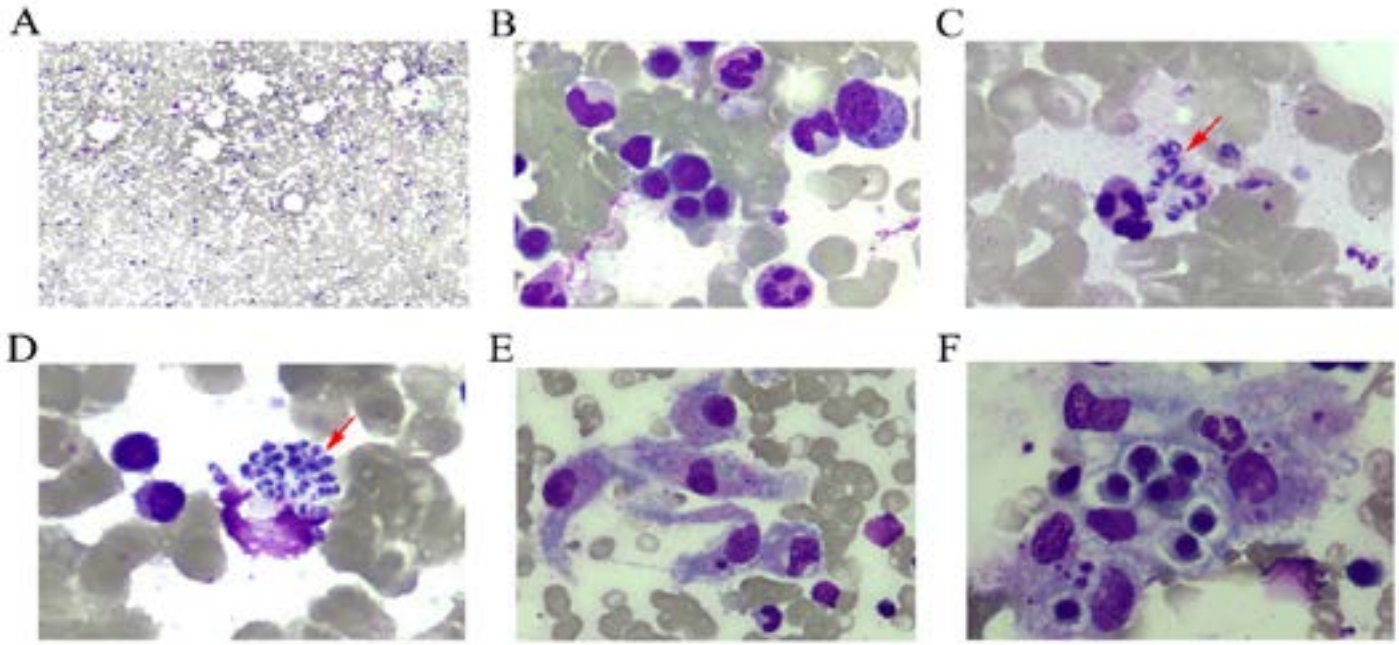

Figure 4. The swiss giemsa-stained bone marrow smear (A-D from 18 May 2022, E and F from 20 May 2022). **A)** A low magnification view (10X) of the bone marrow smear revealed active bone marrow proliferation, **B)** Bone marrow smear in oil microscopic view (100X) showed active cell proliferation of all lineages with approximately normal morphology and proportions, **C and D)** A large number of elliptic and sausage-shaped spores with a morphology consistent with Talaromyces marneffei were observed, **E)** Activated histiocytes were easily seen in bone marrow smears, with cytosol varying in size, elongated oval, incomplete cytomembranes, oval nuclei, coarse reticulated nuclear chromatin, abundant cytoplasm, pale blue in colour, containing small amounts of purplish-red granules and small amounts of phagocytosed cellular debris and **F)** Hemophagocytes with phagocytosis of immature erythrocytes, neutrophilic rod-nucleated granulocytes, and platelets were seen in the cytoplasm.

