INTERNAL MEDICINE

□ CASE REPORT □

Rapidly Progressive Interstitial Pneumonia Associated with Clinically Amyopathic Dermatomyositis Successfully Treated with Polymyxin B-immobilized Fiber Column Hemoperfusion

Tomoyuki Kakugawa[1], Hiroshi Mukae[2], Masataka Saito[3], Koji Ishii[3], Hiroshi Ishimoto[2], Noriho Sakamoto[2], Takahiro Takazono[1], Yuichi Fukuda[1], Nobuharu Ooe[1] and Shigeru Kohno[2]

Abstract

Amyopathic dermatomyositis (ADM) is a clinical subtype of dermatomyositis, characterized by the absence of motor weakness and the presence of normal muscle enzyme levels. ADM is sometimes accompanied by interstitial pneumonia that shows a rapid progressive course associated with a poor prognosis. We describe a 70-year-old man who presented rapidly progressive interstitial pneumonia associated with clinically ADM (C-ADM); he was successfully treated with polymyxin B-immobilized fiber column (PMX) hemoperfusion.

Key words: clinically amyopathic dermatomyositis, interstitial pneumonia, polymyxin B-immobilized fiber column hemoperfusion treatment, acute respiratory distress syndrome

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Introduction

Interstitial pneumonia is frequently identified in patients with polymyositis and dermatomyositis (1). Amyopathic dermatomyositis (ADM) is a clinical subtype of dermatomyositis characterized by the absence of a motor weakness and the presence of normal muscle enzyme levels (2, 3). Other studies, primarily from Asia, have demonstrated that some patients with ADM develop rapidly progressive interstitial pneumonia that remains unresponsive to intensive therapy, such as high-dose corticosteroids plus immunosuppressive agents, leading to fatal respiratory failure (4-8). No proven treatment has yet been reported previously. Here, we describe a patient with rapidly progressive interstitial pneumonia accompanied by clinically ADM (C-ADM) (3, 9), who was treated successfully with polymyxin B-immobilized fiber column (PMX) hemoperfusion.

Case Report

A 70-year-old Japanese man with no medical history was referred to the emergency department in our hospital in May 2006 because of rapidly progressive dyspnea. He was unemployed and a non-smoker. Physical examination on admission showed scaly erythema on the dorsum of the hands (Gottron sign) and periorbital edema with a purplish appearance (heliotropic rash), but no muscle weakness. Auscultation of the chest identified audible fine crackles on the lower aspects of both lungs. Results of laboratory findings on admission revealed a white blood cell count of 9,940/mm^3 with 88% neutrophils. C-reactive protein was elevated [24.6 mg/dl (standard value; 0-0.4 mg/dl)]. The serum creatine kinase concentration was normal. Serum lactate dehydrogenase (LDH) level was elevated [653 IU/l (119-229 IU/l)]. Although anti-nuclear antibody was strongly positive

[1]Department of Internal Medicine, Emergency and Critical Care Medical Center, Kitakyushu Municipal Yahata Hospital, Fukuoka, [2]Department of Anesthesia, Emergency and Critical Care Medical Center, Kitakyushu Municipal Yahata Hospital, Fukuoka and [3]The Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki
Received for publication September 28, 2007; Accepted for publication January 23, 2008
Correspondence to Dr. Hiroshi Mukae, hmukae@net.nagasaki-u.ac.jp

