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A pilot study: a combined therapy using polymyxin-B hemoperfusion and extracorporeal membrane oxygenation for acute exacerbation of interstitial pneumonia

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Abstract. *Background:* Direct hemoperfusion with polymyxin B-immobilized fiber (PMX-DHP) might be beneficial for treating acute exacerbation (AE) of interstitial pneumonia (IP). Venovenous extracorporeal membranous oxygenation (VV-ECMO) is an emerging tool to avoid ventilator-induced lung injury. This is a report presenting the first three patients with AE of IP treated with a combined therapy of PMX-DHP and VV-ECMO. *Case presentation:* Patient 1 was a 68-year-old male with acute interstitial pneumonia, patient 2 a 67-year-old male with AE of idiopathic pulmonary fibrosis, and patient 3 a 61-year-old female with AE of collagen vascular disease-associated interstitial pneumonia. All patients were severely hypoxemic and required mechanical ventilation. A combined therapy using PMX-DHP and VV-ECMO was initiated with support of intravenous corticosteroids and antibiotics. Radiological findings, oxygenation and laboratory findings markedly improved and all patients survived without severe complications. *Conclusion:* A combined therapy of PMX-DHP and VV-ECMO might be a therapeutic option for AE of IP. *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 343-349)*

Key words: lung-protective ventilation, acute respiratory failure, fibrosis, KL-6

List of abbreviations

ABG	arterial blood gas analysis
AE	acute exacerbation
AE-IP	acute exacerbation of interstitial pneumonia
AIP	acute interstitial pneumonia
ARDS	acute respiratory distress syndrome
BAL	brochoalveolar lavage
CPAP	continuous positive airway pressure
CRP	C-reactive protein
CVD-IP	collagen vascular disease-associated interstitial pneumonia
DAD	diffuse alveolar damage
HLA	human leukocyte antigen
HRCT	high-resolution computed tomography
ICU	intensive care unit
IL	interleukin
IP	interstitial pneumonia
IPF	idiopathic pulmonary fibrosis
LDH	lactate dehydrogenase
MCP	monocyte chemoattractant protein
MCTD	mixed connective tissue disease
MMP	matrix metalloproteinase
PEEP	positive end expiratory pressure
P/F	PaO_2/F_1O_2
PMX-DHP	direct hemoperfusion with polymyxin B-immobilized fiber
PS	pressure support
VILI	ventilator-induced lung injury
VV-ECMO	venovenous extracorporeal membranous oxygenation

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Introduction

Although the clinical course of interstitial pneumonia (IP) is usually chronic, some patients may experience acute worsening, termed acute exacerbation (AE) (1-3). Whereas AE of idiopathic pulmonary fibrosis (IPF) is the most common form, AE can occur in other types of IP (4). Diffuse alveolar damage (DAD) is the pathological characteristic of AE of IP (AE-IP) (3,5). AE-IP is defined by acute worsening of symptoms, the presence of new ground glass abnormalities on chest computed tomography, and the absence of identifiable causes including infection, left heart failure or pulmonary embolism (2). The prognosis of AE-IP is very poor, usually leading to death within a few weeks to months (1-3). Although high-dose corticosteroid therapy is widely used, its efficacy is still limited (2).

Direct hemoperfusion with polymyxin B-immobilized fiber (PMX-DHP) was originally developed as an adjuvant treatment for septic shock by the adsorption of endotoxins (6-8). Recent reports suggested that PMX-DHP therapy may improve oxygenation and the systemic inflammation in patients with AE-IP (9). However, its efficacy is still limited and has not been validated.

Mechanical ventilation may cause acute lung injuries, termed ventilator-induced lung injury (VILI). In particular, mechanical ventilation with high driving pressure may worsen chronic fibrotic lung conditions. Venovenous extracorporeal membranous oxygenation (VV-ECMO) is an emerging device that enables sufficient oxygenation and minimizes the VILI by reducing mechanical stresses to the lung. VV-ECMO has been successfully used for patients with severe acute respiratory distress syndrome (ARDS) that did not respond to conventional ventilator management (10).

