INTERNAL MEDICINE

□ CASE REPORT □

Miliary Tuberculosis in a Young Woman with Hemophagocytic Syndrome: A Case Report and Literature Review

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Abstract

We herein report a rare case of miliary tuberculosis-associated hemophagocytic syndrome (HPS) complicated with respiratory failure. A 19-year-old Japanese woman with a fever, general malaise, and chest radiograph abnormalities was referred to our hospital. After admission, she developed respiratory failure with pancytopenia. A histological examination of lung and bone marrow biopsy samples revealed noncaseating granulomas without evidence of acid-fast bacilli or lymphoma. In addition, a bone marrow biopsy showed marked histiocyte hyperplasia with hemophagocytosis, and a bronchoalveolar lavage fluid culture grew *Mycobacterium tuberculosis*. Therefore, a diagnosis of miliary tuberculosis-associated HPS was made. The patient was successfully treated with antituberculous therapy.

Key words: miliary tuberculosis, hemophagocytic syndrome, noncaseating epithelioid granulomatous inflammation

(Intern Med 56: 1591-1596, 2017)
(DOI: 10.2169/internalmedicine.56.8025)

Introduction

Hemophagocytic syndrome [HPS; also known as hemophagocytic lymphohistiocytosis (HLH)] is a disorder characterized by the benign proliferation of mature histiocytes and uncontrolled phagocytosis of the platelets, erythrocytes, lymphocytes, and their hematopoietic precursors in the bone marrow, giving rise to cytopenia. The disorder is classified into primary (familial) and secondary forms. Secondary HPS is usually caused by infectious diseases, autoimmune diseases, malignancies, or drugs. Among infectious diseases, viral infection is the most common cause of HPS, and tuberculosis-associated HPS is relatively rare. To our knowledge, only 10 cases of tuberculosis-associated HPS in subjects less than 20 years of age have been reported in the English literature. We herein present the case of a 19-year-old Japanese woman with miliary tuberculosis-associated HPS.

Case Report

A 19-year-old Japanese woman was admitted to a local community hospital (day 1) with a 6-day history of a fever, chills, dyspnea, and general malaise. Chest computed tomography (CT) obtained at the hospital showed diffuse ground-glass opacity in both lungs and multiple mediastinal lymphadenopathy (Fig. 1), and empiric antibiotic therapy (SBT/ABPC, MINO) was started. She underwent a transbronchial lung biopsy (TBLB) and bronchoalveolar lavage (BAL) on day 4 that disclosed noncaseating epithelioid granuloma without any organisms. Acid-fast staining of the sputum (three sets) and bronchoalveolar lavage fluid (BALF) also showed negative results. After a bronchoscopic examination, she developed respiratory failure, and steroid pulse therapy was started (day 4). After the steroid pulse therapy, her breathing state and pulmonary abnormal findings on computed tomography (CT) improved (day 9). However, on

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Received for publication July 20, 2016; Accepted for publication October 6, 2016
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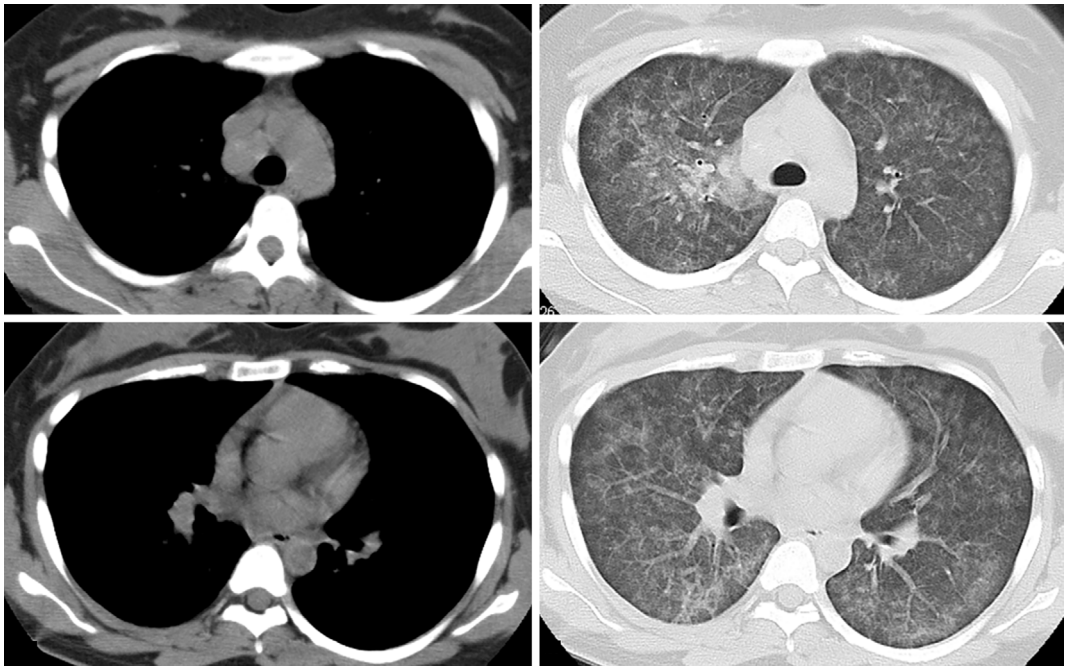

