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ORIGINAL ARTICLE

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Clinical study of 10 cases of acute or subacute interstitial pneumonia associated with dermatomyositis

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Abstract The prognosis for dermatomyositis (DM) with acute interstitial pneumonia (IP) is very poor. In the past 5 years, we have treated 10 DM patients with acute or subacute IP. Six cases were of acute-type IP, and 4 were of subacute-type IP. The treatment was a combination therapy of methylprednisolone (m-PSL) pulse therapy, cyclophosphamide (CPA) pulse therapy, oral cyclosporine A (CsA), and oral PSL. The outcome was 5 deaths and 5 survivals. All 5 cases of death had acute-type IP, four of which were complicated with pneumomediastinum, and these patients died within 40 days of IP onset. Furthermore, 4 of the 5 death cases were diagnosed with amyopathic DM, and one had hypomyopathic DM. The survivors comprised one case of acute-type IP with marked myositis, and 4 subacute cases. These results suggested that the prognosis for DM with IP might be dependent on the type of IP, the severity of the myositis, and the existence of pneumomediastinum. The rapid establishment of a more useful diagnostic technique and therapy for early-phase DM with acute IP is hoped for.

Key words Acute interstitial pneumonia (AIP) · Combination therapy · Dermatomyositis (DM) · Pneumomediastinum

Introduction

Dermatomyositis (DM) and polymyositis (PM) are chronic idiopathic inflammatory diseases that belong to a class of collagen diseases. Marie et al.[1] reported the high mortality rate of 22% in 77 patients with PM/DM; the main causes of death were cancer and lung complications. Lakhanpal et al.[2] reported that 39% of patients with PM/DM had interstitial lung disease (ILD). DM is one of the most common collagen diseases which complicate interstitial pneumonia (IP). Acute-type IP (AIP), in particular, worsens the prognosis of DM, therefore the establishment of a treatment for DM with AIP is important. Generally, a moderate or high dose of steroid is used to treat IP, but for cases of DM with AIP such doses are inadequate. Therefore, a combination of immunosuppressant with steroids is normally used.[3,4] Some recent cases of DM with AIP have shown amyopathy or complicated pneumomediastinum, and the prognosis was very poor.[5,6] Therefore, histopathological data and high-resolution computed tomography (HRCT) findings are very important to evaluate the clinical features of IP and develop a therapeutic strategy. Unfortunately, there have been very few reports reviewing the relationship between the clinical manifestations, histopathological data, and HRCT findings of PM/DM with IP. In this study, we evaluated the clinical course of collagen diseases complicated with IP; these included PM/DM, systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA). The prognosis of DM with acute / subacute IP was the worst of these, and we therefore focused on 10 cases of DM with IP (6 cases of acute-type IP, 4 cases of subacute-type IP), and have clarified the difference between DM patients with AIP and those with subacute IP from aspects of the HRCT findings, histopathological diagnosis, and the effects of combination therapy.

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Patients and methods

In the past 5 years, we have treated 774 patients with main collagen diseases, as shown in Table 1. Of these, there were 34 cases of DM and 9 of PM. Ten of these cases were DM with IP (6 AIP, 4 subacute IP), and one was PM with subacute IP. There was drug-induced AIP in one case each of

DM and PM. With regard to other collagen diseases, we treated 3 cases of SSc with AIP, one case of SLE with AIP, 4 cases of RA with AIP, one case with subacute IP, and 10 cases with drug-induced AIP. The number and ratio of DM patients with AIP plus subacute IP were the highest, and therefore we focused on 10 cases of DM with IP (6 AIP, 4 subacuteIP) (Table 2). With the exception of 6 cases of amyopathic DM (ADM), 4 patients fulfilled the Bohn and Peter criteria for the diagnosis of PM/DM.[7] The DM patients consisted of 2 males and 8 females, with a mean age of 48 years. Nine patients tested negative for anti-Jo-1 antibody and antinuclear antibody (ANA). Six patients who showed low creatine phosphokinase (CPK) and aldolase, and no muscle weakness or pain, were diagnosed as having ADM.[8,9] The diagnosis of IP was confirmed from the clinical features, a pulmonary function test, and HRCT. The definition of acute and subacute IP depended on the interval between the initial pulmonary symptom and respiratory failure due to IP. The interval with AIP was within 1 month, and that with subacute IP was 1–3 months. These patients were classified into 3 groups by clinical course: group 1, recurrent with acute exacerbation (patients 1 and 2); group 2, acute progressive (patients 3, 4, 5, and 6); group 3, subacute (patients 7, 8, 9, and 10). As shown in Table 2, oral cyclosporine A (CsA) and prednisolone (PSL) were administered to all the patients, and both methylprednisolone (m-PSL) pulse and cyclophosphamide (CPA) pulse therapies were performed in 7 patients. Treatment was started within 7 days and 60 days after the onset of IP for the AIP cases and the subacute IP cases, respectively.