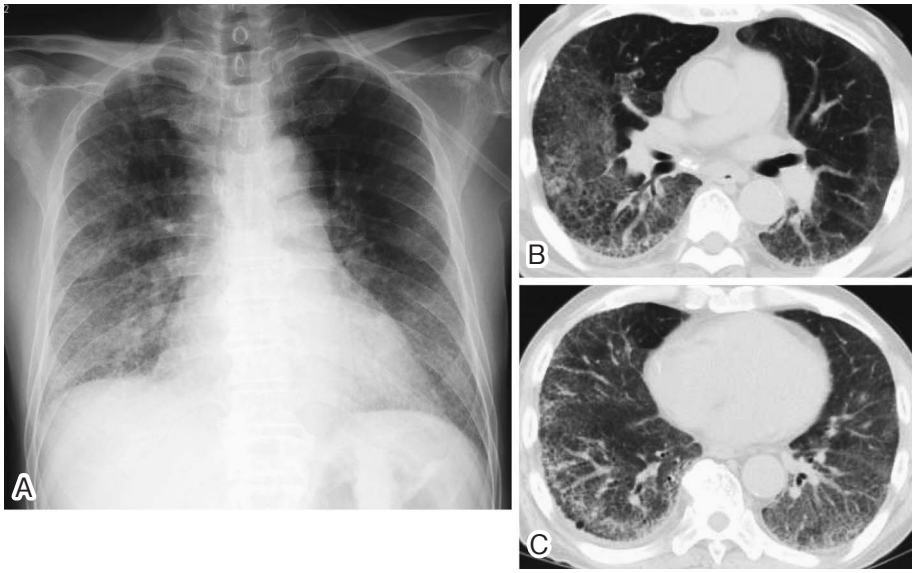

Figure 1. **Images of the patient at admission. (A) Chest radiograph shows reticular shadows with basilar predominance. (B and C) Chest high resolution computed tomographic (HRCT) scans show diffuse ground-glass opacities in both lungs with basilar predominance.**

(2,560×) and anti-double strand deoxyribonucleic acid antibody was positive (20 IU/ml), anti-Jo-1 antibody and other autoantibodies to specific antigens were all negative. Serum concentrations of KL-6, surfactant protein (SP)-A and SP-D were markedly elevated (4,909 U/ml [<500 U/ml], 274 ng/ml [<43.8 ng/ml], and 546 ng/ml [<110 ng/ml], respectively). Arterial blood gas analysis at O_2 inhalation of 5 l/min via a mask revealed pH of 7.41, PaO_2 of 75 Torr and $PaCO_2$ of 37 Torr. Blood endotoxins were undetectable. Cultures of blood, sputum and urine to detect bacteria, fungi and mycobacteria were all negative. Serological tests for *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Chlamydophila psittaci* and *Legionella*, were negative, as were β-D glucan and cytomegalovirus antigenemia. Chest X-rays upon admission revealed bilateral reticular shadows in both lower lung fields (Fig. 1A). High resolution computed tomographic (HRCT) chest scans also revealed diffuse ground-glass opacities in both lungs with basilar predominance (Fig. 1B and C). It was difficult to perform the pathological examination of skin because of the deterioration of respiratory symptoms. Since the patient had the characteristic dermatological manifestation of dermatomyositis with no muscle weakness and a normal muscle enzyme level, clinically ADM (C-ADM) was diagnosed according to the criteria by Sontheimer (9) after consulting with the professional experts of dermatology and collagen disease although the pathological evidence could not be obtained. In addition, the current case also manifested the symptoms of acute respiratory failure and the chest radiological imagines showed characteristic shadow of interstitial pneumonia, and thus, the diagnosis of rapidly progressive interstitial pneumonia accompanied by C-ADM was finally made. Figure 2 shows that although the patient was treated with high-dose methylprednisolone (1 g/day intravenously for three days) followed by oral prednisolone (50 mg/day), the clinical condition and chest radiographic findings deteriorated rapidly and mechanical ventilation was necessary. Treatment with cyclosporin A and sivelestat sodium hydrate was added and high-dose methylprednisolone therapy (1 g/day intravenously for three days) was repeated. The dose of cyclosporine A was adjusted to maintain a blood trough level of 100 to 150 ng/ml. Direct hemoperfusion with PMX (Toraymyxin 20R, Toray Medical Co., Tokyo, Japan) was administered once daily for successive two days at a flow rate of 100 ml/min for 3 hours each. Both the arterial oxygen tension (PaO_2)/inspiratory oxygen fraction (FiO_2) (P/F) ratio, alveolar-arterial difference of oxygen ($AaDO_2$) became dramatically improved during PMX hemoperfusion (Fig. 3). White blood cell count and C-reactive protein decreased to 6,810/mm^3 and 0.9 mg/dl respectively at day 4 after PMX hemoperfusion. Acute hypoxemic respiratory failure also improved and the patient was weaned from mechanical ventilation at day 8 after PMX hemoperfusion. Because chest radiography showed improvement, prednisolone was gradually tapered off. His clinical condition and the skin lesion also gradually improved and the serum levels of KL-6, SP-D and SP-A gradually decreased (Fig. 4). Complication with malignant tumor was not found on the examinations performed after his improvement. Chest radiography and HRCT showed remarkable improvement after 5 months of the treatment (Fig. 5), and the patient survived for over 6 months after PMX treatment.