Figure 1. **CT at the previous hospital showed diffuse ground-glass opacity in both lungs and multiple mediastinal lymphadenopathy.**

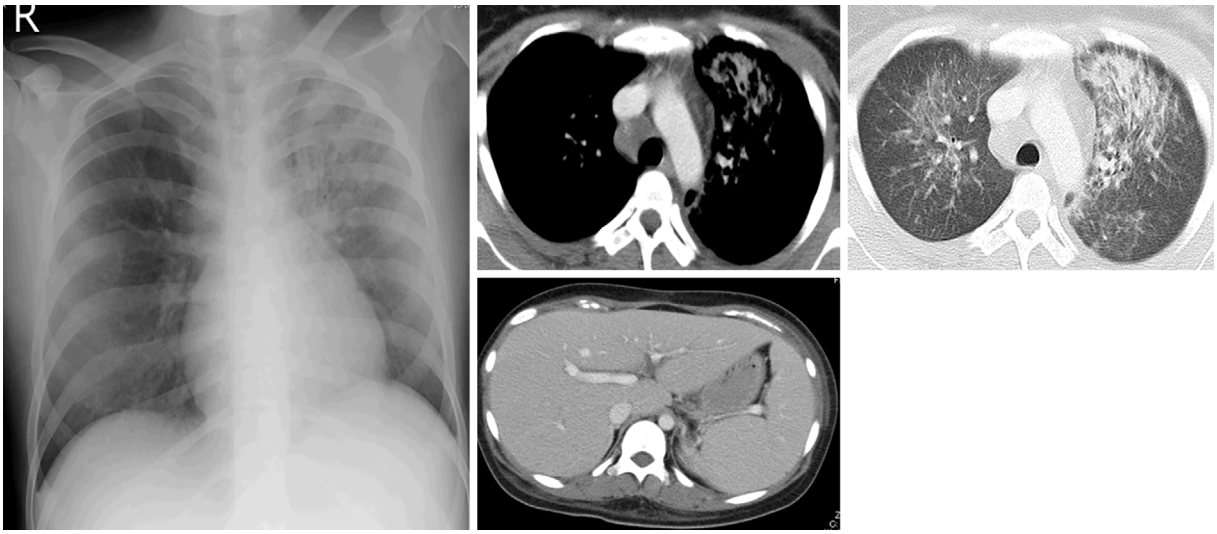

Figure 2. **A chest X-ray and CT obtained on admission revealed consolidation in the left upper lung field, decreased ground-glass opacity in both lungs, and multiple mediastinal lymphadenopathy.**

day 13, the high fever recurred during steroid reduction, and her multiple mediastinal lymphadenopathy persisted. In addition, her plasma soluble interleukin-2 receptor (sIL-2R) level was elevated (2,587 pg/mL). Therefore, the previous doctor suspected malignant lymphoma, and she was referred to our hospital for a definitive diagnosis.

On admission to our hospital (day 15), she presented with a fever and general malaise. She did not smoke or consume alcohol or travel, and she had no remarkable medical history. Her grandfather had a history of tuberculosis three years prior, and she occasionally interacted with him. Her body temperature was 40 °C, heart rate 90 beats/min, blood pressure 109/62 mmHg, respiratory rate 18 breaths/min, and oxygen saturation 93% under normal conditions. On a physical examination, the edge of the liver could be felt 2-3 cm below the right costal margin without splenomegaly or lymphadenopathy. There were no rales on chest auscultation, and a cardiac examination revealed a regular rate and rhythm with no murmurs. Chest X-ray and CT obtained on admission revealed consolidation in the left upper lung field, ground-glass opacity in both lungs, and multiple mediastinal lymphadenopathy (Fig. 2). Abdominal ultrasound showed hepatosplenomegaly with coursing echogenicity of the liver. Laboratory work-up revealed decreased levels of hemoglobin and elevated levels of AST, ALT, ALP, γ-GTP, LDH, CRP, TG, fibrinogen, FDP, D-dimer, ferritinm, sIL-2R, and ACE

Table 1. Laboratory Data Obtained at Our Hospital.