We attempted to augment the efficacy of PMX-DHP by assisting with VV-ECMO, which might be useful for minimizing VILI and accelerating alveolar healing in ventilated patients with AE-IP. We developed a treatment protocol for patients with AE-IP who were refractory to conventional management. A combined treatment of PMX-DHP and VV-ECMO was introduced in addition to a traditional regimen including corticosteroids and other adjunct medicine. Presented here are the first three patients with severe respiratory failure due to AE-IP who were treated with this combined therapy.

Case presentation

Patient 1

A 68-year-old Japanese male was admitted to our intensive care unit (ICU) with a rapidly developed dyspnea and dry cough. Fine crackles were audible in the bilateral lung fields. Chest radiograph and high-resolution computed tomography (HRCT) showed newly developed ground glass abnormalities and partial consolidation in both lungs (Figure 1A). There was no obvious honey-combing change. Laboratory findings showed an increase in leukocytes of 17,670/μL (neutrophil 88%), C-reactive protein (CRP) of 6.3 mg/dL, lactate dehydrogenase (LDH) of 415 IU/L and KL-6, a biomarker for IP, of 1,415 U/mL (normal range, <500 U/mL). Arterial blood gas analysis (ABG) showed severe hypoxia (pH, 7.476; PaO_2, 65.9 Torr; $PaCO_2$, 26.6 Torr; HCO_3^-, 19.4 mmol/L, F_IO_2 1.0). The patient was intubated and required mechanical ventilation. Brochoalveolar lavage (BAL) fluid analysis showed an increased total cell count of $2.31x10^5$ /mL with a neutrophil count of 23%, and was negative for culture. Echocardiogram demonstrated no cardiac dysfunction. Malignancies, infections, collagen vascular diseases and other possible underlying diseases of IP were carefully excluded. The diagnosis of AIP was made based on these findings.

In accordance with the protocol, a double lumen catheter was placed into the femoral vein and PMX-DHP (Toraymyxin®; Toray Medical Co,. Ltd., Chiba, Japan) was started for initial 48 hours. The mechanical ventilation was set as a lung rest mode (continuous positive airway pressure [CPAP], F_IO_2 0.4, positive end expiratory pressure [PEEP] at 14 cmH_2O). Two cannula were placed into the internal jugular and femoral veins and VV-ECMO (Capiox®, Terumo Corp., Tokyo, Japan) at a flow rate of 2.5 L/min (F_IO_2 1.0, Sweep gas 2.0 L/min) was initiated. Anticoagulation was maintained with continuous infusion of heparin. As a traditional regimen, high-dose corticosteroids (methylprednisolone 1 g/day for initial 3 days, followed by 1 mg/kg of intravenous prednisone), sivelestat sodium (300

