Case Report

Efficacy of direct hemoperfusion with a polymyxin B-immobilized fiber column in miliary tuberculosis

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Case: A 75-year-old woman presented with a 10-day history of intermittent fever, general fatigue, and progressive dyspnea. Although she had a low PaO_2/FIO_2 ratio, the cause of acute respiratory distress syndrome was not clear until day 9 in hospital.

Outcome: We treated the patient with direct hemoperfusion with a polymyxin B-immobilized fiber column incidentally; the PaO_2/FIO_2 ratio improved following this therapy. Acid-fast bacilli, which were not seen in the sputum on admission, were detected in cultures from sputum, urine, bone marrow, liver biopsy, and blood samples, with a real-time polymerase chain reaction assay confirming tuberculosis. She was immediately transferred to a specialized tuberculosis hospital, and after a 3-month treatment, was discharged.

Conclusion: Treatment with polymyxin B-immobilized fiber column may provide good results for pulmonary oxygenation in acute respiratory distress syndrome caused by tuberculosis.

Key words: Adjunctive therapy, antituberculosis therapy, ARDS, PMX-DHP, tuberculosis

INTRODUCTION

TUBERCULOSIS REMAINS ONE of the major health concerns worldwide. In 2014, an estimated 9.6 million individuals developed tuberculosis, and 1.5 million died from the disease.[1] Moreover, miliary tuberculosis, which is caused by the hematogenous spread of *Mycobacterium tuberculosis*, accounts for approximately 1–2% of all tuberculosis cases, with a mortality rate of roughly 15–30%.[2] Conversely, although acute respiratory distress syndrome (ARDS) is less frequently complicated by tuberculosis (approximately 1%),[3] the mortality rates of ARDS due to tuberculosis are 60–90%.[4]

Here, we report the first successful application of direct hemoperfusion with a polymyxin B-immobilized fiber column (PMX-DHP) to control ARDS caused by tuberculosis.

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CASE

A 75-YEAR-OLD WOMAN was transferred to our Emergency Department from a nearby hospital with a 10-day history of intermittent fever, general fatigue, and progressive dyspnea. She did not have cough or hemoptysis. She had no history of immunosuppression, contact with a tuberculosis patient, or treatment for tuberculosis. On admission, she presented with the following signs: body temperature, 37.9°C; heart rate, 106 beats/min; blood pressure, 109/80 mmHg; respiratory rate, 23 breaths/min; and coarse inspiratory crackles over the bilateral lower lungs. Laboratory admission tests revealed low platelets, elevated levels of hepatobiliary enzymes and KL-6, and hypoxemia (Table 1). Chest computed tomography revealed a nodule in the apical segment of the left lower lobe and bilateral diffuse ground-glass shadows, which were severe, particularly in the posterior basal segment of the left lower lobe (Fig. 1A and 1B). Because of her severe respiratory condition on admission, bronchoalveolar lavage or histopathological examination could not be carried out. She was managed with non-invasive positive pressure ventilation and treated with piperacillin–tazobactam, azithromycin, and immunoglobulin to address the possibility of a community-acquired

Table 1. Blood analysis on admission of a 75-year-old woman with acute respiratory distress syndrome due to tuberculosis

Cell counts		**Biochemistry**	
WBC	8,600/μL	TP	6.6 g/dL
	(81% neutrophils)	Alb	2.2 g/dL
RBC	408 × 10^4/μL	BUN	18 mg/dL
Hb	12.3 g/dL	Cre	0.9 mg/dL
Hct	35.3%	Na	136 mmol/L
Plt	9.5 × 10^4/μL	K	4.3 mmol/L
Arterial blood gas analysis with supplementary oxygen (10 L/min) through a mask		Cl	102 mmol/L
pH	7.48	T. Bil	8.3 mg/dL
$PaCO_2$	27.8 mmHg	AST	276 IU/L
PaO_2	60.2 mmHg	ALT	228 IU/L
HCO_3^-	20.8 mmol/L	LDH	1,069 IU/L
Base excess	−1.3 mmol/L	ALP	1,840 IU/L
		γ-GTP	709 IU/L
		CRP	12.5 mg/dL
		Endotoxin	<2 pg/mL
		(1-3)-β-D-glucan	<6 pg/mL
		KL-6	3,034 U/mL

γ-GTP, γ-glutamyl transpeptidase; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cre, creatinine; CRP, C-reactive protein; Hb, hemoglobin; Hct, hematocrit; KL-6, Krebs von den Lungen 6; LDH, lactase dehydrogenase; Plt, platelet; RBC, red blood cells; T. Bil, total bilirubin; TP, total protein; WBC, white blood cells.

