Rapidly Progressive Interstitial Lung Disease Associated with Dermatomyositis Treated with Combination of Immunosuppressive Therapy, Direct Hemoperfusion with a Polymyxin B Immobilized Fiber Column and Intravenous Immunoglobulin

Motohisa Takai¹, Naoko Katsurada¹, Tamao Nakashita², Masafumi Misawa¹, Takahiro Mochizuki³, Norihiro Kaneko¹, Shinji Motojima² and Masahiro Aoshima¹

Abstract

Rapidly progressive interstitial lung disease (ILD) is associated with dermatomyositis (DM) and has a high mortality rate even with immunosuppressive agents. For such cases, there is no evidence on the combined effect of direct hemoperfusion with a Polymyxin B immobilized fiber column and intravenous immunoglobulin. We herein report a case of 61-year-old woman who presented with respiratory failure. She showed ILD associated with DM which did not improve with immunosuppressive agents, but was improved with the addition of both direct hemoperfusion with a Polymyxin B immobilized fiber column and intravenous immunoglobulin.

Key words: dermatomyositis, rapidly progressive interstitial lung disease, Polymyxin B immobilized fiber column, intravenous immunoglobulin


Introduction

Rapidly progressive interstitial lung disease (ILD) is a well known complication and a major cause of death in connective tissue disease, especially in polymyositis (PM) and dermatomyositis (DM) (1). In DM, rapidly progressive ILD is often reported (2). However, despite routine use of high dose corticosteroids and immunosuppressive agents, some cases are hard to treat. While some report the efficacy of direct hemoperfusion with a Polymyxin B immobilized fiber column (PMX-DHP) (3, 4) and intravenous immunoglobulin (IVIG) (5), the efficacy and the safety of the PMX-DHP and IVIG combination are controversial. We herein report a case of rapidly progressive ILD associated with DM which survived with the administration of PMX-DHP and IVIG in addition to high dose corticosteroids and immunosuppressive agents.

Case Report

A 61-year-old Japanese non-smoker woman with no notable medical history had occasional albuminuria in her annual medical examination. In the following month, she noticed that both her hands had swollen. A week later her hand swelling diminished, but she started to have a slight fever and her eyelids started swelling. Four days later she had rapidly progressing dyspnea and was diagnosed as having pneumonia by chest radiography at another hospital two days later. She was then admitted to our hospital.

On admission, the eye swelling had disappeared, and although a slight nail fold bleeding was noted, no other DM-specific erythema or muscle weakness was present. Fine crackles were audible on bilateral lower lung fields, and her
body temperature was 37.9°C, and her SpO₂ was 97% with inhalation of 3 liters oxygen per minute. A chest radiograph and CT scan showed diffuse panlobular ground-glass opacity dominant in the lower lobes implying ILD (Fig. 1). A bronchoalveolar lavage cellular profile presented a total cell count 100,000/mL with 7% lymphocytes, 6% neutrophils and 9% eosinophils. The CD4/CD8 ratio of bronchoalveolar lavage fluid was 0.15. Laboratory findings showed that the white blood cell count was 9,400/mm³ with 87% neutrophils, serum lactate dehydrogenase (LDH) was elevated to 528 IU/L, C-reactive protein was 8.57 mg/dL, serum creatinine kinase concentration was elevated to 560 IU/L, serum concentration of KL-6 was 562 U/mL, serum concentration of ferritin was 524.7 nm/mL, and no albuminuria detected. Anti-nuclear antibody was positive (640x), anti-Jo-1 antibody was positive (8x) and anti-cyclic citrullinated peptide (CCP) antibody was positive (78.1 U/mL). The other immunologic tests were negative.

Her clinical course is shown in Fig. 2. Her ILD presented as rapidly progressing. Methylprednisolone pulse therapy (mPSL; 1 g/day intravenously for 3 days) was initiated immediately after admission. During the three-days pulse therapy her dyspnea and chest X-ray findings did improve, and prednisolone (50 mg per day) was initiated on hospital day 4. The following day, the clinical condition including dyspnea and chest X-ray findings worsened. We considered the possibility of ILD associated with DM from the eye swelling, elevated serum creatine kinase (CK) and the CT image which showed thickened bronchovascular bundle, thus cyclosporine (CyA; 150 mg/day) was immediately started fol-
followed by intravenous cyclophosphamide (IVCY; 700 mg) on the next day and by the second course of mPSL pulse therapy on day 8. Dosage of CyA was adjusted to maintain the trough value of blood concentration between 120 and 150 ng/mL, and two-hour post-dose concentration between 800 and 1,000 ng/mL. On day 10, even during the second mPSL pulse therapy she experienced muscle pain in the left shoulder, muscle weakness in both legs and worsening of dyspnea and chest CT demonstrated the extension of interstitial shadows and appearance of mediastinal emphysema and pleural fluid. Anti-Jo-1 antibody was revealed positive on day 9 confirming the diagnosis of DM. On day 12, IVIG infusion (20 g for 5 days) was started. After the IVIG infusion, her clinical condition stabilized and the patient did not use mechanical ventilation. However, she still experienced exertional dyspnea with inhalation of 4 liters oxygen per minute. The third course of mPSL pulse on day 15 and PMX-DHP (flow rate of 100 mL/min for 2 hours) on day 17 and 19 were conducted. The second course of IVCY was given on day 20. Both the respiratory failure and muscle pain began to improve, and a chest X-ray on day 21 showed ILD ameliorating, CT scan on day 27 revealed the ground-glass opacity almost resolving and mediastinal emphysema improving (Fig. 3). The third course of mPSL pulse was followed by oral prednisolone (50 mg/day) which was gradually reduced. The third course of IVCY was administrated on day 34. Weakened muscle strength gradually recovered. No oxygen inhalation was required on day 51 and she was discharged on day 67. After discharge, we succeeded in reducing prednisolone to 8 mg per day without ILD re-exacerbation. It turned out later that anti-melanoma differentiation-associated gene 5 antibody was not detected.

