Case report

Successful combination therapy with corticosteroids, biweekly intravenous pulse cyclophosphamide and cyclosporin A for acute interstitial pneumonia in patients with dermatomyositis : report of three cases

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Summary
We report three patients with dermatomyositis (DM) complicated with acute interstitial pneumonia (AIP). All of them complained of fever and acutely worsening dyspnea and were treated immediately by combination therapies with pulse therapy with methylprednisone (mPSL) followed by corticosteroids, biweekly intravenous pulse cyclophosphamide (IVCY) and cyclosporine A (CSA). They recovered rapidly soon after an initiation of this combination regimen. Early intervention with aggressive combination therapy is life-saving for the treatment of AIP in patients with DM.

Key words — Acute Interstitial Pneumonia; Dermatomyositis; Diffuse alveolar damage; Biweekly Intravenous pulse cyclophosphamide; Cyclosporine A

Introduction

Since its original description in 1956, the association of interstitial lung disease (ILD) with DM has been well established. Among DM-associated ILD (DM-ILD), AIP is of particular concern because of its extremely high mortality rate and poor response to corticosteroid therapy. Although patients with amyopathic DM (ADM) or hypomyopathic DM, both of which have been called clinically amyopathic dermatomyositis (CADM), are known to have AIP, patients with anti-synthetase antibodies-positive DM also develop it. Diffuse alveolar damage (DAD) is the mainstay of histological findings in such patients and a rapidly progressive organizing process of the lung parenchyma prevents them from clinical recovery and leads to unfavorable outcomes. Many studies have been performed to find adequate strategies to overcome this devastating situation; however, an optimal treatment regimen remains to be established. Corticosteroids with an immunosuppressive agent such as IVCY, CSA, or tacrolimus improve the survival rate of patients with DM-associated AIP (DM-AIP), but its efficacy is still limited.

In this study, we report three cases of DM-AIP (among these cases, the clinical course of case 1 was described elsewhere), all of whom were treated by combination therapy with corticosteroids, biweekly IVCY and CSA and could survive without any serious infection.

Case description

Case 1
In May 2007, a 53-year-old man presented to another hospital with complaints of joint pain, digital redness, eyelid edema, and shortness of breath. CT scan of the chest revealed interstitial pneumonia and the patient was admitted to the hospital two months later. The presence of DM-specific erythema over the digits and eyelids, absence of clinical evidence of muscle weakness and interstitial changes in both lung fields with a normal CPK value, led to a diagnosis of CADM with AIP based on the criteria by Sontheimer. Oral prednisolone (60 mg per day) and 650 mg of IVCY was started on hospital day 2 and day 3, respectively, but respiratory distress suddenly developed one month after the initiation of therapy. The patient was transferred to our hospital on July 25, 2007.

On admission, our patient was in respiratory distress and his vital signs were as follows: blood pressure, 126/76 mmHg; temperature, 36.2°C, and heart rate, 90 beats per minute. The patient displayed 89% oxygen saturation (SPO2) while breathing ambient air. Fine crackles were evident in both lung fields. He had a heliotrope rash and Gottron’s papules and manual muscle testing (MMT) revealed no proximal...
muscle weakness. Biochemical analysis revealed a normal CPK value (32 U/L) and elevated level of lactate dehydrogenase (LDH) to 720 IU/L. Blood gas analysis while breathing 3L of oxygen via nasal cannula showed hypoxia (pH 7.438, PaCO2 42.1 Torr, PaO2 62.9 Torr). High-resolution computed tomography (HRCT) of the chest demonstrated non-segmental, patchy GGO predominantly in the subpleural areas and consolidation in the basal parts of both lung fields (Figure 1-a). Serial sputum specimens failed to yield significant pathogen. On hospital day 3, 750 mg of IVCY, 150 mg per day of CSA, and 60 mg per day of prednisone were started on the same day (Figure 2-a). Results of the rheumatological profile were disclosed thereafter. He was negative for anti-nuclear or anti-Jo-1 antibody and his serum KL6 level was elevated to 853 U/mL. On hospital day 17, a second course of IVCY was administered and prednisone was tapered to 50 mg per day. Subsequently, the administered dose of biweekly IVCY was reduced to 500 mg for the remaining four-session courses and prednisone was tapered rapidly. A trough value of CSA was maintained between 100 and 150 ng/mL. Serial results of the chest HRCT obtained during the hospital course were consistently improving (Figure 1-d). Although our patient developed pneumomediastinum on hospital day 51, it resolved itself without further treatment. He was complicated with cytomegalovirus (CMV) viremia in the midst of the course, which was easily treated by valgancyclovir and did not develop any organ involvement. He was discharged from hospital without oxygen supplement on October 13, 2007.