Hematology		Coagulation study	
WBC	7.54×10^3 /μL	PT	89 %
Neu	81.9 %	APTT	34.9 sec
Mon	2.2 %	Fig	466.0 mg/dL
Lym	13.6 %	FDP	8.8 μg
RBC	313×10^4 /μL	D-dimer	5.7 μg/mL
Hb	7.6 g/dL	Serological tests	
Plt	20.1×10^4 /μL	IgG	1,317 mg/dL
ESR	40 mm	IgA	477.1 mg/L
Biochemistry		IgM	109.8 mg/dL
AST	54 U/L	KL-6	1,100 U/mL
ALT	108 U/L	Antinuclear antibody	<40
LDH	386 U/L	RF	10 U/mL
ALP	674 U/L	sIL-2R	5,255 pg/mL
γ-GTP	290 U/L	ACE	28.5 U/L
CPK	8 U/L		
BUN	22 mg/dL		
Cr	0.6 mg/dL		
TP	6.9 g/dL		
Alb	3.0 g/dL		
TG	270 mg/dL		
CRP	3.88 mg/dL		
Ferritin	1,582 ng/mL		

(Table 1). A peripheral blood smear showed monocytosis with hemophagocytosis. Further evaluations, including (1,3) β-D-glucan, legionella, mycoplasma, chlamydia, cytomegalovirus, Epstein-Barr virus antigen titers, and HIV ELISA, were all negative. The result of QuantiFERON-TB 3Gold (QFT-3G) was indeterminate. Several sets of blood cultures were negative, and sputum culture disclosed only yeast-like microorganisms.

On day 22, pancytopenia developed (white blood count cell count of $2,320\times10^3$/μL, hemoglobin 7.3 g/dL, platelet count 8.0×10^4/μL), and these results and clinical course suggested potential diagnoses of HPS, malignant lymphoma, sarcoidosis, hypersensitivity pneumonia, and tuberculosis. Therefore, we performed a bone marrow biopsy and TBLB again (day 23). The biopsy showed hemophagocytosis and noncaseating granulomatous inflammation without evidence of acid-fast bacilli or lymphoma. TBLB also disclosed noncaseating epithelioid granulomatous inflammation without evidence of acid-fast bacilli (Fig. 3). After a bronchoscopic examination, she developed respiratory failure, and steroid pulse therapy (intravenous methylprednisolone 1,000 mg/body for three days) was started on the same day. Both acid-fast staining and tuberculosis-polymerase chain reaction (PCR) testing of the BALF showed negative results. On day 24, we learned that the BALF culture obtained at the previous hospital had grown *Mycobacterium tuberculosis*. The patient then underwent tuberculosis-PCR testing of the urine, and the result was positive. Our patient now met five of the eight criteria for HPS (1). Therefore, a diagnosis of tuberculosis associated with HPS was given.

Antituberculous therapy (isoniazid 5 mg/kg/day, rifampicin 10 mg/kg/day, ethambutol 15 mg/kg/day, and pyrazinamide 20 mg/kg/day) was started on day 24. She responded well to the treatment, and her fever and respiratory failure improved on day 31. In addition, her hematological abnormalities resolved, and her radiological abnormalities improved on day 38. Four weeks later, it was revealed that the sputum culture obtained on admission at our hospital had also grown *M. tuberculosis*. The patient has been in a stable condition without any recurrence during or after treatment for two years.

Discussion

We herein reported a rare case of miliary tuberculosis-associated HPS complicated with respiratory failure.

HPS is a rare disorder of the immune system characterized by the benign proliferation of mature histiocytes giving rise to cytopenias. HPS is classified into primary (familial) and secondary forms. Primary HPS is an autosomal recessive disorder, usually presenting in infancy. Secondary HPS has been associated with infections, autoimmune diseases, malignancies, or drugs. Various infections activate macrophages or T cells, and the overproduction of proinflammatory cytokines by these cells is thought to be important in the monocyte/macrophage activation. Viral infection is the most frequent etiology of HPS, and to our knowledge, only 68 cases of tuberculosis-associated HPS have been reported in detail in the English literature. Furthermore, only 10 cases of tuberculosis-associated HPS in subjects under 20 years of age have been reported (2-15).