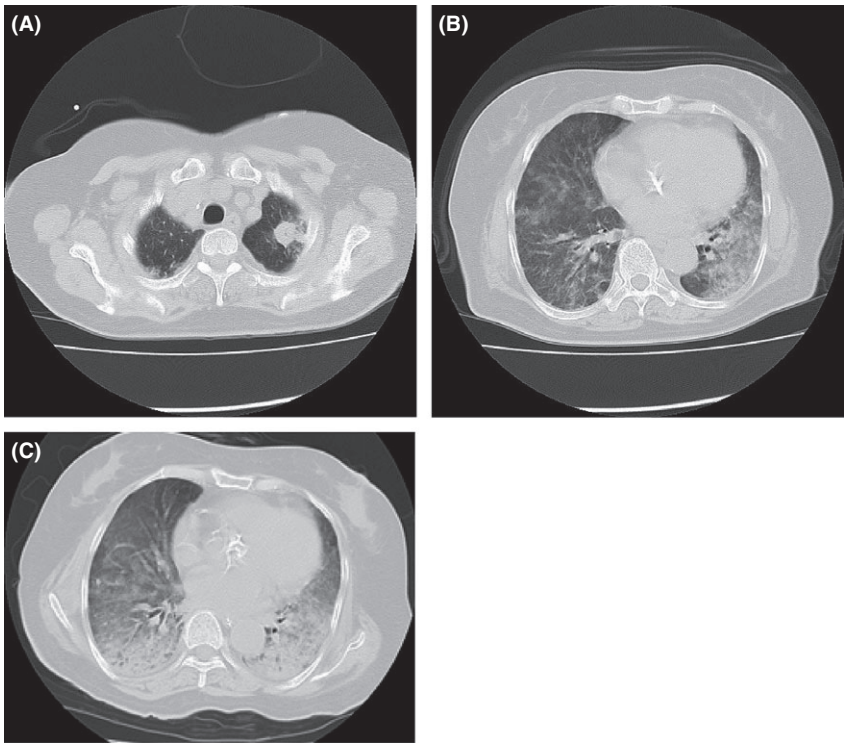

Fig. 1. Chest computed tomography in a 75-year-old woman with acute respiratory distress syndrome due to tuberculosis. A,B The image taken on admission shows a nodule in the apical segment of the left lower lobe and bilateral diffuse ground-glass shadows, which were particularly severe in the posterior basal segment of the left lower lobe. C, The image taken on hospital day 6 shows diffuse ground-glass shadows in the posterior basal segment of the bilateral lower lobe, which were worse compared with the findings on admission.

