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Potential killer in the ICU—severe tuberculosis combined with hemophagocytic syndrome

A case series and literature review

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Abstract

Hemophagocytic syndrome (HPS) is a life-threatening clinical syndrome that has various presentations, shows rapid progression and is associated with a high mortality. Clinical reports about pulmonary tuberculosis combined with respiratory failure accompanied by HPS are rare.

HPS has no special clinical manifestations, and the main presentations include persistent fever, hepatosplenomegaly, hematocytopenia, and rash. In the Intensive Care Unit (ICU), the clinical manifestations of severe infection and secondary HPS overlap, thus there is often a delay in the diagnosis and treatment of HPS.

HPS is not an independent disease but represents an excessive inflammatory response due to immune dysfunction induced by various causes such as infection and tumor.

The 2 cases in this report show that tuberculosis-associated hemophagocytic syndrome is not easy to find, especially in ICU. There are few clinical reports of pulmonary tuberculosis combined with respiratory failure and HPS. Here, we describe 2 such clinical cases and review the relevant literature in order to deepen our understanding of this disease.

Abbreviations: ALT = alanine transaminase, APTT = activated partial thromboplastin time, AST = aspartate transaminase, DBIL = direct bilirubin, FHL = familial hemophagocytic lymphohistiocytosis, FIB = fibrinogen, FiO_2 = fraction of inspired oxygen, HGB = hemoglobin, HLH = hemophagocytic lymphohistiocytosis, HPS = hemophagocytic syndrome, IBIL = indirect bilirubin, INR = international normalized ratio, LDH = lactate dehydrogenase, NEUT% = neutrophil percentage, PCO_2 = partial pressure of carbon dioxide, PLT = platelet count, PO_2 = partial pressure of oxygen, PPD = purified protein derivative, PT = prothrombin time, SO_2 = oxygen saturation, TBIL = total bilirubin, TG = triglycerides, WBC = white blood cells.

Keywords: hemophagocytic syndrome, respiratory failure, tuberculosis

1. Introduction

Hemophagocytic syndrome is a histiocytic disorder characterized by the activation and proliferation of macrophages, leading to uncontrolled phagocytosis of platelets, erythrocytes, and lymphocytes, as well as their hematopoietic precursors throughout the reticuloendothelial system. Hemophagocytic syndrome (HPS) is a life-threatening clinical syndrome that has various presentations, shows rapid progression and is associated with a high mortality. The clinical manifestations of secondary HPS often overlap with those of severe infections encountered in the ICU, thus the diagnosis and treatment of HPS are often delayed. There are few clinical reports of pulmonary tuberculosis combined with respiratory failure and HPS. Here, we describe 2 such clinical cases and review the relevant literature in order to deepen our understanding of this disease.

2. Methods

We provide the detail information of all 2 cases and discuss probability of tuberculosis-associated hemophagocytic syndrome in ICU.

This study was approved by the Fuzhou Pulmonary Hospital of Fujian. Informed consent was obtained from all individual participants included in the study.

2.1. Case 1

The patient was a 20-year-old Chinese man without relevant past medical history presented to the Fuzhou Pulmonary Hospital of Fujian with a 10-day history of chest tightness, cough, and fatigue. During the previous 10 days, he complained of decreasing energy and appetite, as well as paroxysmal cough. He reported the production of a small amount of white sputum without blood and mild dyspnea without night sweat. At the same time, the patient experience fever but without chills, and fever developed with the body temperature reaching 38 °C. His stools were loose and black. After a non-diagnostic outpatient evaluation, he was admitted to hospital for further care.

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LC and HW have contributed equally to this work.

The authors declare that they have no conflict of interest.

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The patient had been physically healthy in the past. He did not use any medications or have any allergies. He denied use of tobacco, alcohol, or illicit substances. He was employed in an office environment, and he had not travelled abroad before the onset of the disease. He had multiple negative tuberculin skin tests in the past, and there was no family history of tuberculosis. His parents were healthy and lived in China.

On physical examination, the patient was extremely cachectic and weight 43.7 kg. The patient was conscious at admission, and physical examination showed his temperature was 36.5 °C, respiratory rate 32 breaths/min, heart rate 108 beats/min, and blood pressure 114/79 mmHg. A small number of rashes were visible on the front of the chest, but there was no itching. The respiratory sounds in the 2 lungs were normal, except that substantial wet rales were heard from the inferior lungs. The heart rate was 108 beats/min, the heart rhythm was regular, and there were no abnormal valve sounds or pericardial friction rub. The right lobe of the liver was not palpable, the spleen was soft, smooth, and palpable at the level of the umbilicus but there was no edema in both lower extremities. There was no cervical, supraclavicular, axillary, or inguinal lymphadenopathy, and genitourinary, and neurological examinations were unremarkable.