Case 2

In September 2009, a 73-year-old female noted morning stiffness of both hands. In the following month, she noticed dyspnea on exertion and it progressively worsened. The patient was seen in an outpatient clinic and X-ray of the chest revealed con-

Figure 1. a-c Chest computed tomography (CT) of three patients with dermatomyositis-associated acute interstitial pneumonia obtained before combination therapy with prednisolone, cyclosporine, and intravenous cyclophosphamide show extensive consolidation and ground-glass opacity (GGO) predominantly in the bilateral lower lobes. Traction bronchiectasis was also noted in all cases (a, case 1; b, case 2; c, case 3). e-f Improved CT findings after the final session of IVCY (d, case 1; e, case 2; f, case 3).
Figure 2. a–c The clinical courses of three patients during hospitalization (a, patient 1; b, patient 2; c, patient 3). PSL prednisolone, IVCY intravenous cyclophosphamide, CSA cyclosporine A, mPSL methylprednisolone, CMV cytomegalovirus, MAC mycobacterium avium complex, CAM clarithromycin, RFP rifampicin, EB ethambutol, P/F PaO2/FiO2

solidations and interstitial changes of both lung fields. She was admitted to another hospital on November 7, 2009 for further evaluation. CT scan of the chest obtained on admission day showed interstitial changes and a diagnosis of interstitial pneumonia was made. Methylprednisolone (mPSL) pulse therapy (500 mg per day for 3 days) followed by 20 mg per day of prednisone were given, but they did not confer any benefit. A second course of mPSL pulse therapy (1000 mg per day for 3 days) followed by 60 mg per day of prednisolone was tried, but they were also not beneficial. The patient was transferred to our hospital on November 18, 2009.

On admission, she was in respiratory distress and complained of muscle pain over both thighs. Her vital signs were as follows: blood pressure, 116/53 mmHg; temperature, 36.2°C and heart rate, 89 beats per minute. The patient displayed 91% SPO2 while breathing 5L of oxygen through a face mask. She had Gottron’s papules and palmer erythema and MMT showed no proximal muscle weakness. Fine crackles were evident in both lung fields and there was no joint swelling or tenderness. HRCT of the chest demonstrated consolidation and GGO predominantly in the subpleural areas of the bilateral lower lobes and traction bronchiectasis was also demonstrated (Figure 1–b). Biochemical analysis revealed a normal CPK value (93 U/L) and elevated level of LDH to 338 IU/L. Her rheumatoid factor level was 30.4 IU/mL (normal <10 IU/mL). Blood gas analysis on hospital day 1 while breathing 5L of oxygen through a face mask revealed the following results: pH 7.47, PaCO2 31.1 Torr, PaO2 64.4 Torr. Our patient continued to take 60 mg of dairy prednisolone. On hospital day 2, her respiratory distress acutely deteriorated. Blood gas analysis breathing 9L of oxygen via a reservoir facial mask demonstrated worsening hypoxia (pH 7.485, PaCO2 38.6 Torr, PaO2 51.8 Torr). She was immediately started on 750 mg of IVCY and 150 mg per day of CSA on the same day, with a continuation of 60 mg per day of prednisolone (Figure 2–b). STIR T2-weighted MRI of the both thighs obtained hospital day 3, demonstrated high signal intensity in the muscle and fascia. Over the next week, her respiratory condition was rapidly improving and she displayed 96% SPO2 while breathing 3L of oxygen through a nasal cannula. On hospital day 7, anti-Jo-1 antibody was found to be positive at a titer of 1:64 and her KL-6 level was elevated to 1438 U/mL. Definite diagnosis of DM–AIP was established. Our patient was given the second course of IVCY with a reduced dose of 500 mg on hospital day 16 and continued to be given biweekly IVCY for a total of five courses. Prednisolone was tapered rapidly and a trough value of CSA was maintained between 100 and 150 ng/mL. The present patient was found to have CMV viremia on hospital day 21 and a mycobacterium avium complex (MAC) infection of the lung on day 84, both of which were easily treated by valgancyclovir and a combination of clarithromycin (CAM), rifampicin (RFP), and ethambutol hydrochloride (EB), respectively. HRCT of the chest obtained on hospital day 163 showed marked improvements in interstitial changes (Figure 1–c). She was discharged from hospital on May 11, 2010, with 2L of oxygen via a
nasal cannula. On an outpatient basis, CAM, RFP, and EB were discontinued in August, 2010 after obtaining a negative result of MAC growing by sputum culture.

