INTERNAL MEDICINE

□ CASE REPORT □

A Case of Successful Treatment with Polymyxin B-immobilized Fiber Column Direct Hemoperfusion in Acute Respiratory Distress Syndrome after Influenza A Infection

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Abstract

We report a case of acute respiratory distress syndrome (ARDS) after influenza A infection who was successfully treated with combined treatment including direct hemoperfusion with polymyxin B-immobilized fiber (PMX-DHP) column. A 56-year-old Japanese man was admitted to our hospital in January 2010 because of progressive dyspnea, hypoxemia, fever and bilateral diffuse infiltration on chest radiograph after pandemic influenza A infection. His chest computed tomography showed diffuse and patchy bilateral ground-glass opacities, and we diagnosed ARDS after influenza A infection. The patient was successfully treated with PMX-DHP in addition to the treatment with oseltamivir, corticosteroid, sivelestat and antibiotics with mechanical ventilation, and the patient recovered with only minor pulmonary fibrotic change. Although the efficacy of PMX-DHP treatment in patients with acute lung injury (ALI)/ARDS after influenza virus infection is not well established, this treatment could be a possible therapeutic modality in treating the patients with this disease.

Key words: acute respiratory distress syndrome, influenza A, polymixin B-immobilized fiber, acute lung injury, PMX-DHP

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Introduction

Influenza A virus infection can occasionally cause acute lung injury and acute respiratory distress syndrome (ALI/ARDS), and high mortality has been seen in those patients with severe respiratory failure (1-3). Treatment of influenza A infection-related severe respiratory failure usually consists of antiviral agents (oseltamivir phosphate, zanamivir and amantadine hydrochloride), intensive respiratory management including mechanical ventilation or extracorporeal membrane oxygenation and high-dose corticosteroid (4). Recently, the efficacy of direct hemoperfusion with polymyxin B-immobilized fiber (PMX-DHP) column in patients with ALI/ARDS due to several causes has been reported (5-7), including pandemic H1N1 influenza A infection (8). Here, we report a case of successfully treated influenza A infection-induced ARDS by combined treatment including PMX.

Case Report

A 56-year-old Japanese man had high-grade fever of approximately 39℃ and a sore throat in December 2009. He was a current smoker (20 packs per year), and he did not receive any exposure to toxic materials, seasonal nor pandemic H1N1 influenza vaccination at least one year prior this situation. High-grade fever (38.8℃) and dyspnea on effort [British Medical Research Council (MRC) dyspnea scale grade 3] developed in December 2009, and he initially visited an internal medicine clinic. Nasal swab showed negative reaction for influenza A and B antigen, and he re-

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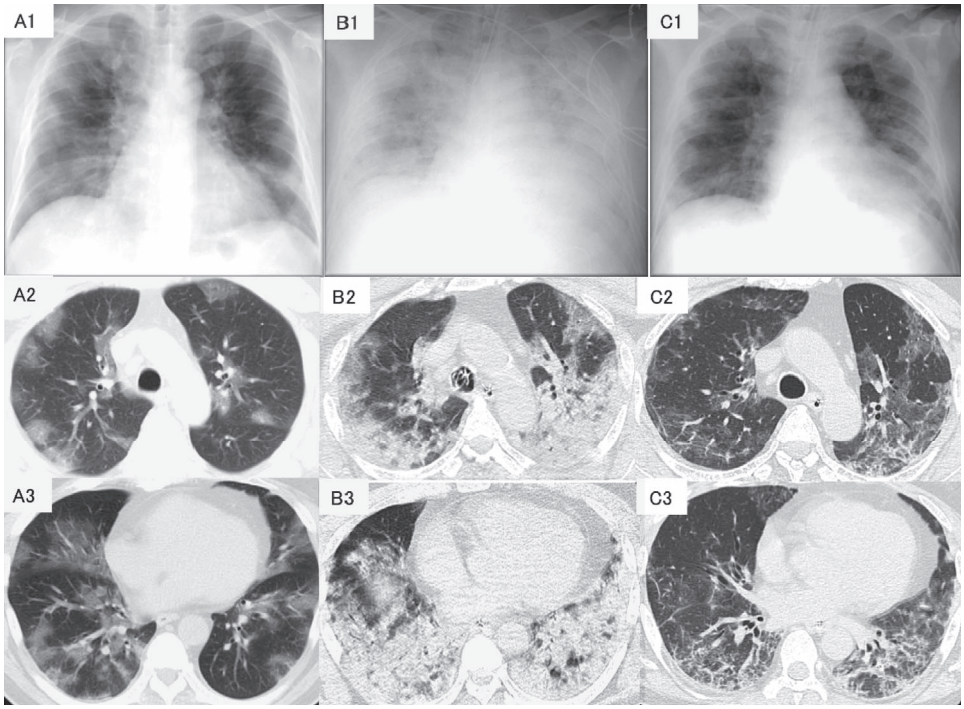

