Hemophagocytic syndrome in patient with long-term stable pulmonary sarcoidosis with progressive spleen and bone marrow lesion

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Abstract

An 83-year-old woman with asymptomatic pulmonary sarcoidosis presented to our hospital with fever and malaise for three months. Abdominal CT showed splenomegaly, and bone marrow examination revealed non-caseating granulomas. Pancytopenia was diagnosed due to bone marrow and splenic lesions of sarcoidosis. Steroid pulses were administered, but the patient died without response to treatment. Pathological autopsy results showed non-caseating granulomas and hemophagocytosis in the spleen and bone marrow. This suggested hemophagocytic syndrome, which was not suspected before death, in addition to sarcoidosis. In patients with splenomegaly and pancytopenia with history of pulmonary sarcoidosis, hemophagocytic syndrome should be considered in differential diagnosis.

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Introduction

Patients with sarcoidosis may occasionally develop pancytopenia [1]. The mechanism of pancytopenia in patients with sarcoidosis is reported to be impairment of hematopoiesis due to granuloma replacement in the bone marrow, peripheral blood cell depletion due to migration of cells to the site of inflammation, blood cell destruction due to increased splenic function, or immunological destruction [2]. Reactive hemophagocytic syndrome (HPS) is another cause of pancytopenia, with sarcoidosis as the underlying disease [3].

Reactive HPS has a high mortality rate of 50-75% and requires immediate treatment with steroid pulses, immunosuppressive agents, and biologics [3]. Consideration and treatment of HPS soon after onset is important for treatment to be successful. Sarcoidosis itself causes pancytopenia due to lesions in the bone marrow and spleen [1]. Consideration of other diagnoses including HPS is therefore difficult, especially when there is progressive bone marrow and spleen lesions related to sarcoidosis. We report a case of reactive HPS in a patient with sarcoidosis with a stable course for 17 years, where progressive spleen and bone marrow lesion ultimately resulted in death.

Case Report

An 83-year-old woman was admitted to our hospital with a chief complaint of general fatigue and anorexia over the previous three months. She was febrile, and in-hospital urinary analysis showed pyuria and bacteriuria. She was diagnosed with pyelonephritis and treated with three days of intravenous cefazolin followed by three days of intravenous cefmetazole, but fever persisted, and pancytopenia developed. Splenomegaly was detected in a routine follow-up CT three months before admission. She had a history of lung sarcoidosis over 17 years, but it had not progressed. Four years previously, she had received direct-acting antiviral medicine as treatment for chronic hepatitis C. She took

levothyroxine 50 µg/day for hypothyroidism and hepatoprotective drugs, ursodeoxycholic acid 300 mg/day and rabeprazole sodium 10 mg/day. She was a current smoker, smoking 10 cigarettes/day, but did not consume alcohol. She had been a housewife and had no family history of sarcoidosis. She was able to walk with a cane to some extent. There was no dyspnea or cough, and her status was otherwise unremarkable.

On hospital evaluation, body temperature was 37.9°C, blood pressure was 127/66 mmHg, pulse rate was 82 beats/min, respiratory rate was 24 breaths/min, the oxygen saturation was 95% while breathing ambient air, and there was no impairment of consciousness. Her height was 149 cm, and the body-mass index 15.3 kg/m^2. Bowel sounds were normal, and the abdomen was soft. No lymph nodes on the body surface were palpable. The remainder of the systemic examination was unremarkable.