Laboratory evaluation revealed the following: total bilirubin (TBIL), 57.3 μmol/L; direct bilirubin (DBIL), 20.55 μmol/L; indirect bilirubin (IBIL), 36.75 μmol/L; alanine transaminase (ALT), 213 U/L; aspartate transaminase (AST), 208 U/L; gamma-glutamyltransferase, 223 U/L; triglycerides (TG), 1.87 mmol/L; blood urea nitrogen, 14.33 mmol/L; lactate dehydrogenase (LDH), 718 U/L; creatine kinase-MB, 656 U/L; and ferritin, 441.25 μg/L. The results of a routine blood test were as follows: white blood cells (WBC), 3.8×10^9/L; neutrophil percentage (NEUT%), 93.4%; platelet count (PLT), 39×10^9/L; and hemoglobin (HGB), 110 g/L. Blood coagulation tests demonstrated the following: prothrombin time (PT), 22.5 second; activated partial thromboplastin time (APTT), 43.8 second; fibrinogen (FIB), 0.71 g/L; international normalized ratio (INR), 1.87; and D-dimer, 1149.4 mg/L. C-reactive protein level was 64.9 mg/L. The results of blood gas analysis (fraction of inspired oxygen [FiO_2]: 45%) were: pH, 7.444; partial pressure of oxygen (PO_2), 85.8 mmHg; partial pressure of carbon dioxide (PCO_2), 28.1 mmol/L; oxygen saturation (SO_2), 96%; and oxygenation index, 190. The tuberculin skin test (purified protein derivative [PPD]-based) was 0 cm × 0 cm. Gram staining of sputum was negative. Sputum-related bacterial and fungal cultures were also negative, as was blood culture. Routine urine tests and urine bacterial and fungal cultures were all negative. A routine stool test was positive for fecal occult blood. Investigations for Epstein-Barr virus antibodies, cytomegalovirus antibodies, HIV, and hepatitis B virus markers (HBsAg, HBSAb, HBeAg, HBeAb, and HBcAb) were all negative. Thoracic and abdominal computed tomography (CT; Fig. 1A and B) demonstrated patchy, nodular and spot-like high-density masses and ground glass opacities with blurred margins in both lungs, an uneven density in the lungs and a large spleen. The CURB-65 score for pneumonia severity was 2 points.

The diagnosis at admission was severe pneumonia combined with acute respiratory distress syndrome. Since there was no positive evidence of a particular infection in sputum-related examinations, empiric anti-microbial therapy with cefepime and moxifloxacin was initiated, methylprednisolone was administered to suppress inflammation, and inhaled oxygen was provided. After 10 days of the above treatment, the patient's hospital course was notable for intermittent fevers to as high as 39.2 °C, worsening pancytopenia, and the dyspnea had not notably improved. Meanwhile, the patient had developed hematemesis, and a large amount of dark-red fluid was observed in the gastric tube. The results of repeat routine blood tests and blood coagulation tests were as follows: WBC, 4.5×10^9/L; NEUT%, 91.1%; PLT, 23×10^9/L; HGB, 98 g/L; PT, 19.9 seconds; APTT, 71.6 seconds; and FIB, 0.5 g/L. At this stage, bone marrow puncture and biopsy were performed. These investigations indicated the presence of chronic granulomatous lesions, which were considered to be tuberculosis (Fig. 2). There was no immunophenotypic evidence of a lymphoproliferative disease by visual or flow cytometric analysis; no monoclonal component was identified. Given the constellation of fever, pancytopenia, and hyperferritinaemia in the presence of hemophagocytosis within the bone marrow, a diagnosis of tuberculosis combined with hemophagocytic syndrome was