Discussion

Polymyositis/dermatomyositis is frequently accompanied by interstitial pneumonia which is known as a significant prognostic factor in this disease (10). C-ADM, which shows

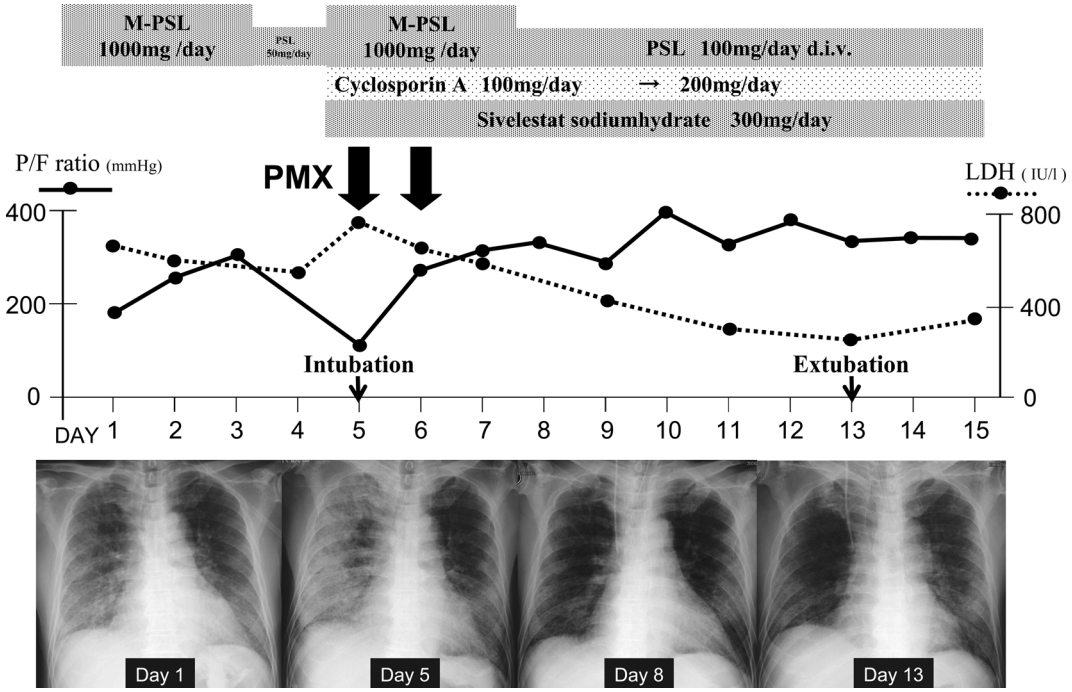

Figure 2. **Clinical course. M-PSL: methylprednisolone, PSL: prednisolone, PMX: polymyxin B-immobilized fiber column hemoperfusion, P/F ratio: arterial oxygen tension (PaO_2)/inspiratory oxygen fraction (FiO_2) ratio, LDH: lactate dehydrogenase.**