Figure 1. **A: Chest radiograph (A1) and CT (A2 and 3) on the first admission to A hospital, showing patchy ground-glass attenuations in bilateral lungs. B: Chest radiograph (B1) and CT (B2 and 3) on the transfer day to our hospital, showing exacerbated diffuse infiltrates, consolidations and ground-glass attenuations in bilateral lungs. C: Chest radiograph (C1) and CT (C2 and 3) on day 12 after the transfer to our hospital, showing improved radiological findings with patchy ground-glass attenuations in bilateral upper lung fields, and linear and reticular opacities in bilateral basilar lung fields.**

ceived only combination cold remedy. Two days after onset, his symptoms continued and he revisited the same clinic. At that time, his nasal swab revealed a positive result for influenza A antigen. His symptoms of dyspnea and fever were exacerbated (MRC dyspnea scale 5) so that he was admitted to hospital A three days after the initial visit to the clinic, and started to receive antimicrobials (meropenem and ciprofloxacin) without anti-influenza agents. His respiratory failure, chest radiograph and computed tomography (CT) findings (Fig. 1A1-3) worsened. As a result, he was transferred to our university hospital seven days after the initial visit to the clinic. On the first day in our hospital (day 1), his blood pressure was 128/73 mmHg, SpO_2 72% (O_2 15 L/min reservoir mask), pulse rate was 114 beats/min (regular), and body temperature was 39.6℃. Fine crackles were audible in the bilateral lung fields on physical examination. Laboratory findings on the transfer day (Table 1) were as follows: WBC 25,900/mm^3 (neutrophils 94%, lymphocytes 4%, monocytes 2%), AST 46 IU/L, ALT 50 IU/L, Na 130 mEq/L, K 4.6 mEq/L, Cl 95 mEq/L, BUN 15 mg/dL, Cre 0.67 mg/dL, lactate dehydrogenase 671 IU/L; C-reactive protein 28.8 mg/dL; KL-6 3,133 U/mL; surfactant protein-D 404 ng/mL. Arterial gas analysis (reservoir mask 15 L/min) showed severe hypoxemia, hypocarbia and respiratory alkalosis (pH 7.509, PaO_2 39 Torr, and $PaCO_2$ 33.7 Torr). Chest radiograph showed diffuse infiltrates in both lung fields, and also chest high-resolution CT (HRCT) demonstrated bilateral diffuse infiltrates, consolidation and ground-glass attenuations (Fig. 1B1-3). Endotracheal aspirate after intratracheal intubation and blood cultivation indicated no evidence of pulmonary bacterial infection or bacteremia. Rapid influenza tests including nasal swab and endotracheal aspirate were both negative. There were no clues of left heart failure by echocardiography. On the transfer day, mechanical ventilation after intratracheal intubation was applied to his deteriorated respiratory failure, and continuous intravenous administration of dopamine was also applied for the treatment of progressive hypotension. The overall clinical course of the patient is represented in Fig. 2. He was treated with oseltamivir phosphate, high-dose corticosteroid (methylprednisolone 1 g per day for 3 days), sivelestat sodium hydrate, and antibiotics (tazobactam/piperacilin, minocycline and azithromycin). However, levels of P/F ratio and blood pressure decreased in spite of these treatments. Then, polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP) for four hours was applied on the day 2. Detailed clinical course after the application of PMX-DHP is shown in Fig. 3. After the induction of PMX-DHP, his blood pressure elevated and infusion of dopamine could be stopped soon after PMX-DHP treatment, and PaO_2/FiO_2 (P/F) ratio also recovered quickly (Fig. 3). After the intensive treatment, his P/F ratio improved from 168 to 403 with rapid improvement of chest radiograph findings on day 3, and he was successfully weaned from mechanical ventilation on day