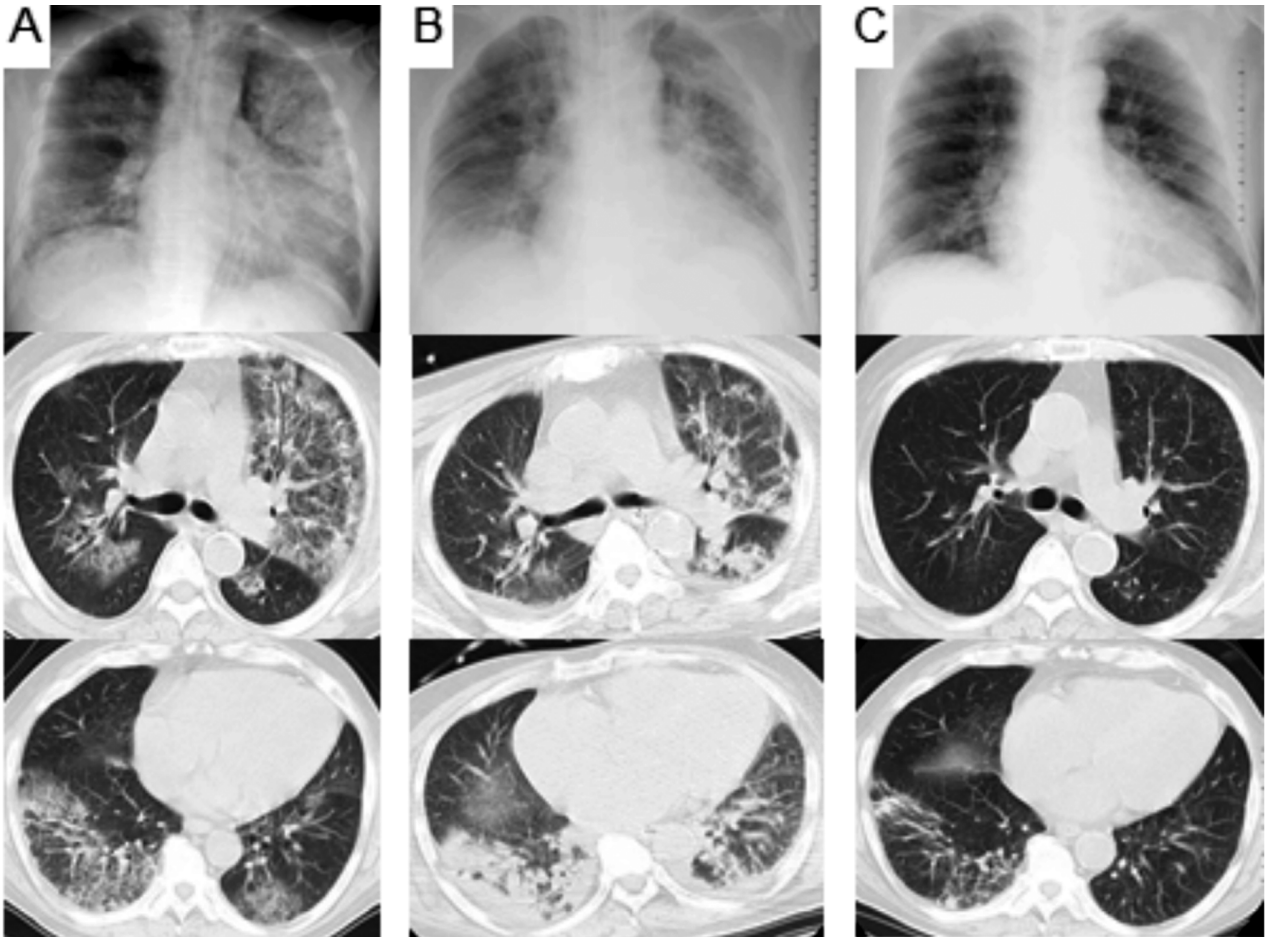

Fig. 1. Chest radiographs and high-resolution computed tomography of patient 1 showing bilateral diffuse ground glass abnormalities and partial consolidation on admission (A), on the 9th day (B) and on the 23th day (C)

mg/day) and antibiotics (intravenous levofloxacin, 500mg/day) were also administered. After starting this combined therapy, leukocyte counts, serum levels of CRP, LDH and KL-6 rapidly decreased (Figure 2), and ABG was improved (pH, 7.467; PaO_2, 129 Torr; $PaCO_2$, 33.9 Torr; HCO_3^-, 24.2 mmol/L) under pressure support (PS) ventilation (F_IO_2, 0.4; PS, 4 cmH_2O; PEEP 4 cmH_2O). The ground glass abnormalities on chest radiographs and HRCT resolved (Figure 1B and C). The patient was successfully weaned from VV-ECMO on the 8th day and extubated on the 12th day post admission. The patient was transported to a long-term care facility on the 27th day and successfully discharged without recurrence 10 weeks later. The patient is still alive during the 31 months of follow-up.

Patient 2

A 67-year-old Japanese male who presented with fever was diagnosed as having IP complicated by bacterial pneumonia at a community hospital. Although he was treated with antibiotics and corticosteroid therapy, the respiratory status deteriorated. The patient was referred to our hospital 2 days later for intensive care management. Chest radiograph and HRCT showed newly developed ground glass abnormalities in both lungs superimposed on the underlying honey-combing change (Figure 3A). Serum LDH and KL-6 level was increased (435 IU/L, 780 U/mL, respectively). ABG showed a severe hypoxemia (pH, 7.442; PaO_2, 61.6 Torr; $PaCO_2$, 34.1 Torr; HCO_3^-, 22.9 mmol/L, F_IO_2 1.0). A cul-

