

[CASE REPORT]

Deep Sternal Wound Tuberculosis with Hypo-gamma-globulinemia

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Abstract:

A 44-year-old man was referred to our hospital for the treatment of a pulmonary and deep sternal wound tuberculosis infection, which is an extremely rare type of extrapulmonary tuberculosis. Laboratory testing revealed a serum immunoglobulin (Ig) G level of 286 mg/dL, IgA of 22 mg/dL and IgM of 13 mg/dL. We therefore diagnosed him with hypo-gamma-globulinemia. He was treated with anti-tuberculosis medications and intravenous immunoglobulin. At present, the tuberculosis has not relapsed in the past six years. It may be useful to assess the humoral immunity status in tuberculosis patients with a normal T cell function, and immunoglobulin therapy may be beneficial for protecting such patients from reactivation of tuberculosis.

Key words: deep sternal wound tuberculosis, extrapulmonary tuberculosis, hypo-gamma-globulinemia, humoral immunity, immunoglobulin therapy

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Introduction

Tuberculosis infection is a public health problem worldwide (1), and the incidence of tuberculosis remains higher in Japan than in other developed countries (2). As immunosuppressive therapy and human immune deficiency virus (HIV) infection have become more common, more patients are now at risk of extrapulmonary tuberculosis. Deep sternal wound tuberculosis infections after cardiac surgery are an extremely rare type of extrapulmonary tuberculosis (3-6). Common pathogens of deep wound infection after cardiac surgeries are *Staphylococcus aureus*, *Escherichia coli* and *Enterobacter* spp. (6). Only 15 patients with deep sternal wound tuberculosis after cardiac surgery have been reported worldwide (6). While tuberculosis patients have received attention for their cell-mediated immunity status (7), humoral immunity dysfunction, such as hypo-gamma-globulinemia, in tuberculosis protection has not been described.

We herein report a case of pulmonary and deep sternal wound tuberculosis, which is an extremely rare type of extrapulmonary tuberculosis, with hypo-gamma-globulinemia.

Case Report

A 44-year-old man was admitted to a community hospital with an ulcer on a sternotomy wound. He had undergone aortic valve replacement for infective endocarditis for which no pathogen had been identified the previous year. A sternal ulcer with pus was observed, and he was diagnosed with a deep sternal wound infection. Chest computed tomography (CT) at the time revealed tree-in-bud pattern opacities in the bilateral upper lobe (Fig. 1). His sputum smear findings for acid-fast bacilli (AFB) and commercial polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* were positive. He was transferred to our hospital for the management of sputum smear-positive *M. tuberculosis*. Notably, his medical history included pneumococcal meningitis twice when he

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Figure 1. Chest computed tomography showed a tree-in-bud appearance and micronodules in the bilateral lungs.

was 41 and 42 years of age. He had no personal, social or family history of tuberculosis. This patient had no risk factors for tuberculosis.

He presented with productive cough. There was no history of night sweats or weight loss. On an examination, he appeared ill and had a fever of 38.0°C. His oxygen saturation was 98% on ambient air. There were no palpable cervical lymph nodes. His cardiovascular examination revealed a soft systolic murmur at the apex. A pulmonary examination demonstrated coarse crackles bilaterally. A sternal ulcer with pus was observed. Laboratory testing revealed a white blood cell count of 18,400 per mm³, lactate dehydrogenase of 321 IU/L and C-reactive protein of 13.1 mg/dL (Table). Chest radiograph showed micronodules in the bilateral lungs.

On the 1st hospital day, he was prescribed 4 anti-tuberculosis medications (isoniazid 300 mg, rifampicin 450 mg, ethambutol 750 mg, and pyrazinamide 1.2 g per day). On the 7th hospital day, he underwent surgery for the deep sternal wound infection and started negative pressure wound therapy, which promotes wound healing by removing fluid from open wounds. After being treated with anti-tuberculosis medications, the tree-in-bud appearance disappeared (Fig. 2). Not only his sputum culture but also his infected site culture showed that the patient was positive for *M. tuberculosis*, and the diagnosis of pulmonary and deep sternal wound *M. tuberculosis* was later confirmed. He had an uneventful post-operative course during his hospital stay. The patient became smear-negative on the 31st day after admission and was discharged from the hospital. He was treated with 4 anti-tuberculosis medications for 2 months, followed by 2 anti-tuberculosis medications (isoniazid 300 mg and rifampicin 450 mg per day) for 4 months.

Given the high incidence of infectious diseases (i.e. pneumococcal meningitis, infective endocarditis and tuberculosis), we assessed the presence of immunodeficiency diseases. Anti-human immunodeficiency virus (HIV) antibodies were negative. The serum level of immunoglobulin (Ig) G was 286 mg/dL, IgA was 22 mg/dL and IgM was 13 mg/dL. A flow cytometry analysis of peripheral blood lymphocytes showed the percentage of B cells to be 1.7%. Electrophoresis of serum protein showed a decreased gamma-globulin fraction of 5.1% (Table). The bone marrow was

normal, and there was no evidence of malignancy in this case. Given these findings, we diagnosed the patient with hypo-gamma-globulinemia. To prevent the recurrence of infectious diseases, the patient was treated with intravenous human immunoglobulin therapy by a monthly 3-day course (300 mg/kg/day), which kept the serum immunoglobulin within the therapeutic range (around 600 to 800 mg/dL) (8). The patient followed an uneventful course and has been free of recurrence of infectious diseases for six years.