Case 3
A 70-year old male was aware of general malaise and dyspnea on exertion in August, 2011. These problems became increasingly worse and he was seen in our outpatient clinic on August 16. An x-ray of the chest revealed consolidations in bilateral lower lung fields and the present patient was admitted to our hospital on the same day. On admission, his vital signs were as follows: blood pressure, 123/97 mmHg; temperature, 35.0°C and heart rate, 61 beats per minute. The patient displayed 96% SPO2 while breathing ambient air and had eyelid erythema. Fine crackles were evident in bilateral lower lung fields and there was no joint swelling or tenderness. MMT revealed no significant muscle weakness. Biochemical analysis revealed a normal CPK value (86 U/L) and elevated level of LDH to 221 IU/L. Serum CRP was 11.57 mg/dL and rheumatoid factor level was 31.1 IU/mL (normal ≤ 10 IU/mL). HRCT of the chest obtained on admission day demonstrated a mixture of multiple consolidations and GGO predominantly in the subpleural areas of both lower lobes (Figure 1–c). Although serial sputum cultures did not grow any significant pathogen, he had been treated by ceftriaxone and clarithromycin for the first 11 days, which did not confer any benefit. The result of transbronchial lung biopsy obtained hospital day 9 was consistent with organizing pneumonia and 40 mg per day of prednisolone was started on hospital day 12. On hospital day 14, his respiratory distress suddenly deteriorated and he displayed 89% SPO2 while breathing ambient air. HRCT of the chest obtained that day demonstrated an expansion of consolidation and ground glass opacities (Figure 1–e). Serum aldolase was marginally elevated to 8.7 U/L (normal 2.7–7.5 U/L). The rheumatology profile obtained on admission day was reported. Neither anti-nuclear nor anti-Jo-1 antibody was positive and his KL-6 level was elevated to 545 U/mL. Electromyography recorded at biceps brachii muscle suggested myogenic change and STIR T2-weighted MRI of the both thighs obtained at hospital day 16, demonstrated high signal intensity in the muscle and fascia. A diagnosis of probable DM with concomitant AIP was established in accordance with the Bohan and Peter criteria and the present patient was immediately started on mPSL pulse therapy (1000 mg per day for 3 days), 750 mg of IVCY (750 mg/body), and 150 mg per day of CSA (Figure 2–c). After mPSL pulse therapy, 40 mg per day of prednisolone was re-started. The patient’s exertional dyspnea was gradually improving over the next two weeks and HRCT of the chest obtained on hospital day 28 demonstrated the disappearance of GGO, although there still remained areas of consolidation in the bilateral lower lobes. The second course of IVCY (750 mg/body) was given on the same day and prednisolone was tapered to 30 mg per day on hospital day 43. Four courses of IVCY were added subsequently and he continued to improve thereafter. A serum sample sent to the university laboratory revealed a positive result for anti-EJ antibody. He developed CMV viremia and glucocorticoid-induced diabetes in the course of treatment, which were readily managed by gancyclovir and oral hypoglycemic agents, respectively. The present patient was discharged from hospital on December 9, 2011 after the end of six courses of IVCY, with 1.5 L of oxygen via a nasal cannula.