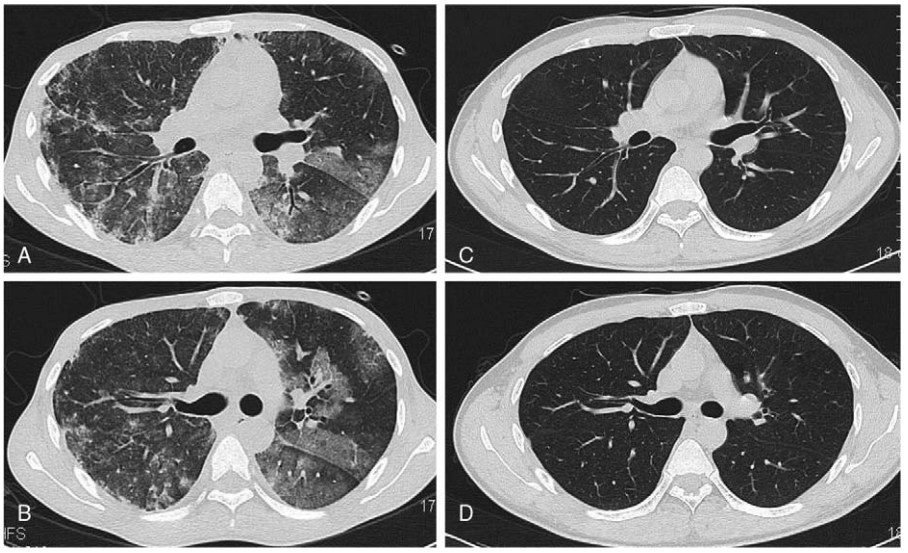

Figure 1. Comparison of chest CT scans for case 1 before and after treatment. CT indicates computed tomography.

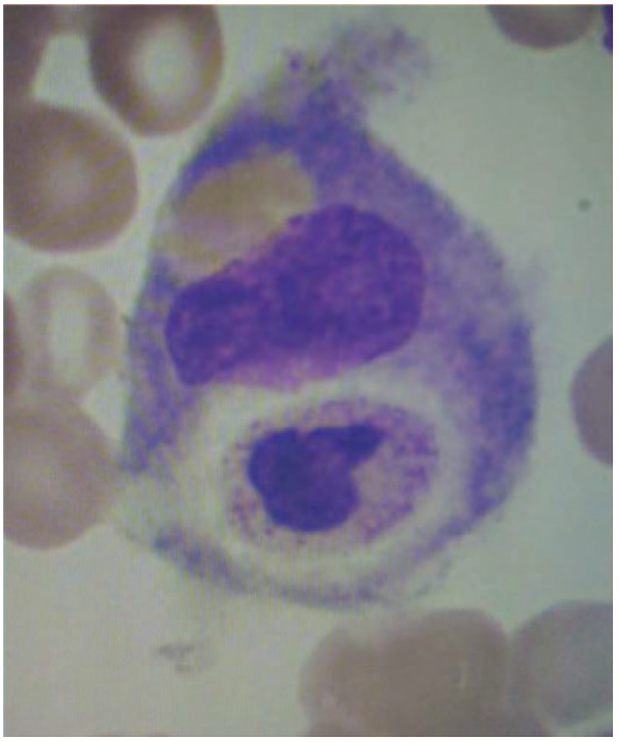

Figure 2. Bone marrow histopathology for case 1.

made. Anti-tuberculosis therapy was administered using amikacin, ethambutol, moxifloxacin and isoniazid, and methylprednisolone was given as an anti-inflammatory agent.

After a week therapy, patient showed clinical improvement. The fever gradually subsided, and the patient's breathing also normalized. Routine blood tests and blood coagulation tests demonstrated the following: WBC, 6.71×10^9/L; NEUT%, 71%; PLT, 103×10^9/L; HGB, 80 g/L; PT, 12.7 seconds; APTT, 35.1 seconds; FIB, 2.25 g/L; INR, 1.05; and D-dimer, 500 mg/L. The blood gas analysis (FiO_2: 41%) revealed: pH, 7.50; PO_2, 124 mmHg; PCO_2, 34 mmHg; SO_2, 99%; and oxygenation index, 302. After discharge from hospital, the patient continued to receive anti-tuberculosis therapy in the outpatient department about 9 months. Now, the patient subsequently recovered and the drugs were discontinued. Thoracic CT (Fig. 1C and D) showed a small number of fibrous cord-like opacities.