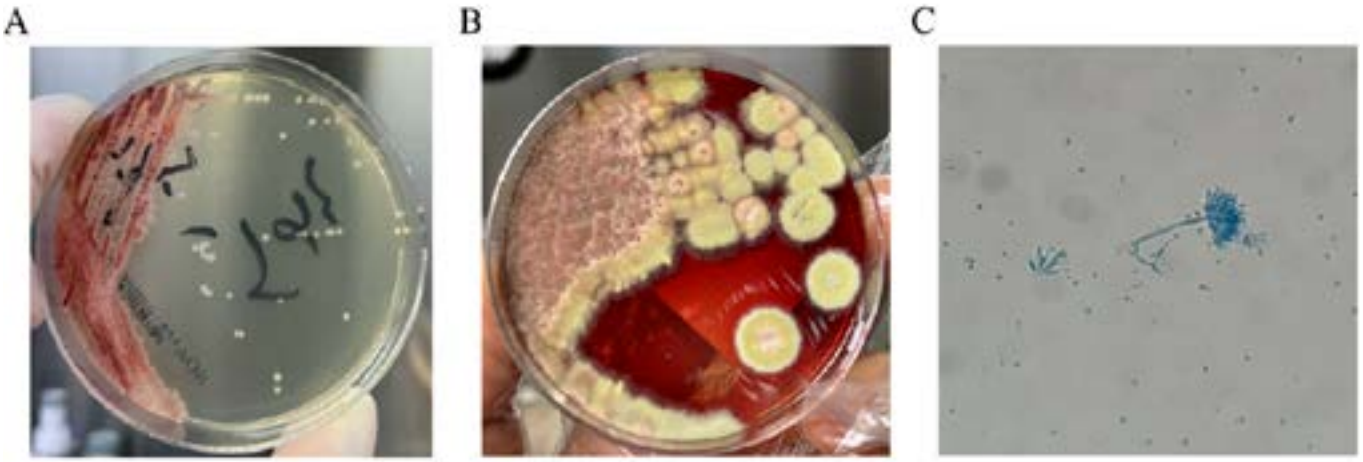

Figure 5. Bone marrow culture confirmed the infection of Talaromyces marneffei. A and B) Bone marrow culture-positive samples were incubated in SDA medium at 37 °C and 25 °C, respectively. **A)** After incubating at 37 °C for 3 days, smooth, pale red, and gray colonies were observed on the surface, **B)** After incubating at 25 °C for 6 days, yielding white, fluffy colonies, which produced red pigment that diffused throughout the entire culture medium and **C)** After staining the bone marrow culture isolate with lactophenol cotton blue at 25 °C, the morphology of branching septate hyphae and typical brush-like claddings could be observed (40X). (SDA, Sabouraud Dextrose Agar).

approaches such as microscopic examination of tissue or secretion smears to identify characteristic TM features, along with the utilization of immunological, molecular biological, and sequencing techniques could contribute to the early diagnosis of the disease [23,24]. However, compared to HIV-positive patients, HIV-negative patients have a longer interval from symptom onset to diagnosis, more severe manifestations, and higher mortality rates [25]. Moreover, the symptoms of TM infection are not typical, and the lack of awareness regarding this condition can contribute to a higher rate of misdiagnoses [26].

HPS are critical conditions characterized by excessive activation of cytotoxic T lymphocytes, NK cells, and macrophages, leading to the development of hypercytokinemia and immune-mediated damage to multiple organ systems [27]. Fever, organomegaly (such as lymphadenopathy, hepatomegaly, and splenomegaly), liver injury, consumptive coagulopathy, hypertriglyceridemia, cytopenias, neurologic dysfunction, dermatologic abnormalities, and elevated acute phase reactants (particularly serum ferritin) of significant magnitude are among the possible manifestations, findings, and signs associated with HPS [28]. As previously mentioned, secondary HPS primarily affects adults who lack an underlying predisposing defect and is commonly triggered by infections, malignancies, and autoimmune diseases [29]. Currently, adult cases account for approximately 40% of HPS cases [9]. It has been suggested that HPS may occur in up to 1 out of every 2,000 adult admissions at tertiary medical centers [30]. Adult HPS progresses rapidly and has a poor prognosis, with a high mortality rate [31]. Without timely diagnosis and treatment, it can lead to multi-organ failure and death. However, the clinical manifestations (including symptoms, signs, and laboratory findings) of HPS also lack specificity, posing significant challenges for its clinical diagnosis. Moreover, there is a lack of unified diagnostic and treatment criteria for HPS in adults. Therefore, the current diagnosis of adults HPS still refers to pediatric criteria [32]. In addition to the diagnostic criteria provided by the pediatric HLH-2004 protocol [32], management recommendations for adult HPS