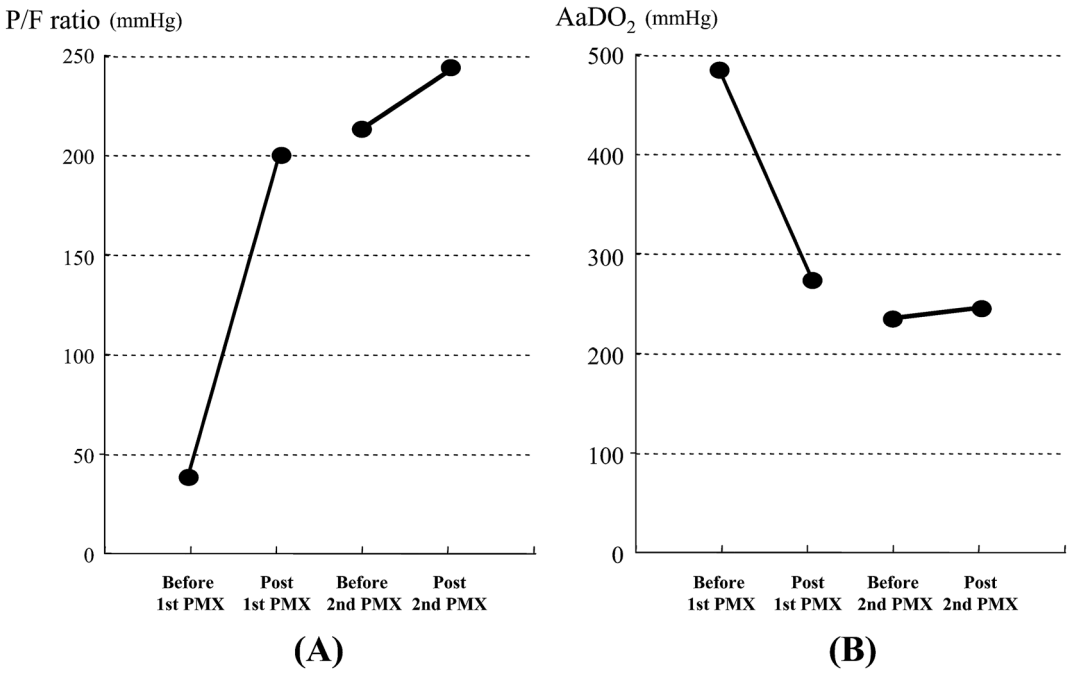

Figure 3. **P/F ratio and $AaDO_2$ before and after PMX therapy. Arterial oxygen tension (PaO_2)/inspiratory oxygen fraction (FiO_2)(P/F) ratio (A) and alveolar-arterial difference of oxygen ($AaDO_2$) (B) are obviously improved.**

lack of motor weakness, presence of normal muscle enzyme levels and negative tests for anti-Jo-1 antibody, is associated with rapidly fatal progressive interstitial pneumonia, especially among Japanese patients (3, 9, 11, 12). Such patients are often resistant to intensive therapy, such as high-dose corticosteroids plus immunosuppressive agents, resulting in fatal respiratory failure (4-8). There is no proven treatment and mortality rates are high (50% or more), with most deaths occurring between the first and the second months of illness onset (13).

Recent reports have suggested that PMX might improve oxygenation in patients with acute lung injury (ALI)/ acute respiratory distress syndrome (ARDS) (14-17). Seo et al recently reported that 4 of 6 patients with acute exacerbation