Table 1. Laboratory Data on the Transfer Day

Peripheral blood:		Serology:	
WBC	25,900 /mm^3	CRP	28.8 mg/dL
RBC	444×10^4 /mm^3	Influenza A Ab (CF)	1024 X
Hb	13.5 g/dL	Influenza Ag	A/B(-/-)
Hct	38.1 %	Influenza B Ab (CF)	4 X
Plt	28.5×10^4 /mm^3	ANA	<40 X
		RF	14.3 IU/mL
		MPO-ANCA	<10 EU
Biochemistry:		PR3-ANCA	<10 EU
TP	7.0 g/dL	KL-6	3313 U/mL
Alb	2.1 g/dL	SP-D	404 ng/mL
T-bil	1.4 mg/dL	β-D-gulucan	<6.0 pg/mL
AST	46 IU/L	*Mycoplasma pneumoniae* Ab	(-)
ALT	50 IU/L	*Chlamydophila pneumoniae* IgA	(-)
LDH	671 IU/L		
BUN	15 mg/dL	Blood gas analysis	
Cr	0.67 mg/dL	(O_2 reservoir mask 15L/min)	
Na	130 mEq/L	pH	7.509
K	4.6 mEq/L	$PaCO_2$	33.7 mmHg
Cl	95 mEq/L	PaO_2	39 mmHg
		HCO_3	26.2 mmHg
		BE	3.6 mEq/L
		SaO_2	79.9 %

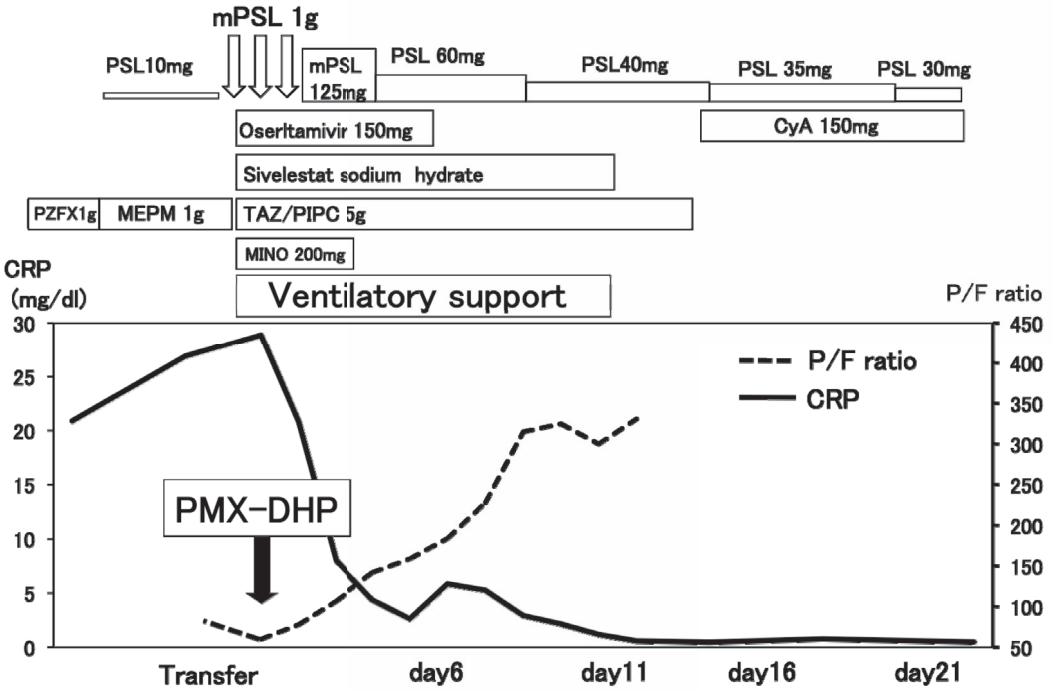

Figure 2. Clinical course of the present case. After the intensive combined treatment including PMX-DHP, he was successfully weaned from mechanical ventilation on day 16. Abbreviations: PSL: prednisolone, mPSL: methylprednisolone, CyA: cyclosporin A, PZFX: pazufloxacin, MEPM: meropenem trihydrate, TAZ/PIPC: tazobactam/piperacillin, MINO: minomycin, PMX-DHP: polymyxin B-immobilized fiber column direct hemoperfusion

16. Chest HRCT on day 12 also demonstrated remarkable improvement of the ground-glass opacities and consolidations (Fig. 1C1-3). Prednisolone (1 mg/kg/day) and cyclosporine A (150 mg/day) was administered orally as a maintenance therapy, and he discharged on day 52 with home oxygen therapy (O_2 1 L/min nasal) that was discontinued two months later.