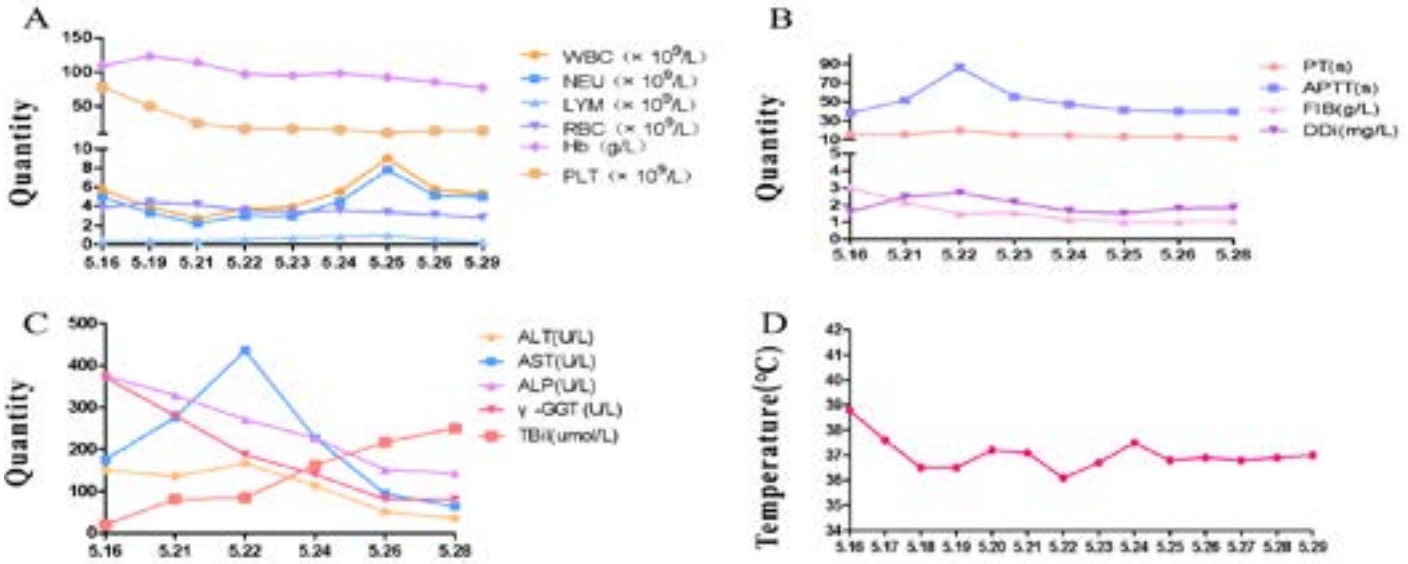

Figure 6. The laboratory parameters and temperature changes during the patient's hospitalization. **A)** The patient's blood cell counts showed fluctuations over the recorded period. Initially, white blood cell count was 5.75 × 10^9/L on May 16th, gradually decreased to 2.75 × 10^9/L on May 21st, then increased to 9.02 × 10^9/L on May 25th, and decreased again to 5.33 on May 28th. Neutrophil and lymphocyte counts followed a similar trend; Red blood cell count increased from 3.83 × 10^9/L on May 16th to 4.43 × 10^9/L on May 19th, then gradually decreased to 2.8 × 10^9/L on May 28th; Hemoglobin levels started at 109 g/l, increased to 123 g/l on May 19th, then decreased to 85 g/l on May 26th, and further dropped to 77 g/l on May 28th; Platelet count decreased from 78 × 10^9/L at admission, reaching a low of 11 × 10^9/L on May 25th, **B)** During the hospitalization period, the coagulation indicators showed the following trends: On May 16th, PT was 15.3s, APTT was 38.5s, FIB was 3.02 g/L, and DDi was 1.604 ng/L. By May 22nd, PT increased to 19.8s, APTT increased to 86.3s, FIB decreased to 1.48g/L, and DDi increased to 2.713 mg/L. From then until May 28th, PT gradually decreased to 11.9s, APTT decreased to 39.7s, FIB decreased to 1.08 g/L, while DDi remained stable at 1.846 ng/L, **C)** During the recorded period, the patient's liver function indicators showed the following trends: On May 16th, ALT was 151 U/L, AST was 175 U/L, ALP was 375 U/L, γ-GGT was 372 U/L, and total bilirubin was 20.7 umol/L; then, by May 28th, ALT, ALP, and γ-GGT gradually decreased to 36 U/L, 143 U/L, and 80 U/L, respectively. However, AST increased to 435 U/L on May 22nd and then gradually decreased to 64. The total bilirubin level increased to 250.6 umol/L on May 28th, and on May 26th, enzyme-bile separation phenomenon was observed and **D)** During the hospitalization period, the patient's temperature showed the following trend: On May 16th, the temperature was 38.9 °C. From May 17th to May 24th, it fluctuated between 36 °C and 38 °C. After May 25th, the temperature remained below 37 °C. (WBC: White Blood Cell; NEU: Neutrophil; LYM: Lymphocyte; RBC: Red Blood Cell; Hb: Hemoglobin; PLT: Platelet; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ALP: Alkaline Phosphatase; γ-GGT: γ-Glutamyl Transpeptidase; TBil: Total Bilirubin; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; FIB: Fibrinogen; TT: Thrombin Time).

suggest that patients should be considered as developing HPS even when PT and fibrinogen levels are normal if they present with hyperbilirubinemia, hepatomegaly, elevated transaminases, increased Lactate Dehydrogenase (LDH), and elevated D-dimer [29]. Moreover, experts have proposed that, in addition to following the HLH-94 protocol for chemotherapy, the treatment of adult HPS should be promptly adjusted based on the patient's triggers, clinical manifestations, and other factors [29].