Laboratory tests showed white blood cell counts of 1370/µL (normal range 4500-8100/µL), with a neutrophil percentage of 91% (40-78%) and lymphocytes of 2% (27-47%), hemoglobin of 6.8 g/dL (12-16 g/dL), platelet counts of 62,000/µL (100-330/µL), activated partial thromboplastin time 43.7 seconds (24-40 sec), prothrombin time 73% (70-100%), alkali phosphatase 818 U/L (104-338 U/L) without other liver enzyme elevation, ferritin 1894 µg/dL (5-152 µg/dL), soluble interleukin-2 receptor 9720 U/mL (157-474 U/mL) and angiotensin converting enzyme 13.5 U/L (8.3-21.4 U/L). Interferon-gamma release assays (T-SPOT.TB) was negative. Blood culture had no growth, urine culture on days nine and 20 showed *Escherichia coli* (*E. coli*) >10^5 colony forming unit (CFU) /mL, <10^3 CFU/mL, and urine culture on day 20 showed extended spectrumβ-lactamase-producing *E. coli* 10^4 CFU/mL. Electrocardiogram showed sinus rhythm and no atrioventricular block. Echocardiography showed that left ventricular ejection fraction was preserved at 78% without wall motion abnormality or thinning of the ventricular septum. Abdominal ultrasonography showed multiple hypoechoic areas in the liver and splenomegaly (91 x 34 mm). Contrast-enhanced computed tomography of the chest (Figure 1 a,b) and abdomen (Figure 1c) showed emphysema, fibrosis, some frosted shadows, enlarged mediastinal lymph nodes, pleural effusion, ascites, and splenomegaly. Posterior iliac crest bone biopsy was dry tap, with findings of non-caseating granuloma. *Mycobacterium tuberculosis* was negative in loop-mediated isothermal amplification assay and acid-fast bacillus culture. Gallium scintigraphy showed no abnormal accumulation. No atypical cells appeared in the peripheral blood or bone marrow tissue, and leukemia and lymphoma were ruled out. Blood tests were negative for human T-cell leukemia virus, human immunodeficiency virus, cytomegalovirus and Epstein-Barr virus. In addition, antibacterial staining of bone marrow biopsy tissue was negative. Due to progressive splenomegaly on CT, non-caseating granuloma on bone marrow biopsy and a history of pulmonary sarcoidosis, we made a clinical diagnosis of pancytopenia due to bone marrow and splenic involvement in sarcoidosis. Prednisolone 0.5 mg/kg/day was initiated from day 21 but was ineffective. Steroid pulse of methylprednisolone 500 mg twice a day was therefore given for three days from day 28. Despite the steroid

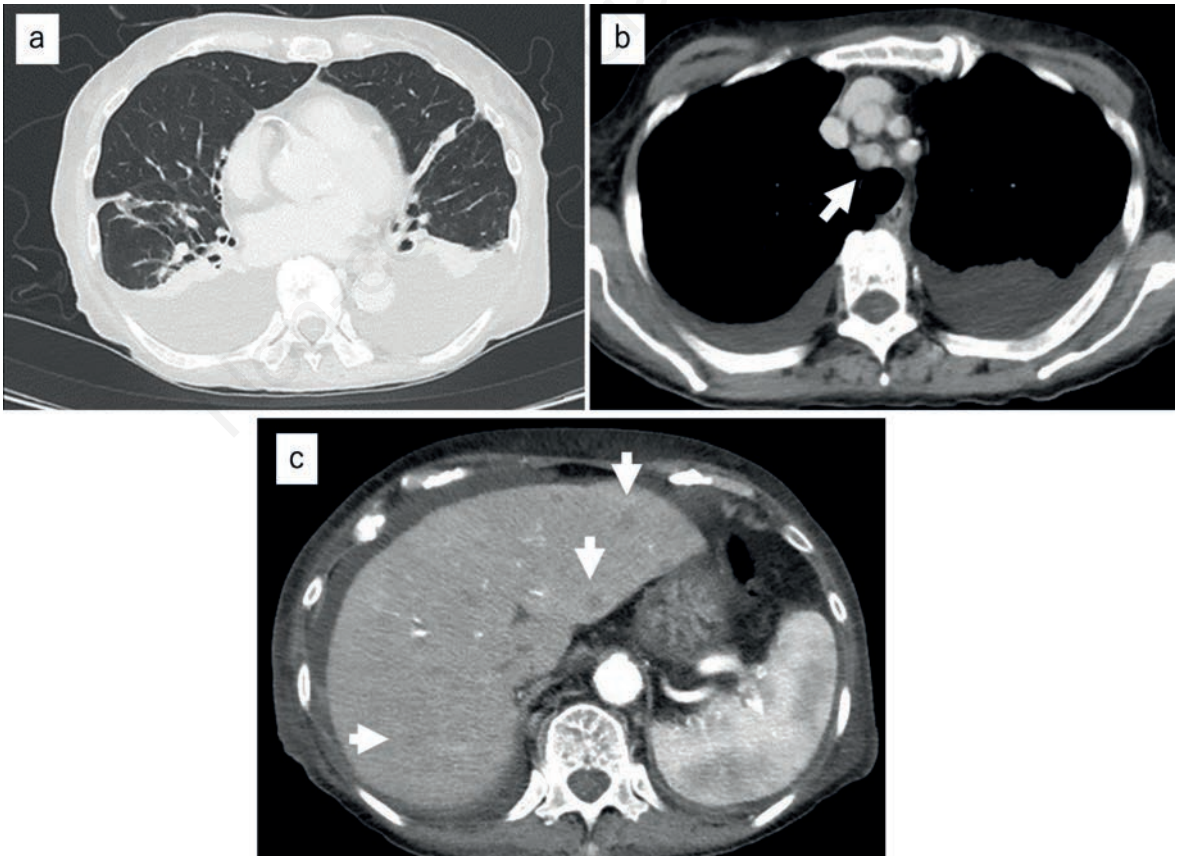

Figure 1. a) Chest CT (lung window) shows emphysema, fibrosis, some frosted shadows, enlarged mediastinal lymph nodes, and pleural effusion. b) Chest CT (mediastinal window) shows enlarged mediastinal lymph node (arrow). c) Contrast enhanced computed tomography shows an enlarged spleen and multiple nodules in liver (arrows), without abdominal lymphadenopathy.