Table 1. Summary of collagen diseases with acute or subacute interstitial pneumonia

Collagen diseases	Number	Interstitial pneumonia		
		Acute	Subacute	Drug-induced
DM	34	6	4	1
PM	9	0	1	1
SSc	28	3	0	0
SLE	61	1	0	0
RA	642	4	1	10
Total cases	774	14	6	12

DM, dermatomyositis; PM, polymyositis; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis

Results

Two patients in group 1 showed improvement in clinical features and HRCT findings after the initial treatment, but deteriorated thereafter. Eventually, both patients died within just 30 days from AIP recurrence, despite the combination therapy of m-PSL pulse therapy, CPA pulse therapy, and CsA. Four patients in group 2 showed a very rapid change in their clinical course, which worsened rapidly in a linear manner. Three of the 4 patients died within 50 days from IP onset. One patient (No. 6), who had severe myositis and a very high CPK level of up to 9531 IU/l, was the only survivor. All cases of subacute IP (group 3) survived. All 5 cases of death were either ADM (patients 1, 2, 3, and 5) or hypomyopathic DM (patient 4). Four out of 5 death cases were complicated with pneumomediastinum (patients 1, 2, 3, and 4). The onset rate of pneumomediastinum was 100%,

Table 2. Characteristics of 10 DM cases with acute or subacute IP

Patient	1	2	3	4	5	6	7	8	9	10
Sex/age	F/60	F/41	M/28	F/55	M/59	F/65	F/32	F/42	F/43	F/58
Heliotrope rash	−	+	+	−	+	−	+	+	−	−
Gottron's sign	+	+	+	−	−	+	+	+	+	−
Erythema	+	+	+	+	+	+	+	+	+	+
Skin ulcer	−	−	−	+	−	++	++	++	−	−
CPK (IU/l)	17	76	97	612	72	9531	87	47	222	1433
Aldolase (IU/l)	8.6	6.7	8.1	22.5	8.3	65	14.4	6.1	6.2	17.5
ANA	−	−	−	−	−	×640	−	−	−	−
Anti Jo-1 antibody	−	−	−	−	−	−	−	−	−	+
HRCT finding	GrGl	GrGl	GrGl	GrGl	GrGl	GrGl	Cp/s	Cp/s	Cp/s	Cp/s
Histopathological diagnosis	NSIP3	DAD	nd	nd	DAD	nd	NSIP2	nd	NSIP2	nd
Pneumomediastinum	+	+	+	+	−	−	−	−	−	−
Therapy: m-PSL pulse	+	+	+	+	+	+	+	−	+	+
CPA pulse	+	+	+	+	+	−	+	−	+	−
CsA	+	+	+	+	+	+	+	+	+	+
Days from IP onset to therapy	4	1	3	7	3	4	60	60	37	17
Days from IP onset to death	30	30	40	40	50	*	*	*	*	*
Type of DM	ADM	ADM	ADM	HDM	ADM	MDM	HDM	ADM	ADM	HDM
Type of IP	Acute	Acute	Acute	Acute	Acute	Acute	Subacute	Subacute	Subacute	Subacute
Group	1	1	2	2	2	2	3	3	3	3

