□ CASE REPORT □

Miliary Tuberculosis not Affecting the Lungs but Complicated by Acute Respiratory Distress Syndrome

Isao MIYOSHI, Masanori DAIBATA, Naoto KURODA*, Hirokuni TAGUCHI and Hideaki ENZAN*

Abstract

A 61-year-old woman was admitted with fever and headache of 10-day duration. She was found to have anemia, jaundice, and signs of meningitis. The erythrocyte sedimentation rate was increased and the tuberculin skin test was positive. A provisional diagnosis of miliary tuberculosis was made and antituberculous therapy was started, although no miliary lesions were seen on chest radiography. However, her condition rapidly deteriorated with diffuse opacification of both lungs and she died on the 7th hospital day. Postmortem examination revealed miliary tuberculosis in several organs but not in the lungs with acute respiratory distress syndrome accounting for the lung pathology. It should be noted that on rare occasions the lungs may not be involved by miliary tuberculosis.
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Key words: miliary tuberculosis, acute respiratory distress syndrome

Introduction

In most adults, miliary tuberculosis results from hematogenous spread of *Mycobacterium tuberculosis* from reactivated primary foci and it virtually always involves the lungs, sometimes only microscopically. Here, we report a rare case of miliary tuberculosis not affecting the lungs. Failure to recognize this condition may delay the start of antituberculous therapy and may make a curable patient incurable.

Case Report

A 61-year-old jaundiced woman with a 10-day history of fever and headache was referred to us for not responding well to antibiotic treatment. Two years previously, she had developed left-sided pyothorax which resolved following treatment with antibiotics (β-lactam antibiotics plus clindamycin). The effusion fluid was purulent with 79% neutrophils but was culture-negative for bacteria and *M. tuberculosis*. On admission, she was found to have nuchal rigidity and a positive Kernig sign. The erythrocyte sedimentation rate was 174 mm/h and C-reactive protein 38.5 mg/dl. Hematological examination revealed hemoglobin 6.5 g/dl, white cell count 30,200/mm^3 with 89% neutrophils, and platelet count 440,000/mm^3. A bone marrow aspirate showed toxic granulations in neutrophils, an increase of metamyelocytes (21.7%) and a decrease of lymphocytes (6.1%) with a myeloid/erythroid ratio of 2.2. Marrow clot section revealed scattered non-caseating granulomas; this was reported by the pathologist one day before the death of the patient. The abnormal liver function tests included total bilirubin 9.4 mg/dl, direct bilirubin 7.0 mg/dl, alkaline phosphatase 375 IU/*l*, and lactic dehydrogenase 610 IU/*l*. Blood culture was negative for bacteria. A spinal tap yielded xanthochromic fluid with an initial pressure of 280 mmH_2O, protein 65 mg/dl, glucose 178 mg/dl (blood glucose 270 mg/dl), and 136 cells/mm^3 with 91% lymphocytes. The cerebrospinal fluid grew no bacteria on culture and was negative for *M. tuberculosis* by polymerase chain reaction. The tuberculin skin test was positive with 20×15 mm redness and 15×10 mm induration. Serology for hepatitis B surface antigen, hepatitis C antibody, human T-cell lymphotrophic virus type I, and human immunodeficiency virus was all negative. Chest radiography on admission was unremarkable except for old pleural changes on the left (Fig. 1). Computed tomography of the chest revealed small bilateral pleural effusions but no miliary nodules were seen. The results of the physical and laboratory examinations (Table 1) suggested that she was suffering from meningitis, hepatic dysfunction, and blood dyscrasia. In view of the systemic inflammatory nature of the disease and lack of response to β-lactam antibiotics and tetracycline given by the referring physician, the patient was suspected of

From the Department of Hematology and Respiratory Medicine and *the Department of Pathology, Kochi University School of Medicine, Kochi
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Reprint requests should be addressed to Dr. Masanori Daibata, the Department of Hematology and Respiratory Medicine, Kochi University School of Medicine, Kochi 783-8505

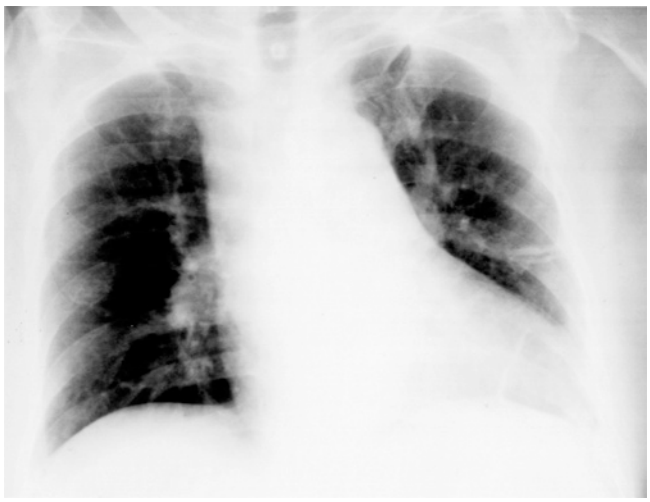

Figure 1. Chest radiograph on admission showing old pleural changes on the left.

having miliary tuberculosis and was started on antituberculous therapy (isoniazid, rifampin, streptomycin) along with broad-spectrum antibiotics. On day 3, she became delirious and the antituberculous therapy had to be discontinued. Then her clinical condition rapidly deteriorated with progressive bilirubinemia and hypoxemia despite supplemental oxygen. On day 5, patchy infiltrates suggestive of acute respiratory distress syndrome appeared in both lungs and methylprednisolone, 1,000 mg daily, was started. On day 6, both lungs showed confluent opacification with air bronchograms (Fig. 2) and she expired the next day.