pulse, the patient's fever continued and there was no improvement of pancytopenia. With consideration of the patient's poor general condition, we discussed the situation with the outpatient physician, the patient, and her family, deciding on a policy of palliative treatment. The patient's general condition continued to slowly deteriorate, and she died on day 35.

Pathological autopsy was performed 18 hours after death. There was mild emphysema in the lungs, and fibrosis without granuloma in the lung parenchyma. Fibrosis was due to old inflammation and was thought to be unlikely to be related to the sarcoidosis. Hilar and mediastinal lymph nodes were enlarged, with findings of non-caseating granulomas without hemophagocytes or giant cells. The liver was slightly enlarged at 1150 g, with necrosis and fibrosis due to chronic hepatitis C. The patient was in a pre-cirrhotic state with no bile stasis. Neutrophils were migrating around the bile ducts, and there were giant cells and hemophagocytes. Cytomegalovirus was negative. Ascites was 300 ml. The myocardium had fibrotic changes and the coronary arteries had calcification. There were no specific findings in the pancreas or kidneys. The spleen weighed 96 g and had non-caseating granulomas, hemophagocytes, and giant cells (Figure 2 b,c). The bone marrow of the sternum was hypoplastic with non-caseating granulomas and hemophagocytes (Figure 2 d,e). Immunohistochemical analyses (CD3, L-26, CD68, CD15, CD30, Bcl-2, Ki-67) were performed, to examine the possible involvement of malignant lymphoma. Sarcoid-like lesions were shown to have massive infiltration of CD68-positive macrophages. However, activated macrophages with nuclear inclusion bodies did not show immunoreactivity against CD15, CD30 or Ki-67. Malignant lymphoma (intravascular lymphoma and Hodgkin lymphoma) was therefore excluded. In addition, the patient had no history of malignant neoplasm throughout her life. We therefore concluded that the patient did not have malignant lymphoma.

Discussion

Although the patient had a 17-year history of asymptomatic pulmonary sarcoidosis, she developed pancytopenia due to bone marrow lesions, splenomegaly and hypersplenism due to splenic lesions. This resulted in a month-to-month course of developing pancytopenia, which was complicated by hemophagocytic syndrome, leading to her death. This was supported by the pathological results, which showed non-caseating granulomas in the hilar and mediastinal lymph nodes, and granulomas, giant cells, and hemophagocytosis in the spleen and bone marrow, similar to those in the lymph nodes.

Bone marrow lesions in sarcoidosis are present in 3.9-17% of cases [1,4-6] and splenic lesions in 41.9% of cases [7]. Most are asymptomatic, but some cause pancytopenia, an uncommon clinical problem. Mechanisms of pancytopenia in sarcoidosis have been reported to include decreased hematopoietic capacity due to granuloma replacement in the bone marrow, peripheral blood cell depletion due to migration of cells to the site of inflammation, blood cell destruction due to increased splenic function, and immunologic destruction [2]. At the time of bone marrow biopsy on the ninth day of hospitalization, there was no hemophagocytosis, which was later seen at autopsy, and there were no complications of hematologic diseases, such as autoimmune hemolytic anemia, leukemia, or myelodysplastic syndrome. Initially, lymphoma, myeloproliferative diseases, leukemia, and viral and antibiotic infections were considered as differential causes of splenomegaly and pancytopenia in this patient, but the bone marrow biopsy showed non-caseating granuloma without suggestive findings of hemophagocytosis; this led to the diagnosis of bone marrow lesions of sarcoidosis.

Auto-immune diseases, viral infections, malignant tumors, and inflammatory diseases have been reported as underlying causes of reactive hemophagocytosis in adults. HPS due to sarcoidosis has also been reported, although it is rare. We found 11 single-case reports of reactive hemophagocytic syndrome due to sarcoidosis. Of these eleven featured patients, only three patients survived, with the mortality rate of 73% [3].