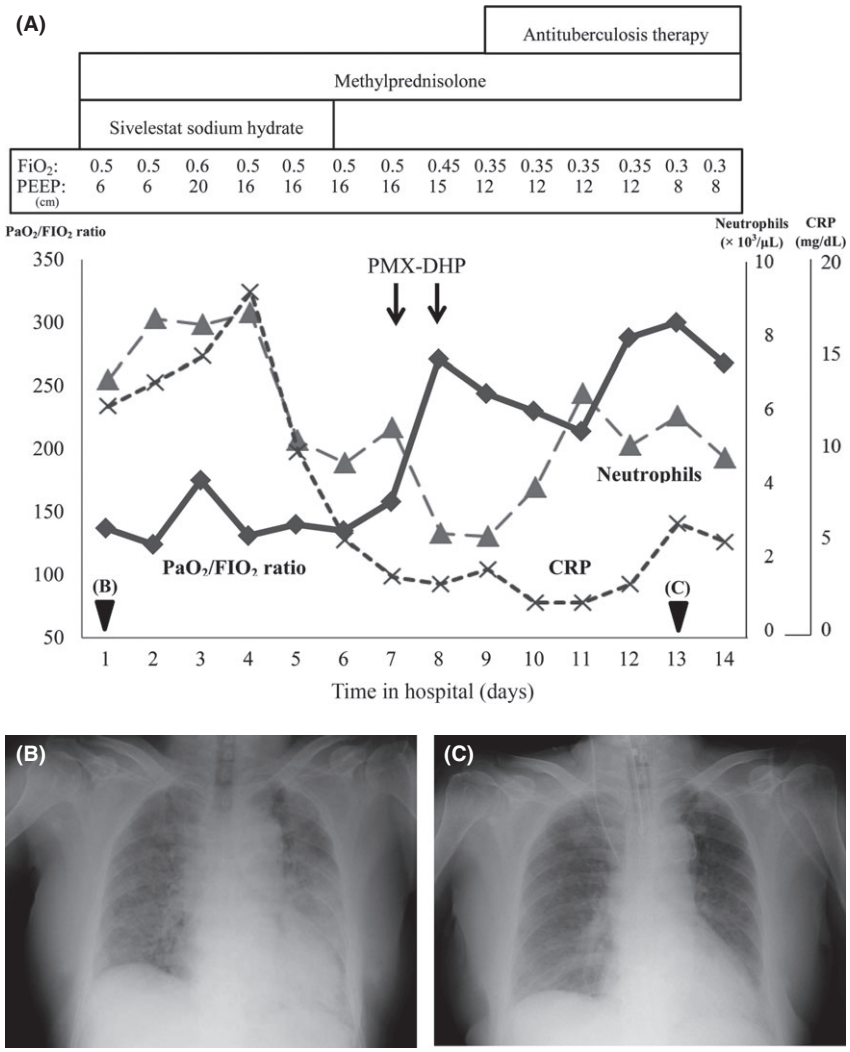

Fig. 2. A, Clinical course of the PaO_2/FiO_2 ratio, C-reactive protein (CRP) levels, neutrophil count, treatment, ventilator settings, and chest X-ray findings (black arrowheads) of a 75-year-old woman with acute respiratory distress syndrome due to tuberculosis. Direct hemoperfusion with a polymyxin B-immobilized fiber column (PMX-DHP) likely initiated fast improvement of the PaO_2/FiO_2 ratio before initiation of antituberculosis therapy. In addition, neutrophils decreased after PMX-DHP. PEEP, positive end expiratory pressure. B, Chest X-ray showing the presence of bilateral diffuse interstitial infiltrates on admission. C, Chest X-ray findings greatly improved on day 13 in hospital.

pneumonia. Furthermore, a diagnosis of moderate ARDS was established based on the ratio of PaO_2/FIO_2 (P/F) being 137,[5] with no evidence of left atrial hypertension, as determined by ultrasonic cardiography. Therefore, sivelestat sodium hydrate (0.2 mg/kg/h) and low-dose methylprednisolone (1 mg/kg/day) were given. However, her condition worsened, and invasive mechanical ventilation was initiated on hospital day 2. In addition, pancytopenia occurred on day 6. As we suspected that the pancytopenia was drug-induced, the antibiotics were changed from piperacillin–tazobactam to biapenem, and sivelestat sodium hydrate was discontinued. Despite aggressive fluid management and treatment with broad-spectrum antibiotics, there was no improvement in respiratory function for 1 week. As the KL-6 values were elevated on admission and diffuse ground-glass shadows worsened, as indicated by chest computed tomography on day 6 (Fig. 1C), we suspected acute interstitial pneumonia, and PMX-DHP was given at a flow rate of 80 mL/min for 24 h once daily for 2 days from hospital day 7 without continuous renal replacement therapy. Following this treatment, the P/F ratio improved to over 200 (Fig. 2A), and the levels of inflammation-related