2.2. Case 2

A 57-year-old man, not known to be diabetic and hypertensive, was admitted in our hospital with history of fever over 39 °C with stills and night sweat for last 1 month. Patient had history of intermittent cough with sputum production and respiratory distress in the past. The patient had previously been engaged in employment that resulted in the inhalation of a large amount of dust. There was no history of headache, abdominal pain, haemoptysis, joint pain, photophobia, any rash, projectile vomiting, chest pain, palpitation, paroxysmal nocturnal dyspnea, and facial swelling. There was no past history of jaundice, tuberculosis, or any contact, any significant family history, or drug intake.

On admission, the patient had disturbed consciousness and was unresponsive. Physical examination revealed a temperature of 36.8 °C, a heart rate of 89 beats/min, a respiratory rate of 25 breaths/min and a blood pressure of 103/85 mmHg. The computational ability of the patient had diminished, and there was slight stiffness of his neck. The superficial lymph nodes were not palpable. Ecchymoses were observed on the front of the chest and abdomen, but there was no itching. Both lungs were resonant on percussion, but the respiratory sounds were reduced, and wet rales were heard from the left lung. The heart rate was 89 beats/min, the heart rhythm was regular, the valve sounds were normal, and pericardial friction rub was absent. The right lobe of the liver was not palpable, the spleen was soft, smooth, and palpable 1 cm above the level of the umbilicus, and there was no edema in both lower extremities. There was no cervical, supraclavicular, axillary, or inguinal lymphadenopathy, and genitourinary, and neurological examinations were unremarkable.

On admission, routine blood tests showed the following: WBC, 2.6×10^9/L; NEUT%, 95.3%; HGB, 135 g/L; and PLT, 41×10^9/L. C-reactive protein was 134.2 mg/L. Blood gas analysis (FiO_2: 29%) demonstrated: pH, 7.51; PO_2, 53 mmHg; PCO_2, 25 mmHg; HCO_3^-, 19.9 mmol/L; SO_2, 90%; and oxygenation index, 182. The results of laboratory biochemistry tests were: TBIL, 22.02 μmol/L; DBIL, 7.18 μmol/L; IBIL, 14.24 μmol/L; ALT, 42 U/L; AST, 57 U/L; total protein, 48.3 g/L; albumin, 27.8 g/L; LDH, 804 U/L; TG, 2.08 mmol/L; and ferritin, 369.65 μg/L. Blood coagulation tests indicated the following: PT, 24.7 seconds; INR, 2.01; D-dimer, 1246 mg/L; and FIB, 1.4 g/L. The PPD-based tuberculin skin test was 0 cm × 0 cm. All the following investigations were negative: Gram's staining of sputum; sputum-related bacterial and fungal cultures; blood culture; routine urinalysis; urine bacterial and fungal cultures; routine stool test; Epstein-Barr virus antibodies and cytomegalovirus antibodies; HIV test; and various Hepatitis B virus markers (HBsAg, HBeAg, HBeAb, and HBcAb), although HBsAb tested positive. Chest CT

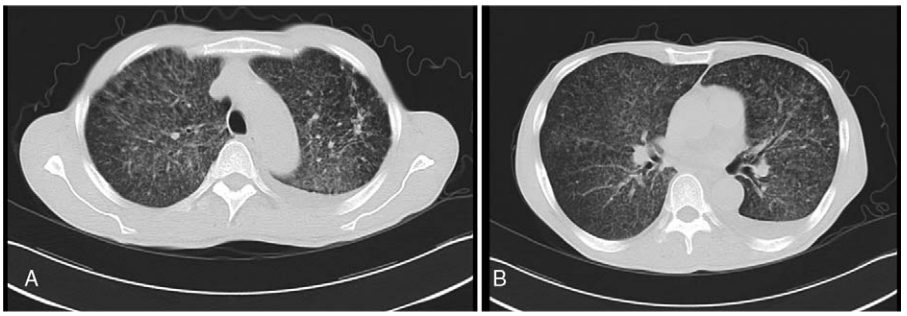

Figure 3. Pulmonary CT at onset for the patient in the second case. CT indicates computed tomography.

(Fig. 3A and B) revealed diffuse lesions in both lungs, which were considered to be pneumoconiosis combined with tuberculosis. Moreover, interstitial changes were visible in some parts of the lungs, and there were cavities in the left upper lobe. Abdominal color Doppler ultrasound demonstrated an increased liver echo and swelling of the spleen with a thickness of about 43 cm. The CURB-65 score was 3 points.