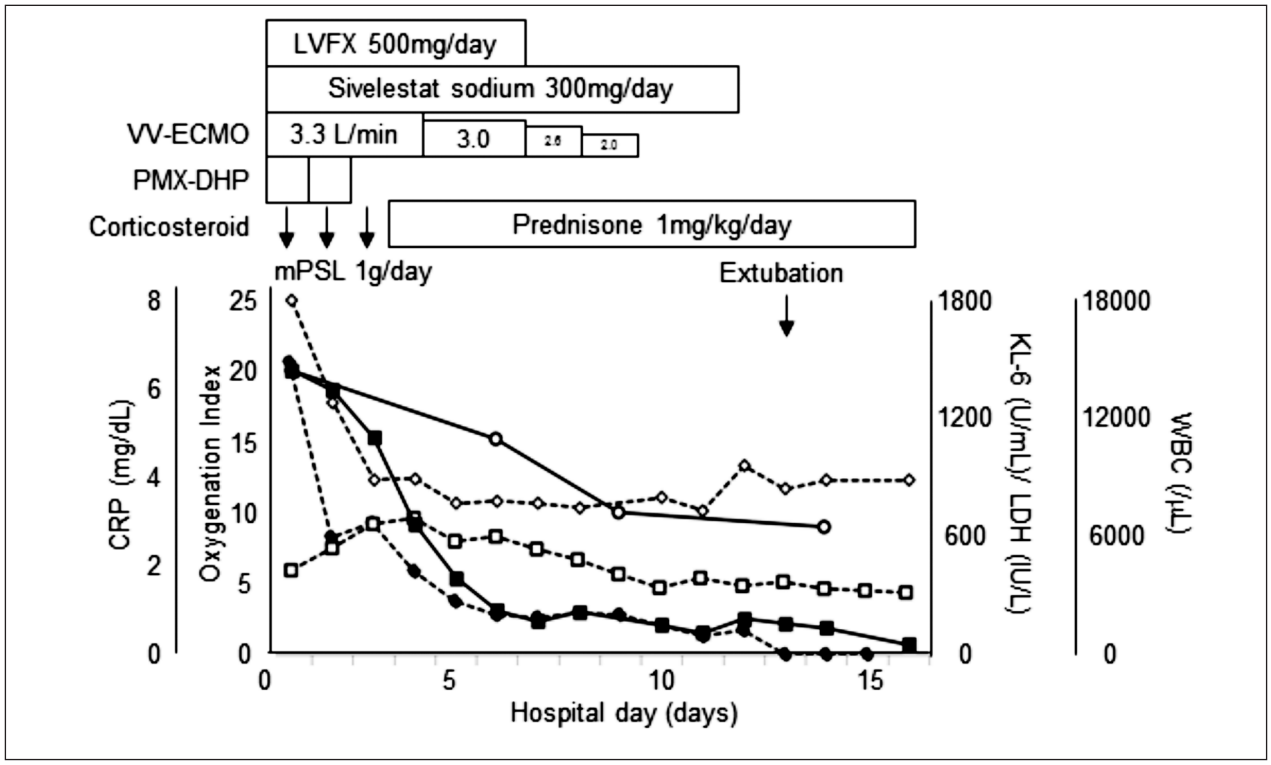

Fig. 2. Clinical course of patient 1. After starting the combined therapy with direct hemoperfusion with polymyxin B-immobilized fiber (PMX-DHP) and venovenous extracorporeal membranous oxygenation (VV-ECMO), oxygenation, leukocyte count in whole blood, serum KL-6, and CRP levels were rapidly improved. After the transient increase, serum LDH levels were also improved. The closed circles indicate oxygenation index, the closed squares indicate serum CRP level, the opened circles indicate serum KL-6 level, the opened squares indicate serum LDH level, and the opened diamonds indicate leukocyte count in whole blood. LVFX, levofloxacin

ture of bronchial aspirates was negative. Based on these findings, a diagnosis of AE of IPF was made.