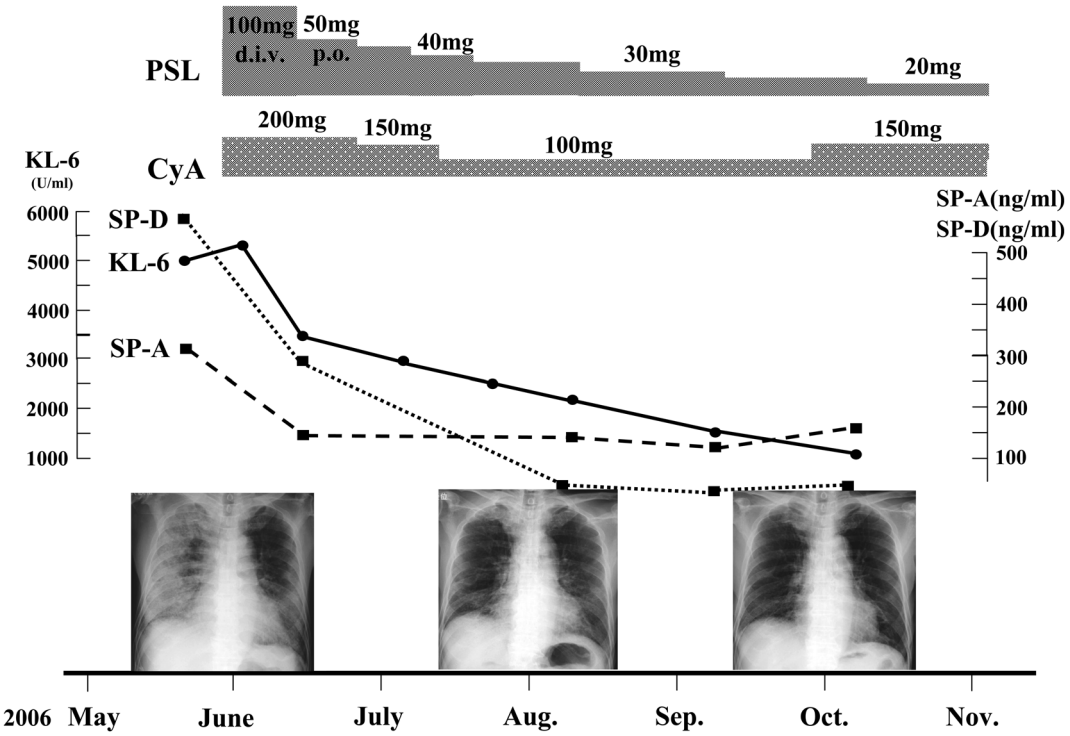

Figure 4. Clinical course after extubation. PSL: prednisolone, CyA: cyclosporine A, SP-A: surfactant protein-A, SP-D: surfactant protein-D.

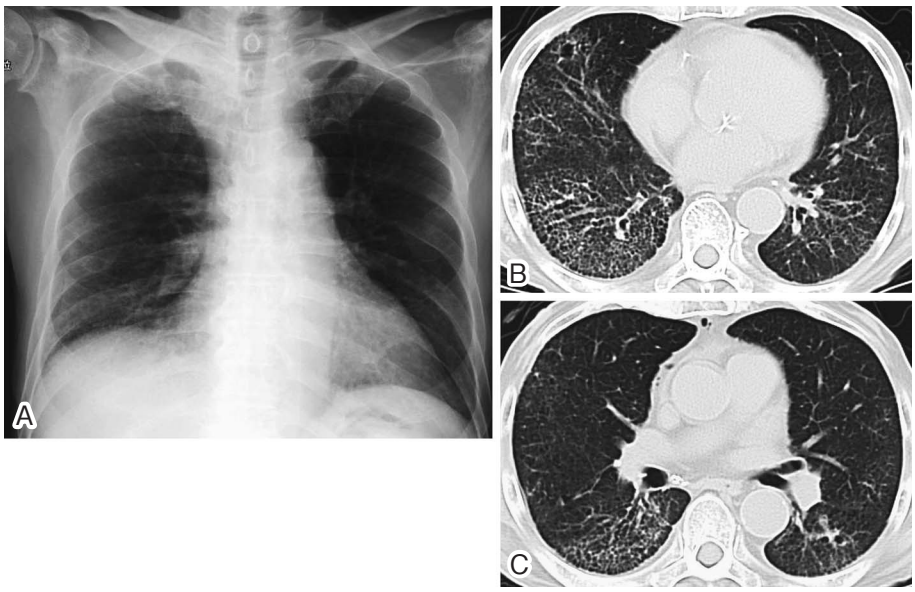

Figure 5. The chest images of the patient after 5 months of PMX therapy. Chest radiography (A) and HRCT (B and C) show remarkable improvement.

of idiopathic pulmonary fibrosis were weaned from mechanical ventilation and survived for over 30 days after initial PMX treatment (18). Noma et al also recently reported that PMX treatment was effective in two patients with acute exacerbation of interstitial pneumonia (19). Although the present patient was resistant to steroid therapy, progressed rapidly and required mechanical ventilation, PMX was very effective and the patient survived for over 6 months after admission. The present case together with those of others suggest that direct hemoperfusion with PMX could be effective against rapidly progressive interstitial pneumonia which is resistant to conventional therapy such as high-dose corticosteroids plus immunosuppressive agents.