At postmortem examination, the cut surface of the spleen was studded with yellowish white small nodular lesions. Histologically, tuberculous granulomas with or without caseation necrosis were seen in the spleen, liver (Fig. 3), hilar and paratracheal lymph nodes, bone marrow, and meninges. Acid-fast bacilli were detected in the bone marrow and lymph nodes. The lungs weighed 1,942 g—approximately 2.5 times the normal weight. The lung pathology was consistent with acute respiratory distress syndrome in that the alveolar spaces were full of fluid containing inflammatory leukocytes with hyaline membranes lining some of the alveoli (Fig. 4) . No bacteria, fungi, viral inclusions, or tubercles were seen in the lungs.

Table 1. Laboratory Data on Admission

Complete blood counts		Serological studies	
WBC	30,200/mm^3	HBs Ag	(–)
Metamyelocytes	1%	Anti-HCVAb	(–)
Neutrophils	88%	Anti-HTLV-I Ab	(–)
Lymphocytes	5%	Anti-HIV Ab	(–)
Monocytes	1%	Anti-IgG-EA-EBV Ab	<×10
Eosinophils	5%	Anti-IgM-VCA-EBV Ab	<×10
Basophils	0%	Anti-IgG-VCA-EBV Ab	×160
RBC	215×10^4/mm^3	Anti-legionella Ab	(–)
Hgb	6.5 g/dl	Anti-leptospira Ab	(–)
Hct	20.5%	Weil-Felix reaction	(–)
Platelets	44.0×10^4/mm^3	Vidal reaction	(–)
Reticulocytes	5.1%	Anti-toxoplasma Ab	(–)
ESR	174 mm/h		
		C-ANCA	<×10
Blood chemistry		LE test	(–)
TP	6.3 g/dl	Anti-DNA Ab	×80
Alb	2.5 g/dl	Anti-nuclear Ab	(–)
Glob	3.8 g/dl	Anti-mitochondrion Ab	(–)
α1-Glob	8.7%		
α2-Glob	6.9%	IgG	1,590 mg/dl
β-Glob	13.5%	IgA	612 mg/dl
γ-Glob	34.7%	IgM	714 mg/dl
T-Bil	9.4 mg/dl	CH50	40.5 U/ml
D-Bil	7.0 mg/dl	C3	108.6 mg/dl
AST	23 IU/*l*	C4	22.7 mg/dl
ALT	22 IU/*l*		
LDH	610 IU/*l*	Ham test	(–)
ALP	375 IU/*l*	Sugar-water test	(–)
γ-GTP	30 IU/*l*		
ChE	164 IU/*l*	Coagulation studies	
BUN	17 mg/dl	PT	45.6%
Crn	0.7 mg/dl	APTT	96.6%
CRP	38.5 mg/dl		
Na	136 mEq/*l*		
K	4.8 mEq/*l*		
Cl	103 mEq/*l*		
Ca	4.4 mEq/*l*		
Fe	45 μg/dl		
UIBC	89 μg/dl		
Ferritin	5,078 ng/ml		

Discussion

The present case had no apparent risk factors for reactivation of tuberculosis. There was no history of diabetes mellitus or use of corticosteroid prior to the present illness. Since her pyothorax 2 years prior to admission was successfully treated with conventional antibotics, this was probably not tuberculous pleuritis. One point worth noting in retrospect is that she used to consume Japanese wine, as much as 1,800 ml formerly and 360 ml recently, every night. This habbit may have predisposed her to develop miliary tuberculosis as well as pyothorax.

The tuberculin skin test remains a useful tool in establishing the diagnosis, as the skin test is positive in 90% of cases of miliary tuberculosis (1). In Japan, many of the aged people are skin test-positive due to latent infection of *M. tuberculosis*. It is this population that continues to be a major source of active tuberculosis. It is to be noted, however, that a positive skin test reaction may revert to negative (false-negative) in diverse clinical conditions such as corticosteroid/immunosuppressive treatment and fulminant tuberculosis.