Table 2. Changes in inflammation-related substances before and after treatment using direct hemoperfusion with a polymyxin B-immobilized fiber column in a 75-year-old woman with acute respiratory distress syndrome due to tuberculosis

Variable	Before (hospital day 7)	After (hospital day 9)
HMGB-1, ng/mL (normal range, 1.61–1.69)	5.3	4.2
MMP-9, ng/mL (normal range, 1.3–12.1)	19.8	14.6
Soluble interleukin 2 receptors, U/mL (normal range, 124–466)	12,900	11,000

HMGB-1, high mobility group box-1; MMP-9, matrix metalloproteinase-9.

substances, including neutrophils, in blood decreased (Table 2, Fig. 2A). Acid-fast bacilli, which were not detected in sputum collected for examination on admission, were detected in cultures from sputum, and a real-time polymerase chain reaction assay confirmed the presence of *M. tuberculosis* DNA on the hospital day 9. We then recognized that PMX-DHP was incidentally used for tuberculosis-related ARDS. Antituberculosis therapy (isoniazid, rifampicin, and streptomycin) was immediately initiated, and the patient was transferred to a hospital specialized in treating tuberculosis. Cultures from the sputum, urine, bone marrow specimens, liver biopsy specimens, and blood samples (these cultures were collected on day 9 or 10 in hospital) later established the presence of *M. tuberculosis*, thus confirming miliary tuberculosis. Despite the P/F ratio improvement, KL-6 levels of 5,442 U/mL, which were high compared with the data on admission, were recognized on day 14 in hospital. Although the patient was still severely ill at the time of hospital transfer, she was discharged after the 3-month in-hospital treatment for tuberculosis.

DISCUSSION

ALTHOUGH ARDS CAUSED by tuberculosis is uncommon, it is associated with a high mortality rate.[4] Early administration of antituberculosis therapy is as important as with other infectious diseases, and delays in the diagnosis of tuberculosis and initiation of antituberculosis therapy may worsen the outcome.[4] However, PMX-DHP likely initiated fast improvement of the P/F ratio before the initiation of antituberculosis therapy in the present case. To our knowledge, there has been no report of PMX-DHP in the treatment of tuberculosis. Initially, PMX-DHP was developed for removing endotoxins from the blood. However, it was also found to be effective in absorbing activated neutrophils and blood matrix metalloproteinase-9 (MMP-9),[6] or high mobility group box-1.[7] Therefore, PMX-DHP was beneficial in patients with not only gram-negative bacterial infections but also acute exacerbation of idiopathic pulmonary fibrosis.[6,7] Matrix metalloproteinase-9 is an inducible enzyme produced mainly by mononuclear phagocytes and stimulated neutrophils, and its elevation is affected by the augmentation of synthesis and/or secretion of this enzyme by inflammatory cells in response to infections.[8] Therefore, MMP-9 was reported to be a marker for estimating the activity of pulmonary tuberculosis.[8] Furthermore, MMP-9 was reported to critically contribute to lung tissue damage in ARDS,[8] and MMP-9 levels were shown to be well correlated with improvement of the P/F ratio in ARDS patients.[9] In the present case, the blood levels of various inflammation-related substances, included MMP-9, were decreased after PMX-DHP. Because of a slight reduction in these substances, details of the mechanisms by which PMX-DHP improves gas exchange in the tuberculosis patient could not be clearly shown. Alternatively, the adsorption function of PMX-DHP for other cytokines and/or chemokines that could not be evaluated in the present study might have contributed to the improvement of gas exchange in tuberculosis. Although the optimal treatment duration with PMX-DHP is unclear, a recent study reported that a longer duration of PMX-DHP could be safe and effective for improving the hemodynamics and pulmonary oxygenation capacity.[10] In the present case, the tuberculosis patient was treated with PMX-DHP for 48 h in total, and there were beneficial effects in terms of improved P/F ratio and no adverse events of PMX-DHP, similar to previous reports.

CONCLUSION

POLYMYXIN B-IMMOBILIZED fiber column may be a useful adjunctive therapy in the treatment of tuberculosis patients with ARDS, which has a high mortality rate.

CONFLICT OF INTEREST

NONE DECLARED.

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