Discussion

We report a case of successfully treated ARDS due to influenza A with early application of PMX-DHP, oseltamivir phosphate, high-dose corticosteroid and sivelestat sodium with mechanical ventilatory support.

ALI/ARDS is one of the severe and important complica-

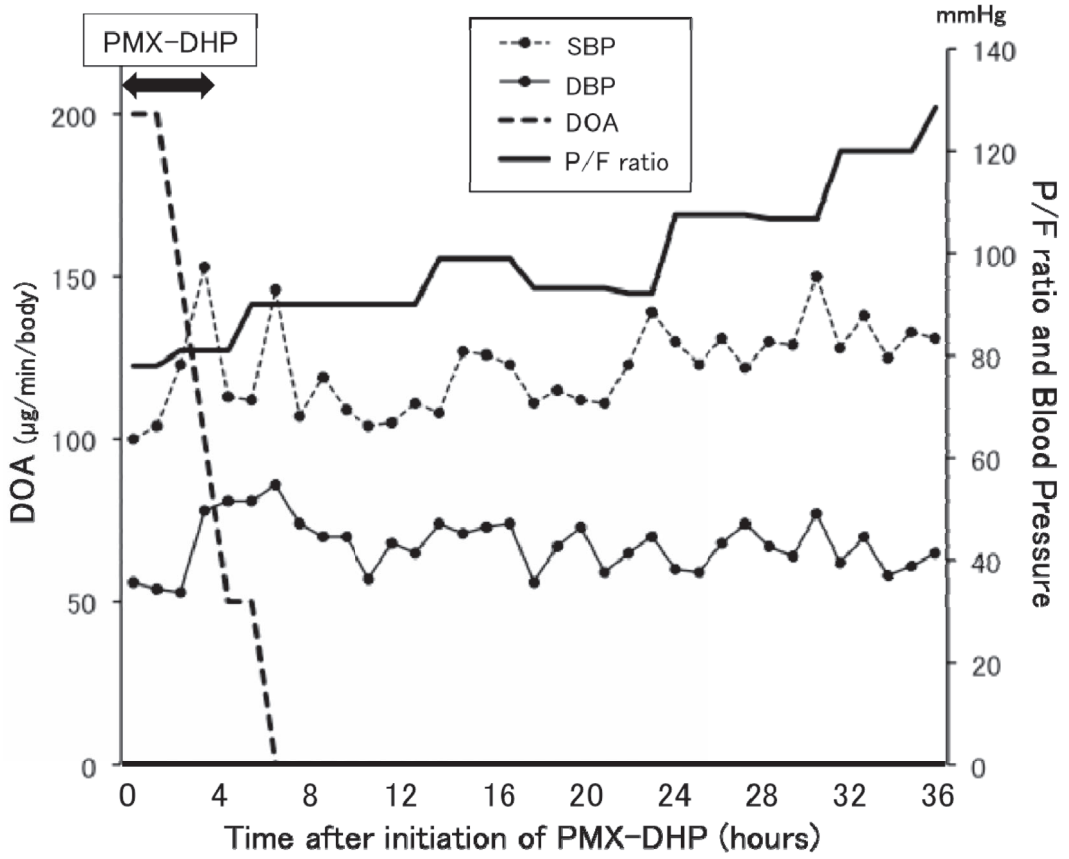

Figure 3. **Detailed clinical course after the initiation of PMX-DHP treatment of the present case. Time 0 represents the time of initiation of PMX-DHP treatment. Blood pressure and PaO_2/FiO_2 (P/F) ratio were improved soon after the PMX-DHP treatment. Abbreviations: SBP: systolic blood pressure, DBP: diastolic blod pressure, DOA: dopamine, P/F ratio: PaO_2/FiO_2 ratio, PMX-DHP: polymyxin B-immobilized fiber column direct hemoperfusion**