Tuberculosis-associated HPS has a high mortality rate

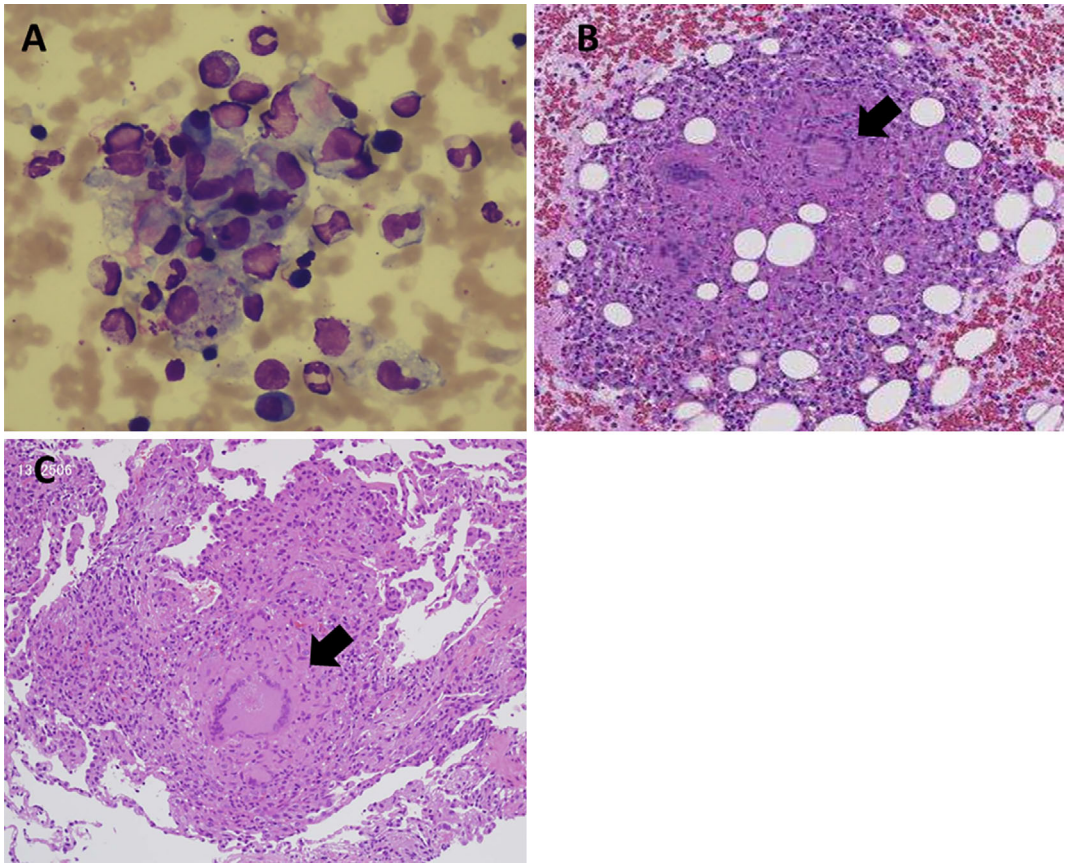

Figure 3. **Bone marrow biopsy showed hemophagocytosis (A) and non-caseating granulomatous inflammation without evidence of acid-fast bacilli or lymphoma (B). TBLB also disclosed noncaseating epithelioid granulomatous inflammation without evidence of acid-fast bacilli (C) and show Langhans giant cells (arrow on B and C).**

(approximately 45%) that reaches nearly 100% without antituberculous treatment (2, 16). This high mortality rate is mainly due to the under-recognition of this condition and delayed initiation of treatment. In our patient, the diagnosis of miliary tuberculosis was difficult because CT did not show a typical miliary nodular pattern, the acid-fast stains of the sputum and BALF were negative, and the results of QFT-3G were indeterminate. Therefore, we had to wait on the results of mycobacterial culture. The indeterminate results on the QFT-3G test in our patient were thought to be due to the influence of steroid pulse therapy performed at the previous hospital. The possibility of adult-onset immunodeficiency (patients with anti-interferon-γ-specific autoantibody) was also considered; however, our patient did not show any characteristic clinical manifestations, such as neutrophilic dermatosis, lymphatic obstruction, pain, neuropathy, hypercalcemia, erythema nodosum, or exanthematous pustulosis (17). Furthermore, in our patient, noncaseating granulomas were detected in the lung and bone marrow biopsy specimens. In the absence of caseating granulomas, it is difficult to differentiate tuberculosis from other diseases. Noncaseating granulomas are a typical pathological finding in nontuberculous mycobacterial infection, sarcoidosis, hypersensitivity pneumonitis, mycosis, and Crohn's disease. In tuberculosis, caseating granulomas are the typical pathological finding, although noncaseating granulomas are also found in about 45% of patients (18, 19).