In this patient, miliary tuberculosis was probably produced by hematogenous dissemination of *M. tuberculosis* from the enlarged hilar and paratracheal lymph nodes that had caseous areas. It is unusual that her lungs were not involved by tuberculosis in the presence of miliary tubercles in several other organs. According to the report of Slavin et al

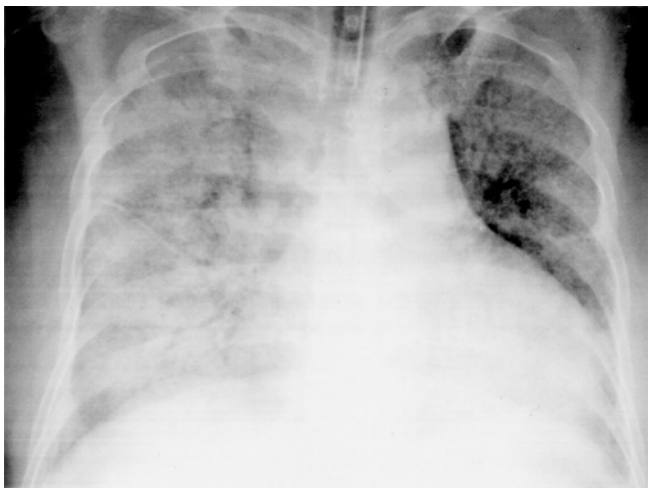

Figure 2. Chest radiograph on the sixth hospital day demonstrating bilateral diffuse air-space disease.

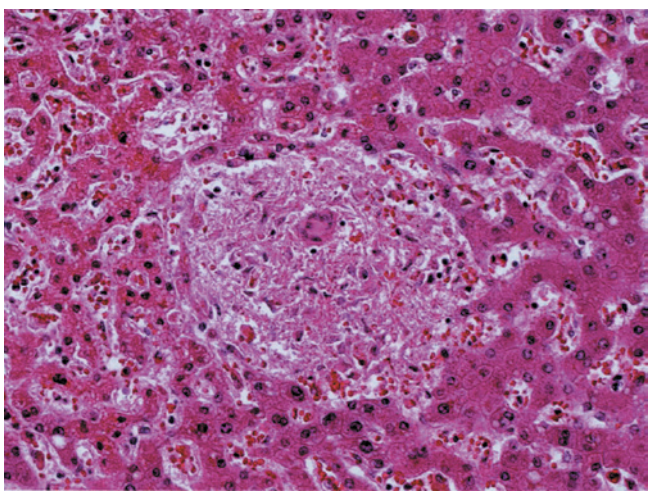

Figure 3. Tuberculous granuloma with a Langhans' giant cell in the liver (HE stain, ×100).

(2), the lungs were not affected by miliary tuberculosis in 14 of 100 autopsied cases of late generalized tuberculosis. In another review, pulmonary involvement was not observed in 3 of 34 autopsied cases of disseminated tuberculosis (3). These lung-negative cases pose diagnostic difficulties since characteristic radiographic abnormalities are lacking, and sputum bacteriology and transbronchial lung biopsy are unhelpful. In this respect, biopsy of the liver or bone marrow is recommended in reaching a diagnosis (3, 4). In fact, our patient's sternal bone marrow aspirate did contain non-caseating granulomas, which were reported to be positive for acid-fast bacilli after her death. Miliary tuberculosis is known to be associated with acute respiratory distress syndrome (5, 6).

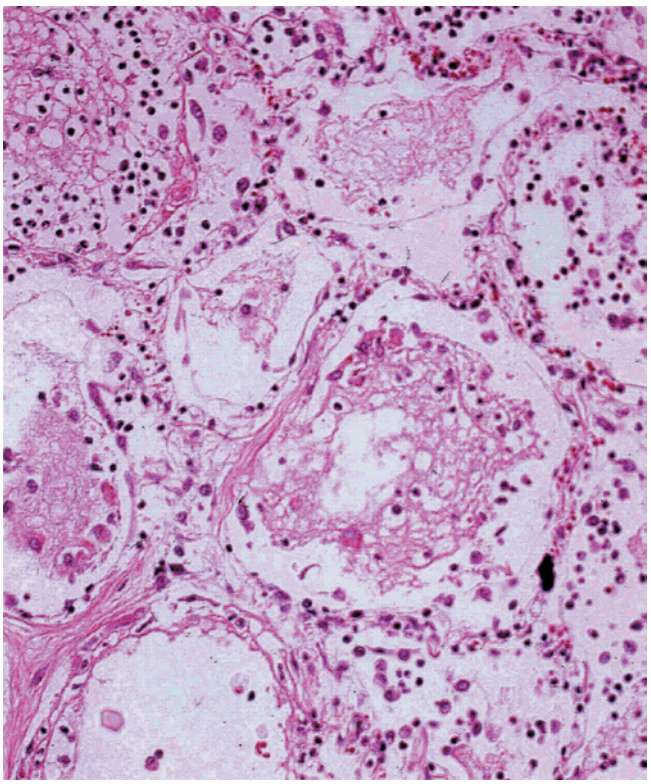

Figure 4. Alveoli filled with dense exudative material consisting of inflammatory cells and fibrin (HE stain, ×100).

In all the reported cases of this association, unlike the present case, miliary tubercles were present in the lungs and were considered the causal factor of acute respiratory distress syndrome. It is likely that our patient developed acute respiratory distress syndrome secondary to the extensive tissue damage due to extrapulmonary miliary tuberculosis.

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