The patient had a prolonged fever lasting over 20 days, with normal white blood cell count, mild anemia, and moderate thrombocytopenia. Peripheral blood smear showed reduced platelets and leukocyte toxicity. Liver function tests indicated liver damage, and coagulation function tests showed a slight elevation in D-dimer. Elevated levels of PCT, CRP, ESR, and ferritin were observed. Imaging studies revealed lung abnormalities, enlarged lymph nodes, and hepatosplenomegaly. Despite supportive treatment, the patient's condition did not improve. Two days after admission, a bone marrow aspiration revealed TM infection. Treatment with Amphotericin B was initiated, which was identified as an effective antifungal drug against TM [33]. However, a second bone marrow smear showed a proliferation of histiocytes and phagocytes, and the patient's condition rapidly deteriorated to HPS. Chemotherapy with drugs such as etoposide, cyclosporine and dexamethasone were initiated, but the patient's condition remained severe. Literature reports suggest that in adult HPS patients over 50 years of age, a PLT count below 40, high ferritin levels, low albumin levels, and splenomegaly are associated with a poor prognosis [28]. Despite efforts, the patient's family decided to discontinue further treatment due to the severity of the condition.

Conclusion

In conclusion, the clinical and laboratory manifestations of TM infection in HIV-negative patients exhibit atypical features. Early pathogen detection and prompt initiation of antifungal therapy are crucial to prevent the progression to conditions such as HPS with an unfavorable prognosis.

Ethics Statement

Written informed consent was obtained from the patient for publication of this case report and any potentially identifying information. The work was exempt from the ethics committee review/approval.

Availability of Data and Materials

The data used to support this case are included within the article.

Competing Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Not applicable.

Authors' Contributions

Xianping Luo and Yong Luo were responsible for the collection and organization of radiological data. Taimei Duan and Xinlu Bai conducted the cultivation and identification of pathogens. Dongmei Huang, Sitian Tang, and Zhu Mei collected laboratory data. Lunyu Yang and Yuling Yi designed the figures and contributed to the writing of the manuscript. Ling Liu and Liyi Hu discovered the case and provided guidance for the overall conceptualization of the article. All authors revised and approved the final manuscript.

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