We were unable to classify our patient with primary or secondary tuberculosis. She likely did not develop primary tuberculosis via exposure to her grandfather, because her grandfather's tuberculosis had been treated three years prior and did not recur after that. Furthermore, she had no striking radiologic findings, such as pulmonary parenchymal opacities with ipsilateral hilar and contiguous mediastinal lymphadenopathies, or pleural effusions. However, because primary tuberculosis shows a non-specific appearance and military tuberculosis is seen in both primary and secondary tuberculosis, the possibility of primary tuberculosis resulting from exposure to another person with tuberculosis cannot be wholly ruled out. However, we were unable to identify any potential carrier.

Regarding the possibility of secondary tuberculosis, she had no typical radiologic findings of this condition, such as patchy consolidation, poorly defined linear and nodular opacities, or cavitary lesions in the lung in the posterior segments of the upper lobes or superior segments of the lower lobes. She also had no old inflammatory parenchymal changes or lymphadenopathies. Furthermore, she was believed to be immunocompetent because laboratory tests of her immune status were normal and because no tuberculosis

Table 2. Summary of Previous Reports of Tuberculosis-associated HPS Patients under 20 Years of Age.

Reference	Sex	Age	Sites where TB was isolated	Co-morbidities	Immunotherapy	TB treatment	Outcome
[6]	F	14 days	Lungs, blood	N/As	Yes (hydrocortisone)	Yes	Survive
[7]	F	7 weeks	Lungs	N/A	No	No	Death
[8]	M	52 days	Lungs, liver, and lymphnodes	Seborrhoeic dermatitis	Yes (IVIG)	Yes	Death
[9]	M	2 months	Bone marrow	No	No	Yes	Survive
[10]	F	9 years	Lungs, bone marrow, liver, spleen, and central nervous	N/A	Yes (prednisone)	Yes	Survive
[11]	F	14 years	Lungs and bone marrow	No	Yes (dexamethasone/IVIG)	Yes	Survive
[12]	F	14 years	Lungs and bone marrow	N/A	Yes (epipodophyllotoxin)	Yes	Survive
[13]	M	15 years	Bone marrow, liver, spleen, and lymph node	N/A	Yes (IVIG)	Yes	Survive
[14]	M	17 years	Bone marrow, and lymph nodes	N/A	Yes (dexamethasone)	Yes	Survive
[25]	F	18 years	Lungs	No	Yes (corticosteroids)	Yes	Survive
Our case	F	19 years	Lungs and bone marrow	No	Yes (prednisone)	Yes	Survive

IVIG: intravenous immunoglobulin, N/A: not available, TB: tuberculosis
Modified from Shea et al. Hong Kong Med J 2012; 18: 517-525. (2)

or other infectious diseases has developed in the two years since her anti-tuberculosis treatment.

Our patient was complicated with acute respiratory failure with diffusely distributed ground-glass attenuation of both lungs. Miliary tuberculosis accounts for around 2% of cases of acute respiratory distress syndrome (ARDS), and the mortality rate of this condition is high (ranging from 58-88%) (20-23). Our patient underwent steroid pulse therapy at the previous hospital and our hospital before the initiation of anti-tuberculosis drugs, which seemed to be temporarily effective. Treatment with corticosteroids in patients with tuberculosis remains controversial. Critchley et al. reported that corticosteroid therapy reduced the mortality rate by 17% for all forms of tuberculosis (24), and Smego et al. also reported that corticosteroid therapy can provide clinical benefits in patients with advanced pulmonary tuberculosis (25). We therefore believe that the adjunctive steroid therapy was a somewhat effective treatment in the present patient.

In addition to this case, we reviewed another 10 cases reported in the English literature of subjects under 20 years of age with tuberculosis-associated HPS (Table 2) (4, 7-14). In these cases, only two died, one of whom did not receive antituberculous therapy. Therefore, the early diagnosis and appropriate treatment is thought to be very important, especially in relatively young patients.

In conclusion, tuberculosis should be considered in the differential diagnosis for patients presenting with HPS at any age. The early diagnosis and appropriate treatment can increase the chances of survival.

The authors state that they have no Conflict of Interest (COI).

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