According to the protocol, PMX-DHP was started for 48 hours. The mechanical ventilation was set as a lung rest mode (CPAP, F_IO_2 0.4, PEEP 8 cmH_2O). VV-ECMO was started at a flow rate of 2.5 L/min (F_IO_2 1.0, Sweep gas 2.0 L/min). As a traditional regimen, high-dose corticosteroids (methylprednisolone 1g/day for initial 3 days, followed by 1 mg/kg of intravenous prednisone), sivelestat sodium (300 mg/day) and antibiotics (intravenous meropenem 3 g/day) were also administered. After starting this combined therapy, significant improvements were observed in oxygenation (pH, 7.460; PaO_2, 106 Torr; $PaCO_2$, 40.9 Torr; HCO_3^-, 28.7 mmol/L; F_IO_2, 0.35; CPAP 6 cmH_2O) and in the radiological abnormalities (Figure 3B). The patient was successfully weaned from VV-ECMO on the 4th day and extubated on the 5th day post admission. The patient was sent back to the community hospital on the 18th day and successfully discharged without recurrence. The patient is still alive during the 19 months of follow-up.

Patient 3

A 61-year-old Japanese female who had mixed connective tissue disease (MCTD) and collagen vascular disease-associated interstitial pneumonia (CVD-IP) since 28 years was transported to our hospital. On arrival, she presented with severe dyspnea, tachypnea, tachycardia and impaired consciousness. Fine crackles were bilaterally audible. Chest radiograph and HRCT showed newly developed ground glass abnormalities in both lungs superimposed on the underlying honey-combing change (Figure 4A). ABG showed a severe hypoxemia (pH, 7.393; PaO_2, 58.0 Torr; $PaCO_2$, 48.8 Torr; HCO_3^-,

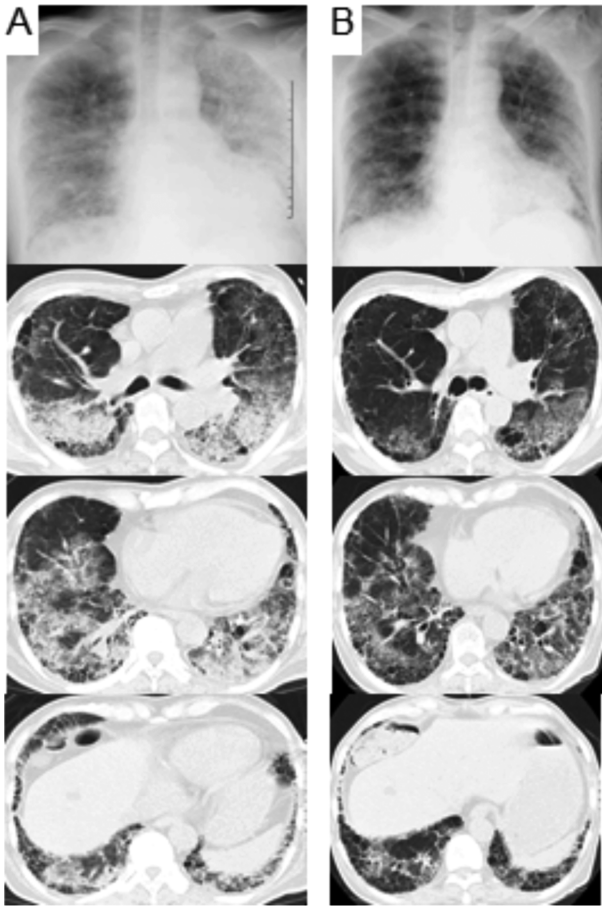

Fig. 3. Chest radiographs and high-resolution computed tomography of patient 2 showing bilateral diffuse ground glass abnormalities superimposed on the underlying honey-combing change on admission (A) and the 12th day (B)

29.1 mmol/L, F_IO_2 1.0). A culture of bronchial aspirates was negative and a diagnosis of AE of CVD-IP was made.