tions of pandemic H1N1 influenza 2009, and the morbidity of ALI/ARDS is reported to be higher than seasonal influenza (9). In this report, high percentages of hospitalized cases showed severe conditions, with more than 30%, mostly adults, requiring intensive care, with 11% mortality rate mostly due to viral pneumonia and ARDS. Hospitalized persons aged fifty years old or older with pandemic H1N1 influenza A infection had high mortality in spite of the lower hospitalization rates. In relation to morbidity of ALI/ARDS and mortality of pandemic H1N1 2009 influenza, it is reported that 1.6% of H1N1 influenza cases received intensive care, and the mortality was 0.77% of all H1N1 cases in Greece (10), and the reported mortality rate in H1N1 cases with ARDS was 16.6% in Ecuador (1). In the present case, even though the direct evidence of pandemic H1N1 influenza infection was not confirmed, this case was considered to be infected with pandemic H1N1 2009 influenza. The reason supporting this fact is that almost all cases infected with influenza A were pandemic H1N1 epidemiologically in Japan from 19th to 51st week of 2009, according to the report from National Institute of Infectious Diseases Infectious Disease Surveillance Center, Japan (http://idsc.nih.go.jp/disease/swine_influenza_e/idsc_e2009/09idsc27e.html).

We applied the early PMX-DHP treatment on day 2 for the present patient, and a rapid improvement of gas exchange, hemodynamic status and radiographic findings was obtained (Figs. 1-3). In a report comparing survivors and non-survivors in 38 patients with ARDS due to pneumonia, application of PMX-DHP significantly improved the PF ratio, HR and systolic blood pressure in the survivors compared to the non-survivors (11). Early induction of PMX-DHP is indicated for directly induced ARDS or respiratory failure in patients with sepsis (12). Improvement of circulatory disturbance and oxygenation despite the underlying diseases was also reported in ARDS patients treated with PMX-DHP, and compared with that before induction of PMX-DHP, the mortality at day 30 improved from approximately 80% to 20% (5). Some reports have described the mechanism of PMX-DHP in ALI/ARDS, and the estimated mechanisms are neutrophil absorption (6), improvement of hypercytokinemia (13), reduction of endotoxin, high mobility group box-1 protein, and oxidative stress (14). It is implicated that the cases with ALI/ARDS after influenza infection are favorable candidates of treating respiratory failure with early PMX-DHP. This is because most patients have no remarkable pulmonary underlying disorders that may be related to the favorable outcome of PMX-DHP treatment.

Antiviral treatment was delayed to start on the seventh

day from the onset of the symptom of influenza considering the present case. This delay of anti-influenza treatment may ameliorate the clinical course of influenza virus infection in this case. Some reports show the effectiveness of the neuraminidase inhibitors (oseltamivir or zanamivir) in patients with pandemic H1N1 2009 (15), and, accordingly, current World Health Organization guidance strongly recommends the use of oseltamivir or zanamivir for severe or progressive infection with pandemic H1N1 2009 [World Health Organization: WHO Guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses. August 20, 2009]. Initiation of antiviral therapy within 2 days was significantly associated with a positive outcome compared to receiving antiviral agents more than 2 days after the onset of illness, and also a positive outcome was highly expected with the treatment with antiviral drugs within 2 days of the onset of illness in hospitalized patients with severe pandemic H1N1 2009 (16). In the case of severe respiratory complication, the early application of anti-influenza agents soon after the diagnosis of pandemic H1N1 influenza is reported to be particularly effective (15, 17).

Early administration of high-dose corticosteroid treatment was applied in the present case, and it might have contributed to the favorable outcome. On the other hand, current World Health Organization guidance does not recommend the use of corticosteroid for severe or progressive infection with pandemic H1N1 2009. However, it does describe the occasional usage of corticosteroid as an adjunctive therapy for the treatment of ARDS in severe influenza virus infection due to their potentially immunomodulatory properties for virus-mediated cytokine dysregulation (13, 18). In ARDS patients with pandemic H1N1 influenza, corticosteroid treatment was well tolerated and it mostly promised substantial improvement in ALI, multiorgan dysfunction scores and low hospital mortality (4). We also used cyclosporine as an additional option to high-dose corticosteroid for the treatment of ALI/ARDS, according to the several reports showing beneficial effects of cyclosporine in the management of acute exacerbation of idiopathic pulmonary fibrosis (19).

In summary, we report a case of successfully treated ARDS after pandemic H1N1 influenza A infection with early PMX-DHP treatment in combination with oseltamivir phosphate, high-dose corticosteroid, sivelestat sodium and ventilatory support. In conclusion, we speculate that early application of PMX-DHP treatment may contribute to the treatment of ALI/ARDS caused by influenza infection.

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

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