Discussion
We herein reported three cases of DM–AIP, all of whom showed acute respiratory decompensation during their clinical courses despite the use of corticosteroid and were successfully treated by simultaneous combination therapy with prednisolone, biweekly IVCY, and CSA. Of note, the three cases dramatically recovered from respiratory distress soon after initiation of this combination regimen.

There have been a number of reports that DM–AIP is a variant of DM-associated interstitial pneumonia, which is an extremely poor prognosis5–7,15). Patients with DM–AIP develop devastating respiratory failure within weeks to a few months. Huh et al reported a mortality rate of 72.7% within 1–2 months in patients with DM–AIP who were treated by corticosteroid and immunosuppressant therapy15. The reported incidence of AIP among DM-associated ILD is 16%–33%5,7 and the reported characteristics of DM–AIP include the lesser complaints of muscle weakness, a lack of elevation in serum CPK, and negative tests for autoantibodies (anti-Jo-1 antibodies)16–18. Although two among three patients described here had positive results for anti-aminoacyl-transfer RNA synthetase (anti-Jo-1 antibody and anti-EJ antibody, respectively), all of them equally showed a rapid decline in the PaO2/FiO2 ratio day by day regardless of treatment with high-dose prednisolone, no complaint of muscle...
weakness, and a normal value of CPK (Table 1). We therefore concluded that these patients had typical DM–AIP.

There have been many reports that DAD is the main pathological pattern in patients with DM–AIP. The features of DAD are traditionally divided into an early (or exudative) phase that is followed by a late (or proliferative and fibrotic) phase. The early phase develops during the first week, characterized by interstitial and intra-alveolar edema, formation of hyaline membranes, and interstitial infiltrate of mononuclear inflammatory cells. The late stage usually begins after the second week and is characterized by vigorous fibroblastic proliferation and resultant dense fibrosis within both the interstitium and alveolar space. Major HRCT findings of patients with AIP correlate with the pathological stage of DAD. Patchy GGO represents the early phase and consolidation and distortion with traction bronchiectasis relate to the late phase (> 7 days). In the present cases, HRCT findings were patchy GGO and subpleural consolidations with occasional traction bronchiectasis (Table 1); therefore, they were considered to be between the early and late phase of DAD, when aggressive interventions were initiated.

There have been several case reports of the addition of an immunosuppressive agent including IVCY, CSA, or tacrolimus to corticosteroid rescued patients with DM–AIP, but the efficacy of this is still anecdotal. Recently, several small studies demonstrated the potency of combination therapy with corticosteroids, IVCY, and CSA. Miyazaki et al introduced three cases of DM–AIP who were rescued by combination of immunomodulation agents. Although a detailed regimen was not described, two of the three cases were successfully treated by IVCY and CSA in addition to corticosteroids. Kameda and coworkers also reported the efficacy of this combination therapy. They gave patients with DM–AIP 10 mg–30 mg/kg of IVCY (maximum dose 750 mg–1500 mg) every 3–4 weeks and 2–4 mg/kg of CSA with > 0.5 mg/kg/day of corticosteroids. Five among the ten DM–AIP patients could survive using this combination. The rationale for combining CSA and IVCY is that they inhibit the immune system via different inhibitory mechanisms. Cyclophosphamide acts as a cytotoxic drug for all dividing-stage cells and among immunocompetent cells, it mainly targets B cells. Stone et al reported daily cyclophosphamide (2 mg per kg of body weight) reduced peripheral-blood CD19+ B cell counts in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. El-Zammar et al demonstrated that there were numerous Ki-67-positive interstitial fibroblasts and alveolar epithelial cells in cases of DAD, which indicated these cells were in the dividing-stage and thus may be targeted by IVCY. On the other hand, CSA inhibits calcineurin in T cells, blocks dephosphorylation and translocation of NFATc, inhibits cytokine production from memory CD4+ T cells, and prevents the differentiation of naive CD4+ T cells into cytokine-producing memory CD4+ T cells. Ito et al described a higher CD4+ / CD8+ lymphocyte ratio in the peripheral blood of DM patients with rapidly progressive-ILD than with chronic-ILD. Mukae et al also reported a significantly higher CD4+ / CD8+ ratio in the bronchoalveolar lavage fluid of patients with CADM–ILD than that of classic DM-associated ILD. Taken together, a combination of IVCY and CSA is reasonable to efficiently treat patients with DM–AIP in an additive or synergistic manner.