According to the protocol, a combined therapy using PMX-DHP and VV-ECMO was started at a flow rate of 2.5 L/min (F_IO_2 1.0, Sweep gas 2.0 L/min). High-dose corticosteroids, sivelestat sodium (300mg/day) and antibiotics (intravenous meropenem 3g/day and azithromycin 500mg/day for initial 3 days) were also administered. After starting the combined therapy, the oxygenation (pH, 7.364; PaO_2, 84.1 Torr; $PaCO_2$, 45.7 Torr; HCO_3^-, 25.4 mmol/L; F_IO_2, 0.3; CPAP 10 cmH_2O) and the radiological abnormalities were improved (Figure 4B and C). The patient was weaned from VV-ECMO on the 4th day and extubated on the 5th day post admission. The patient was referred to a long-term care facility 42 days later and successfully discharged without recurrence. The patient is still alive during the 15 months of follow-up.

Discussion

This report indicates a potential benefit of the combined therapy with PMX-DHP and VV-ECMO in patients with AE-IP. Little is known about the precise pathogenesis of AE-IP, while numbers of factors including impaired epithelial cell integrity, cellular inflammation, fibrocyte function, cytokine production, coagulation cascades and genetic factors seem to be intricately involved (2). No single medication has been proven to improve survival of patients with AE-IP to date. Lung transplantation remains the only definitive treatment for this fatal condition. The rationale to use this combined therapy was to modify cytokine and inflammatory cell activities by PMX-DHP, and to protect the lung from the high driving pressure imposed during conventional mechanical ventilation.

Although the exact mechanism of the beneficial effect of PMX-DHP therapy needs to be clarified, adsorption of neutrophils, monocytes, interleukin (IL)-8, monocyte chemoattractant protein (MCP)-1 and matrix metalloproteinase (MMP)-9 appears to be associated with its efficacy (11,12). The cells adsorbed by PMX-DHP highly express human leukocyte antigen (HLA)-DR, CD14, CD62L and CD114, suggesting that the removal of active inflammatory neutrophils may be one of the mechanisms of PMX-DHP on favorable outcomes (11). Tachibana *et al*. have demonstrated that the increase in serum IL-7 after PMX-DHP therapy was a sensitive surrogate marker to predict the good survival in patients with AE of IPF treated with PMX-DHP (13).

VV-ECMO has been shown to improve outcomes of patients with severe, potentially reversible acute respiratory failure and unresponsive to conventional management (10). H1N1 influenza pneumonia has been shown to be a good indication for VV-ECMO (14, 15). The novel Berlin definition of ARDS addresses the best treatment options in respect of the severity of illness and allocates ECMO as a potential therapeutic option for patients with se-