Discussion

Based on his histories of severe bacterial infection and tuberculosis, we measured the serum Ig levels in this patient and diagnosed him with hypo-gamma-globulinemia. Antibodies are essential for protection against *Streptococcus pneumoniae*, a common pathogen of bacterial meningitis, as in the present case. This is compatible with the fact that this patient had hypo-gamma-globulinemia.

We noted two important clinical issues concerning the present patient. First, it might be beneficial to assess the humoral immunity as well as the cell-mediated immunity status in tuberculosis patients. Second, immunoglobulin therapy in patients with hypo-gamma-globulinemia might help protect against the reactivation of tuberculosis.

Cell-mediated immunity is known to contribute to immunity against *M. tuberculosis*. Patients with HIV infection or who have been treated with anti-tumor necrosis factor- α monoclonal antibodies are at an increased risk to contract tuberculosis (7, 9). Although the role of B cells and antibodies in the defense against tuberculosis has not been described in detail, some cases have shown that a lack of anti-tuberculosis antibodies increases the risk of extrapulmonary tuberculosis. A case of endobronchial tuberculosis in X-linked agammaglobulinemia with intact cell-mediated immunity has been reported (10). Tuberculosis also developed in a patient with autosomal recessive hyper-IgM syndrome, which is characterized by an impaired humoral immunity. Children with humoral immune deficiency harboring defective antibodies against lipoarabinomannan appear to have an increased risk of disseminated tuberculosis (11). A recent study showed that the IgA antibody titers against *M. tuberculosis* were associated with the status of tuberculosis patients (12). These reports suggest that humoral immune deficiency might increase the risk of developing tuberculosis. Some reports have revealed the mechanisms underlying the antibody activity to protect against tuberculosis. Antibodies against surface-expressed antigens opsonize tuberculosis and promote the Fc receptor-mediated phagocytosis of tuberculosis (13). Antibodies against tuberculosis augment the cell-mediated immunity through the activation of T cells, antigen presentation to CD4+ T cells and increased secretion of IL-12 and tumor necrosis factor (TNF)- α (14). Because tuberculosis is likely to develop in patients with an immunosuppressed status, tuberculosis patients should have not only their cell-mediated immunity but also their humoral immu-

Table. Laboratory Data on Admission.

WBC	18.4×10 ³ /μL	TP	6.4 g/dL	IgG	286 mg/dL
Neutro	69.3 %	Alb	4.3 g/dL	IgA	22 mg/dL
Lymph	20.3 %	T.Bil	0.74 mg/dL	IgM	13 mg/dL
Mono	8.5 %	AST	29 IU/L	Serum protein	
Eosi	1.7 %	ALT	27 IU/L	Alb	4.11 g/dL
Baso	0.2 %	LDH	321 IU/L	α1	0.19 g/dL
Hb	12.9 g/dL	γ-GTP	70 IU/L	α2	0.45 g/dL
Plt	40.4×10 ⁴ /μL	BUN	13 mg/dL	β	0.66 g/dL
peripheral lymphocyte		Cre	0.69 mg/dL	γ	0.29 g/dL
T cell	94.6 %	CRP	13.1 mg/dL	HIV Ab	(-)
CD4+	62.5 %	Na	136 mmol/L	HCV Ab	(-)
CD8+	26.5 %	K	4.5 mmol/L	HBs Ag	(-)
B cell	1.7 %	Cl	100 mmol/L		
		Glucose	107 mg/dL		
		HbA1c	6.1 %		

**Figure 2.** After treatment with anti-tuberculosis medications, the tree-in-bud appearance disappeared.

nity status assessed.

Furthermore, immunoglobulin therapy in patients with hypo-gamma-globulinemia might help prevent the reactivation of tuberculosis. Experimental evidence has demonstrated the crucial role of humoral immunity in the protection against tuberculosis. Some reports have shown that intravenous immunoglobulin administration is protective against progressive tuberculosis in murine models, suggesting the importance of humoral immunity in ensuring tuberculosis protection. The administration of human monoclonal antibodies reduced the dissemination of tuberculosis in mice (15). However, one-quarter of patients developed recurrence of deep sternal wound tuberculosis within two years (6). Since our patient started immunoglobulin therapy, the pulmonary and deep sternal wound tuberculosis has not recurred, and the sternal wires have not needed to be removed. These results suggest that immunoglobulin administration may help protect against tuberculosis infection, especially in patients with humoral immune deficiency.

Recently, a case of refractory chronic wound with X-linked agammaglobulinemia was reported (16). Patients with humoral immunity deficiency develop severe wound infections. The incidence of severe infections is reportedly associated with the concentration of serum immunoglobulin (17).

In the present case, no severe infections occurred after immunoglobulin therapy, suggesting the potential efficacy of such therapy for preventing severe infections.

In conclusion, it might be beneficial in tuberculosis patients to assess the humoral immunity status, and intravenous immunoglobulin therapy might help prevent the reactivation of tuberculosis. Further reports should be accumulated to establish the role of humoral immunity in pulmonary tuberculosis and the efficiency of immunoglobulin therapy in preventing tuberculosis and severe wound infection in patients with humoral immunity deficiency.

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

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