The diagnosis made at admission was severe pneumonia with respiratory failure. After admission, empiric anti-infection therapy was initiated using rifamycin combined with cefoperazone and sulbactam, and a non-invasive ventilator was used to assist breathing. However, the shortness of breath did not improve, and intermittent fever still occurred. Blood gas analysis (FiO_2: 61%) demonstrated the following: pH, 7.51; PO_2, 53 mmHg; PCO_2, 23 mmHg; HCO_3^-, 18.4 mmol/L; SO_2, 90%; and base excess, 2.5 mmol/L. A routine blood test yielded results as follows: WBC, 2.04×10^9/L; NEUT%, 93.1%; HGB, 109 g/L; and PLT, 30×10^9/L. Consequently, bronchoscopy was performed, and alveolar lavage fluid was found to contain tuberculosis DNA at 3.67×10^5 copies. The patient was diagnosed with secondary tuberculosis combined with severe pneumonia. Therefore, anti-tuberculosis therapy was started using rifampicin, ethambutol, amikacin and isoniazid, and a non-invasive ventilator was used to assist breathing. However, the fever was not relieved, and body temperature gradually increased to reach as high as 40 °C. Moreover, the patient complained of coldness and chills. There were manifestations of severe cardiac failure, and tracheal intubation was performed so that the patient could be ventilated to assist breathing. Bone marrow puncture and biopsy showed that the hematopoietic function of the bone marrow had decreased and that hemophagocytosis had occurred. Bone marrow puncture and biopsy revealed 3 granulomatous lesions but no significant caseous necrosis, in line with granulomatous inflammation; therefore, tuberculosis was excluded (Fig. 4). The diagnosis suggested that the patient had suffered from severe pulmonary tuberculosis with HPS. The patient's family decided to discontinue treatment, and the patient died.

3. Results

In this study, both cases showed manifestations of systemic dissemination of severe pulmonary tuberculosis together with respiratory failure, with the resultant induction of HPS. The 2 cases in this report show that tuberculosis-associated hemophagocytic syndrome is not easy to find, especially in ICU.

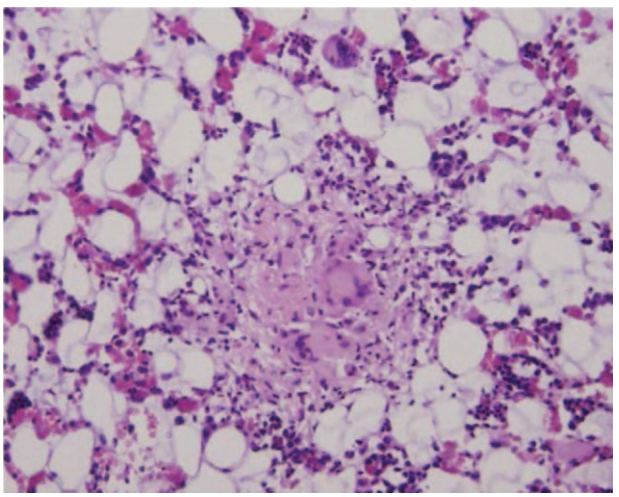

Figure 4. Bone marrow histopathology for case 2.

4. Discussion and literature review

HPS, also known as hemophagocytic lymphohistiocytosis (HLH), is a rare reactive hyperplastic disease of the mononuclear phagocytic cell system. HPS was first reported by Scott and Robb-Smith in 1939 and was differentiated from atypical Hodgkin disease as a new entity.[1] HPS is clinically classified into 2 types, primary HPS and secondary HPS. Primary HPS, also known as familial hemophagocytic lymphohistiocytosis (FHL), is a recessive genetic disease of autosomal or sex chromosomes that most commonly occurs in infants and young children <2 years old. Secondary HPS is mainly associated with diseases such as infection, drug hypersensitivity, autoimmune diseases, and malignancy[2] and can occur in people of all ages.

HPS is a life-threatening syndrome that has various clinical manifestations, a rapid disease course, and high mortality.[3–5] HPS is not an independent disease but represents an excessive inflammatory response due to immune dysfunction induced by various causes such as infection and tumor. The basic characteristic of HPS is that there is over-activation and proliferation of mononuclear macrophages and/or lymphocytes, infiltration of organs and tissues, and the occurrence of a "cytokine storm," ultimately resulting in multiple organ damage.[6,7] HPS secondary to severe infection has been reported in several patients and rapidly caused life-threatening multiple organ failure; among hospital departments, the ICU had a high incidence of secondary HPS and was the unit in which HPS could best be treated.[5]