Discussion

This case suggests the potential of additional treatment with both PMX-DHP and IVIG to usual treatment for rapidly progressive ILD associated with DM. Some reports in which PMX-DHP or IVIG was used in addition to them are found. However, to the best of our knowledge, no reports used both PMX-DHP and IVIG. Thus, we presented here a case who survived from immunosuppressive agents resistant ILD with combination of PMX-DHP and IVIG.

ILD associated with DM is known mainly as being slowly progressive, and still certain subgroup can progress rapidly and are fatal. A five-year mortality rate is reported from 0% to 50% (6). DM which has anti-aminocyl tRNA synthetase antibodies such as anti-Jo-1 antibody is reported...
to be complicated by a higher rate of ILD (7). These fatal ILD accompanied by DM is usually treated with corticosteroids and immunosuppressive agents including CyA and IVCY pulse, but still a portion of patients die even with these combination therapies (8). It is difficult to elucidate the candidates for these ILD combination treatments, because no randomized controlled study has been conducted. This case implies applying IVIG and PMX-DHP in addition to the combination of immunosuppressive agents may be promising. The efficacy of IVIG for muscular symptoms in the treatment of resistant cases of PM or DM is reported. A double-blind, placebo-controlled study of 15 patients with DM who were treated with IVIG at 2 g/kg monthly, showed improvement of muscle strength and neuromuscular symptoms with no complication (9). The efficacy of IVIG for ILD is reported but not known enough. In a small series, five patients were treated with IVIG for refractory ILD associated with PM/DM and two patients survived (5). Likewise, the neuromuscular symptoms were slight in our case and IVIG was mainly used for ILD, which succeeded in improving the rapidly progressive ILD.

Evidence of PMX-DHP for the treatment of ILD is limited. It is unclear why PMX-DHP relieves rapid progression of ILD but several mechanisms are suggested: such as the adsorption of highly activated neutrophils (10), and plasminogen activator inhibitor-1, and IL-8 (11). PMX-DHP was administered for a series of 33 patients with rapidly progressive ILD with resistance to high dose corticosteroid therapy. Their arterial oxygen tension/inspiratory oxygen fraction (P/F) ratio, the alveolar-arterial difference of oxygen (AaDO2) and the number of positive criteria for systemic inflammatory response syndrome improved while no major complication of PMX-DHP was detected (4). In our case PMX-DHP showed only a slight improvement in P/F ratio and in AaDO2, but no complications occurred during and after PMX-DHP.

In this case, the IVIG was added because her clinical symptoms were deteriorating even with a combinatorial immunosuppressive therapy of corticosteroid, CyA and IVCY. However, her condition did not improve immediately. Since the slow effect of the immunosuppressive therapy and IVIG was predicted, we then administered PMX-DHP, which rapidly improved the P/F ratio, to successfully manage this condition.

Several questions remained unanswered for our case. First, contributions of CyA and IVCY for the improvement could not be ignored. In other words, since the treatment with the PMX-DHP and IVIG overlapped with the administration of CyA and IVCY, it is possible that the improvement of this case was due to delayed effects of the immunosuppressive treatments which had been administered earlier. Even if that is the case, however, we think that PMX-DHP, whose effects appear immediately (12), may have helped to prevent the deterioration of the patient respiratory status until the effect of CyA or IVIG appears. Secondly, the candidates of IVIG and PMX-DHP need to be validated. Cases with predicting factors for poor ILD prognosis in PM/DM may be good candidates; factors such as acute onset of ILD, reduced forced vital capacity (FVC) and DLCO values, older age, a pattern of usual interstitial pneumonia on high-resolution computer tomography (HRCT), steroid-refractory ILD and increased ferritin (13-16). Thirdly, the timing to administer PMX-DHP and IVIG remains controversial. In terms of gaining time until immunosuppressive agents work, the usage of PMX-DHP may follow in cases refractory to immunosuppressive treatments. The IVIG alone is shown to have a curative effect on ILD (17), thus IVIG should be administered in its early phase. Fourthly, the number of courses and the time duration per one course may be critical. Reports which used PMX-DHP treated with different durations for 3-24 hours with 1-6 courses (3, 4, 12). While the number of courses and the time length per one course may be critical, the best protocol still remains to be determined. One to six courses are reported with a duration from 3 to 24 hours per course. Further study is required to clarify the optimal duration and the number of courses of PMX-DHP. Fifthly, the long-term prognosis is unknown and the long-term effect of PMX-DHP remains to be elucidated. The efficacy of IVIG is considered to diminish quickly (9) and repeated administration may be required to sustain any improvement.

In conclusion, this case report suggests the possibility that the combination of both PMX-DHP and IVIG with immunosuppressive agents and corticosteroid may further improve the treatment of ILD in DM. We consider that concomitant use of PMX-DHP and IVIG is a promising treatment option for rapidly progressive and refractory ILD in DM.

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

This case was treated at the Department of Pulmonary Medicine, Kameda Medical Center, Kamogawa-city, Chiba, Japan.

References
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