Our patients were started on biweekly IVCY (750 mg/body) and CSA (150 mg per day) soon after revealing respiratory deterioration and the dose and

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Muscle Weakness</th>
<th>Anti-synthetase</th>
<th>CPK IU/l</th>
<th>KL-6</th>
<th>Initial chest CT findings</th>
<th>P/F* ratio</th>
<th>PSL, mg/day</th>
<th>IV CY, interval**/does mg/day</th>
<th>CSA, mg/day</th>
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<tr>
<td>1</td>
<td>53 M</td>
<td>—</td>
<td>—</td>
<td>32</td>
<td>853</td>
<td>GGO and consolidation</td>
<td>196.6</td>
<td>60</td>
<td>Biweekly 750</td>
<td>150</td>
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<tr>
<td>2</td>
<td>73 F</td>
<td>—</td>
<td>Jo-1</td>
<td>93</td>
<td>1438</td>
<td>GGO and consolidation</td>
<td>57.5</td>
<td>60</td>
<td>Biweekly 750</td>
<td>150</td>
</tr>
<tr>
<td>3</td>
<td>70 M</td>
<td>—</td>
<td>EJ</td>
<td>86</td>
<td>545</td>
<td>GGO and consolidation</td>
<td>117.1</td>
<td>40</td>
<td>Biweekly 750</td>
<td>150</td>
</tr>
</tbody>
</table>

Anti-synthetase = anti-synthetase antibody; CPK = creatinine phosphokinase; KL-6 = Krebs von der Lungen-6; P/F ratio = PaO2/FiO2 ratio; PSL = prednisolone; IV CY = intravenous pulse cyclophosphamide; CSA = cyclosporine A; GGO = ground glass opacity

* The lowest value during clinical course

** The first interval between first and second IV CY course
interval of these agents were then adjusted according to patients’ overall conditions. All of them dramatically recovered from respiratory decompensation within two weeks after the initiation of this combination therapy and continued improving thereafter. DAD progresses irreversible late, i.e. the fibrotic stage occurs within a few weeks and thus treatment needs to begin so as not to miss the “window of therapeutic opportunity”. According to the HRCT findings in our patients, they were considered to be in the relatively early stage of DAD, when combination therapies were started. Rapid initiation of aggressive therapy is mandatory to obtain a favorable outcome.

Recently, a low-dose IVCY regimen has been increasingly reported to be similarly effective and associated with less toxicity than the high-dose IVCY regimen for treating patients with lupus nephritis. Houssiau et al compared a low-dose IVCY regimen (6 fortnightly pulses at a fixed dose of 500 mg) with a high-dose IVCY regimen (6 monthly pulses and 2 quarterly pulses; doses increased according to the white blood cell count nadir) to treat patients with proliferative lupus glomerulonephritis. They reported that there were fewer episodes of severe infection in the low-dose group than in the high-dose group, while renal remission was achieved more frequently in the low-dose group, albeit both results were not significantly different. It is noteworthy that there were few adverse events throughout the entire clinical course in our patients. Although all of them were found to have CMV viremia during hospital courses, they were easily treated by valganciclovir and none of them developed any organ involvement in the collagen vascular diseases. The American review of respiratory disease 119: 471–503, 1979.

References

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