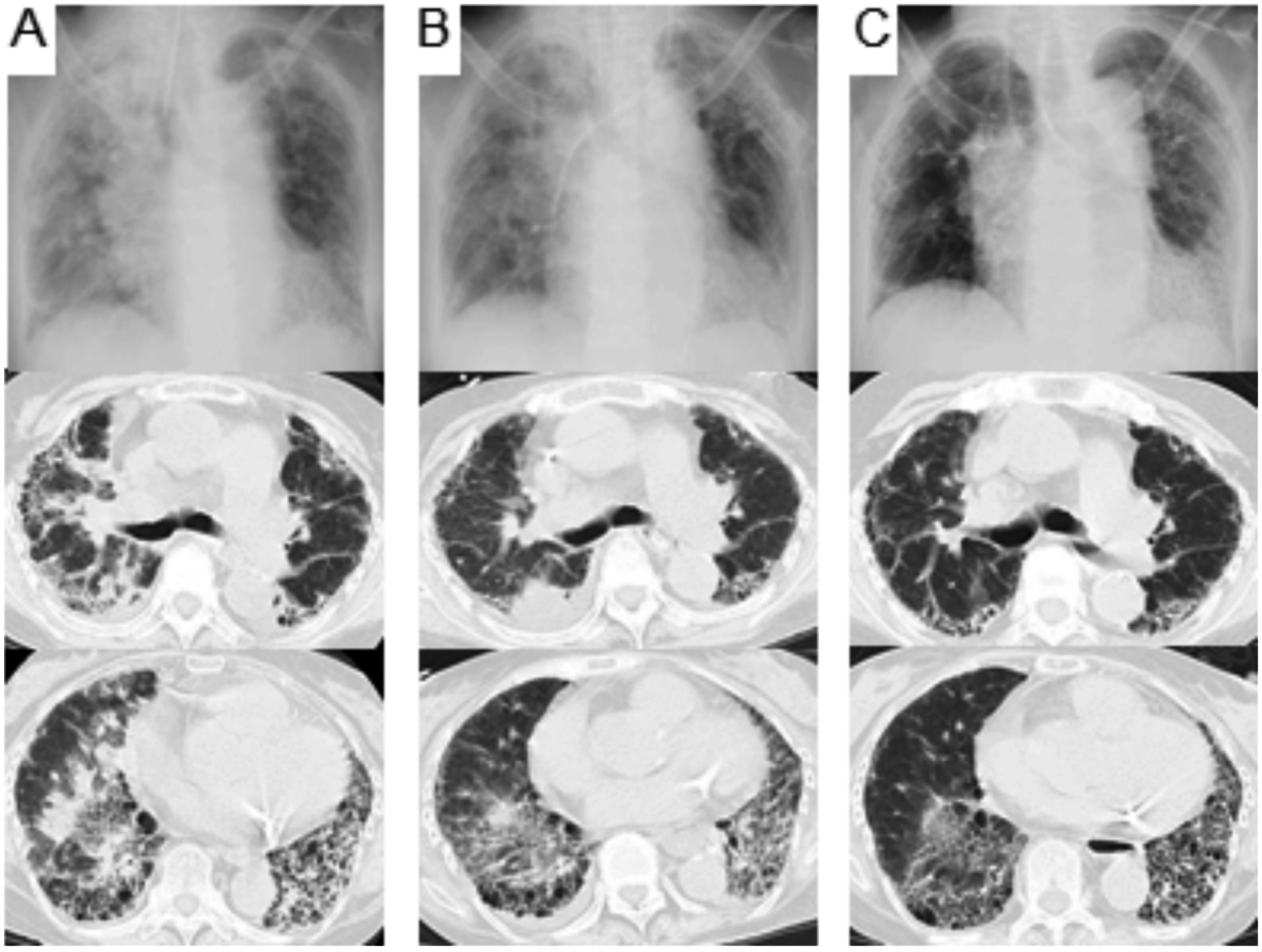

Fig. 4. Chest radiographs and high-resolution computed tomography of patient 3 showing bilateral diffuse ground glass abnormalities superimposed on the underlying honey-combing change on admission (A) and on the 6th day (B) and on the 13th day (C)

vere ARDS with a P/F ratio of lower than 100 (10). The clinical and molecular similarities between AE-IP and ARDS support lung-protective ventilation as a beneficial treatment option for AE-IP.

KL-6 is a biomarker for IP reflecting the severity of alveolar epithelial damage and the excessive type II pneumocytes regeneration. KL-6 is also a pathogenetic molecule promoting the accumulation and proliferation of fibroblasts (16, 17). The decrease in serum KL-6 levels in our patients was likely associated with the healing process of the injured alveolar epithelium. The monitoring of KL-6, therefore, may be useful for evaluating the response to treatment in AE-IP.

The potential limitation of our study was its study design of a pilot study. We should conduct a prospective study for validating the benefit of PMX-DHP alone, VV-ECMO alone and a combined use of PMX-DHP and VV-ECMO as a therapy for AE-IP. We currently speculate that the combined use of PMX-DHP and VV-ECMO as the most promising therapy for AE-IP, and accumulate the number of ventilated patients with AE-IP treated with this combined regimen, if patients have no contraindications.

Conclusions

In summary, we here present 3 patients with AE-IP or AIP who were successfully treated with a combined therapy of PMX-DHP and VV-ECMO.

Further studies are needed to determine whether this therapy is superior to other therapies.

Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Authors' contributions

JI carried out the patient collection, treated the patients and drafted the manuscript. SO conceived of the study, treated the patients, carried out the data collection and helped to draft the manuscript. YK and KO carried out the patient treatment and collected the data. YI and NH instructed the procedure of patient treatment. NK and KT reviewed the diagnosis, the treatment procedure and helped to draft the manuscript. FB, JG and UC confirmed the diagnosis of the patients enrolled and helped to draft the manuscript. All authors read and approved the final manuscript.

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