The present case of HPS occurred 17 years after the diagnosis of sarcoidosis, and there is also one previous case of HPS after a 30-year period [8]. Of the eleven reported cases, five had viral or tuberculous infections, and six had HPS without a specific trigger [3]. In the present case, urinary tract infection was suspected, but

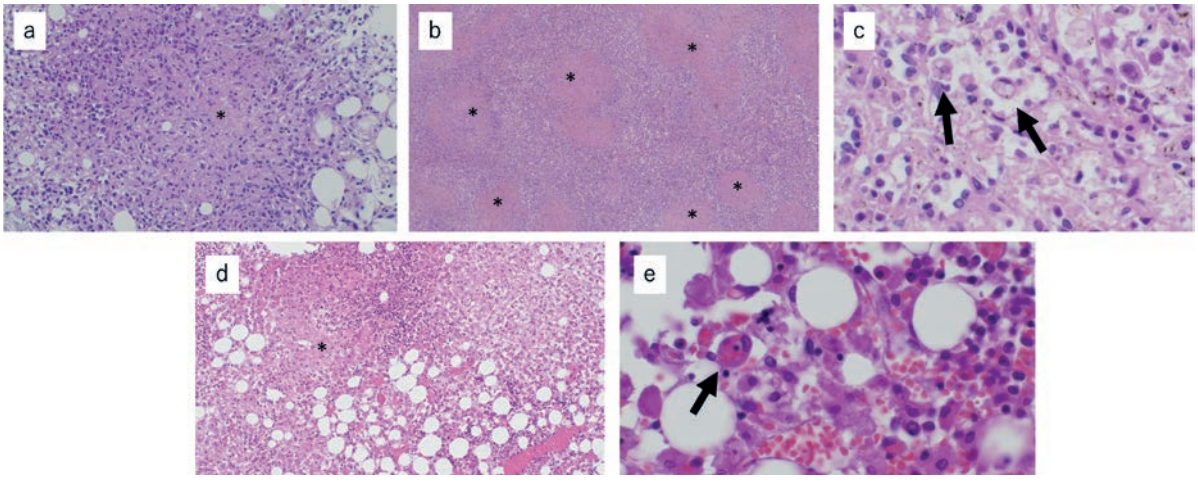

Figure 2. a) Posterior iliac bone marrow biopsy on day 9 (H&E stain) shows non-caseating granuloma (asterisk); magnification: 200x. b,c) H&E stain of the spleen shows multiple non-caseating granulomas (asterisk) and hemophagocytic macrophage (arrows); magnification: b) 40x, c) 400x. d,e) H&E stain of sternum shows hypoplastic, non-caseating granulomas (asterisk) and hemophagocytes (arrow); magnification: d) 200x, e) 400x.

no other infections could be identified, although we searched for cytomegalovirus, Epstein-Barr virus, and *M. tuberculosis*. Sarcoidosis itself was considered to be the underlying disease of HPS in the present case.

The HPS-2004 protocol is used as the diagnostic criteria for primary HPS in children [9], while the HS score is used as the diagnostic criteria for reactive HPS in adults with underlying infection, malignant disease, or collagen disease [10,11]. HS score includes original immunosuppressive status, body temperature, organ enlargement, hematophagy, ferritin, triglyceride, fibrinogen, and AST levels on blood tests, and hemophagocytosis on bone marrow biopsy. A score of ≤130 points indicates a <9% likelihood of reactive HPS, while a score of ≥180 points indicates a >70% likelihood of reactive HPS (>90% for a score of 210 points). In our patient, ferritin, triglyceride, and fibrinogen levels could not be evaluated, so HPS could not be considered as a differential diagnosis. Prenatal diagnosis of HPS might have been possible if the suspicion score could have been calculated at an earlier stage.

In a review of reactive HPS with underlying collagen disease, 114 of 116 patients (98.3%) were treated with corticosteroids [12]. Intravenous immunoglobulin G (IVIG), cyclosporine, and cyclophosphamide (CYC) were given to 24.1%, 20.7%, and 14.7% of patients, respectively, and small number of patients received biologic agents, such as infliximab, etanercept, rituximab, and tocilizumab.

In all cases of rescued patients with HPS due to sarcoidosis, PSL and other drugs were used in combination [8,13]. In this case, the sarcoidosis had been asymptomatic for 17 years and no treatment was required. The trigger for the development of HPS was unknown, and because the diagnosis was not made before death, the patient was treated only with corticosteroids as treatment for sarcoidosis.

Conclusions

In splenomegaly and pancytopenia in patients with a history of pulmonary sarcoidosis, it is important to consider extrapulmonary lesions of the spleen and bone marrow, even without exacerbation of pulmonary lesions. If the pancytopenia progresses rapidly, however, other differential diagnosis including reactive HPS should be considered, even if spleen and bone marrow lesions of sarcoidosis are present.

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