HPS has no special clinical manifestations, and the main presentations include persistent fever, hepatosplenomegaly, hematocytopenia, and rash. In the ICU, the clinical manifestations of severe infection and secondary HPS overlap, thus there is often a delay in the diagnosis and treatment of HPS. A postmortem study demonstrated that HPS is not readily identified in patients in the ICU,[8] and this is also illustrated by the 2 cases of severe pulmonary tuberculosis reported in this study, especially the second case. Both cases were diagnosed after admission as sepsis, and HPS was not initially considered. As a result, empiric anti-microbial treatment was given, which introduced a delay in the diagnosis and treatment of HPS. However, it should be noted that hemophagocytic phenomena are rare at the early stage of the disease but become more common as the disease progresses. It is also noteworthy that some patients in the ICU may not undergo certain examinations due to the presence of severe disease. Buyse et al[9] reported that the detection rate of HPS in the ICU was only 43%. The occurrence of sepsis after severe infection may conceal HPS. Studies have demonstrated that in patients with sepsis but without HPS, the chances of observing activation of erythrocytes and macrophages is only 0.8% to 4%.[9–11]

Infection is the most common etiology underlying secondary HPS,[12] which can be induced by viruses, bacteria, fungi, parasites, and protozoa. Among these, Epstein-Barr virus and cytomegalovirus infections are the most common causes, while HPS associated with tuberculosis is rare. It has been reported that extrapulmonary tuberculosis is found in 83% of patients with tuberculosis-associated HPS,[13] and about half the patients have underlying diseases. The pathogenesis of HPS is associated with over-activation of macrophages and natural killer cells, increased phagocytic and infiltrative activity, abnormal lymphocyte

function, and excessive release of cytokines. The immune functions of patients with tuberculosis are usually compromised, but specific cellular and humoral immunity are generated after infection with *Mycobacterium tuberculosis*, with cellular immunity playing a key role in the immunity to tuberculosis.[14] Secondary HPS is often associated with intracellular bacteria that induce classical Th1 immune responses. In animal models, strong Th1 cell-mediated immunity is needed for the control of *M tuberculosis* infection,[15] and this may be the reason why tuberculosis can induce HPS. In this study, both cases showed evidence of extrapulmonary tuberculosis: the first patient had bone marrow tuberculosis and the second had bloodborne, disseminated tuberculosis. Bone marrow culture of *M tuberculosis* was positive in both cases. We believe that the 2 patients in this study were infected by *M tuberculosis* that involved the lymph nodes and bone marrow as well as activated macrophages. On the one hand, the pathogens were phagocytized; on the other, immune regulation was imbalanced. Thus, there was excessive cytokine secretion by lymphocytes and mononuclear cells and activation of macrophages that induced HPS.

There is still no effective treatment for HPS. Based on the main characteristics of HPS, Janka[16] proposed that the main aim of therapy should be to control the life-threatening pathologic state of HPS; meanwhile, active treatment of the primary diseases or causes should be performed. The current management guidelines for HPS are based on the standards recommended in HLH-2004, and the treatments include immunotherapy combined with chemotherapy. Simple hormone therapy has some effect against secondary HPS but should be adjusted to etoposide-based chemotherapy for patients who are not sensitive to hormone therapy. The prognosis of tuberculosis-associated HPS is poor, with a mortality rate of about 50%, but the prognosis can be improved by anti-tuberculosis treatment and immunomodulatory therapy. Therefore, tuberculosis should be considered as soon as possible in the differential diagnosis of HPS associated with infectious disease. The PPD-based tuberculin skin test was negative in both patients reported in this study, indicating that infection with tuberculosis cannot be excluded by a negative PPD-based skin test. Mortality is high because the disease progresses rapidly, thus early diagnosis and timely initiation of anti-tuberculosis therapy are of great importance.

In this study, we can find that both patients underwent fiberoptic bronchoscopy and bone marrow biopsy to screen for infectious pathogens at an early stage. The first patient improved rapidly, likely because the patient was young with no underlying diseases and because anti-tuberculosis and immunoregulatory (hormonal) therapy was administered at an early stage. By contrast, the second patient deteriorated after anti-tuberculosis therapy, and organ failure occurred rapidly. This may have been related to the age of the patient and the presence of underlying immune problems. In addition, although anti-tuberculosis agents were administered to the second patient, immunomodulatory treatment was not given, and this may have been the key to failure.

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