As PMX potentially absorbs plasma endotoxin, this therapy is mainly used to treat septic shock as it results in decreased plasma endotoxin levels and improved hemodynamic stability (20). Aoki et al have suggested that reducing the endotoxin concentration might reduce pulmonary vasoconstriction and intrapulmonary shunting (17). However, PMX is effective against both gram-negative and gram-

positive sepsis (17). The $AaDO_2$ and P/F ratio improved in our patient after PMX treatment even though the endotoxin level was undetectable. Accordingly, PMX might be effective because of properties other than endotoxin removal. Nakamura et al have reported that blood levels of metalloproteinase (MMP)-9 and tissue inhibitor of MMP (TIMP)-1 are significantly reduced after PMX treatment and closely correlate with an improvement in the P/F ratio (15). In an animal model of sepsis, PMX improves oxygenation through the suppression of nitric oxide production (21). Kushi et al recently reported that the improvement in the P/F ratio induced by PMX treatment is related to decreased blood neutrophil elastase and IL-8 levels (16). Naka et al also reported that PMX significantly inhibits neutrophil-reactive oxygen species, which play an important role in the pathogenesis of ARDS in patients with sepsis and septic shock (22). Inflammatory cells including activated monocytes and neutrophils producing such mediators might be absorbed by PMX treatment (23, 24). Further investigation is necessary to determine the precise mechanisms through which PMX improves oxygenation in rapidly progressive interstitial pneumonia.

High-dose corticosteroid therapy might be effective in the present case. However, the clinical condition and chest radiographic findings deteriorated rapidly just after the corticosteroid was tapered off to prednisolone (50 mg/day). Accordingly, it was thought to be difficult to treat this case by administrating corticosteroid alone. After the PMX therapy, corticosteroid was successfully tapered off. The administration of oral cyclosporine A might be also effective. Cyclosporine A is an immunosuppressive agent that acts by inhibiting calcineurin, and it reversibly suppresses cytokine production mainly from helper T cells (25). Recent studies of rapidly progressive interstitial pneumonia in C-ADM have highlighted the effectiveness of cyclosporine A combined with corticosteroids (13). However, cyclosporine A usually requires at least 1 to 2 weeks to induce therapeutic effects (13). The present case suggests that PMX treatment in combination with corticosteroid and cyclosporine A was very effective to rapidly progressive interstitial pneumonia.

The dramatic improvement of $AaDO_2$ and P/F ratio might be partly due to the well-known efficiency of mechanical ventilation in patient with respiratory failure status, as intubation and PMX were administrated to the patient almost simultaneously. However, the dramatic improvement of acute hypoxemic respiratory failure in our patient was thought to be due mainly to the PMX treatment, because the patient's general condition and chest radiography also showed remarkable improvement just after the PMX treatment.

We applied PMX hemoperfusion once daily for successive two days for 3 hours each, but some controversy surrounds the choice of appropriate cycles and frequencies. One or two administrations for 4 hours each have improved the survival of patients with sepsis (26). A recent paper has suggested that more frequent applications will be effective against severe sepsis (27). Seo et al reported that 1-5 administrations for 2-6 hours each improved acute exacerbation of idiopathic pulmonary fibrosis (18). Noma et al reported that a protocol of 3 administrations for 2-24 hours each was effective in two patients with acute exacerbation of interstitial pneumonia (19). However, there have been only limited reports on the length and frequency of the PMX administration in treatment. Further investigation will be necessary to determine and confirm the appropriate cycles and frequencies of PMX treatment in rapidly progressive interstitial pneumonia.

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