IP, interstitial pneumonia; CPK, creatine phosphokinase; ANA, antinuclear antibody; HRCT, high-resolution CT; GrGl, ground glass pattern; Cp/s, consolidation pattern with patchy and/or subpleural distribution; DAD, diffuse alveolar damage; NSIP, nonspecific IP; nd, not detected; m-PSL, methylprednisolone; CPA, cyclophosphamide; CsA, cyclosporine A; ADM, amyopathic DM; HDM, hypomyopathic DM; MDM, myopathic DM

Group 1, recurrent with acute exacerbation; Group 2, acute progressive; Group 3, subacute

* Alive

50%, and 0% in groups 1, 2, and 3, respectively. These ratios correlated with the mortality rate in the three groups (Table 3). HRCT findings for AIP (groups 1 and 2) showed a ground-glass pattern (GrGl), and all cases of subacute IP (group 3) showed a consolidation pattern with patchy and/or subpleural distribution (Cp/s).[10] We made a histopathological diagnosis of diffuse alveolar damage (DAD) in 2 patients, and nonspecific IP3 (NSIP3) in one patient (groups 1 and 2, respectively), and of NSIP2 in 2 patients (group 3). Skin ulcers appeared in 4 patients, and were deep and incurable in 3 patients (Nos. 6, 7, and 8). Typical cases in the 3 groups are described below.

Patient 2 was referred to our hospital for finger joint pain, erythema of Gottrons' sign, and heliotrope rash on January 4, 2002, and was admitted on January 8. She was given daily oral doses of 30 mg prednisolone (PSL). Soon after, most of the joint pain, erythema, and the consolidation pattern shown by HRCT disappeared (Fig. 1). In mid-February, the erythema was exacerbated, and the patient complained of fever, dry cough, and exertional dyspnea. On February 27, HRCT showed the diffuse GrGl pattern of IP, and a poor prognosis was suspected. Immediately after the recurrence, a combination therapy of m-PSL pulse therapy, CPA pulse therapy, and oral CsA was initiated for AIP. Nevertheless, the clinical features and HRCT findings deteriorated. In addition, her serum level of KL-6, which is an excellent IP marker, increased to over 3000 U/ml. Eventually, there were complications with pneumomediastinum and subcutaneous emphysema on March 9. The patient was put on mechanical ventilation on March 16, and died of respiratory failure 2 days later.

Table 3. Summary of the three groups associated with DM–IP

Group	1	2	3
Number of cases	2	4	4
HRCT finding	GrGl	GrGl	Cp/s
Histopathological diagnosis	DAD (1) NSIP3 (1)	DAD (1)	NSIP2 (2)
Frequency of pneumomediastinum (%)	100	50	0
Mortality rate (%)	100	75	0

Patient 5 complained of multiple finger joint pain on September 15, 2001. He was referred to our hospital on October 2 without any respiratory symptoms. At that time, fine crackles were audible in the middle and lower lungs bilaterally, and immediate chest radiography and chest CT showed IP in the same area. The PO_2 in arterial blood gas was a low of 53 mmHg. The patient was admitted to hospital immediately. After a video-assisted thoracic surgery (VATS) examination on day 2 after admission, m-PSL pulse therapy, CPA pulse therapy, oral CsA, and PSL were started. Prior to starting mechanical ventilation on October 24, m-PSL pulse therapy and CPA pulse therapy were performed three times and twice, respectively, but the patient's clinical condition and GrGl pattern on HRCT deteriorated rapidly, and his serum level of KL-6 increased to 6000 U/ml. On day 50, he died of respiratory failure (Fig. 2).

Patient 6 was somewhat different from the above cases of AIP. She noticed erythema on her face and arms and muscle weakness of the lower limbs in mid-February, 2001. She was admitted to hospital on February 19, and laboratory tests revealed a high titer for CPK at over 9000 IU/l, and for aldolase at over 60 IU/l. She was diagnosed as DM with severe myositis, and was treated with m-PSL pulse therapy (m-PSL 1.0 g/day for 3 consecutive days) and oral PSL (40 mg/day). Thereafter, her CPK level decreased to 617 IU/l and her myositis improved gradually. On March 28, she suddenly complained of high fever, dry cough, and exertional dyspnea. Chest radiography and HRCT showed a GrGl pattern. Fortunately, additional m-PSL pulse therapy (m-PSL 1.0 g/day for 3 consecutive days) and oral

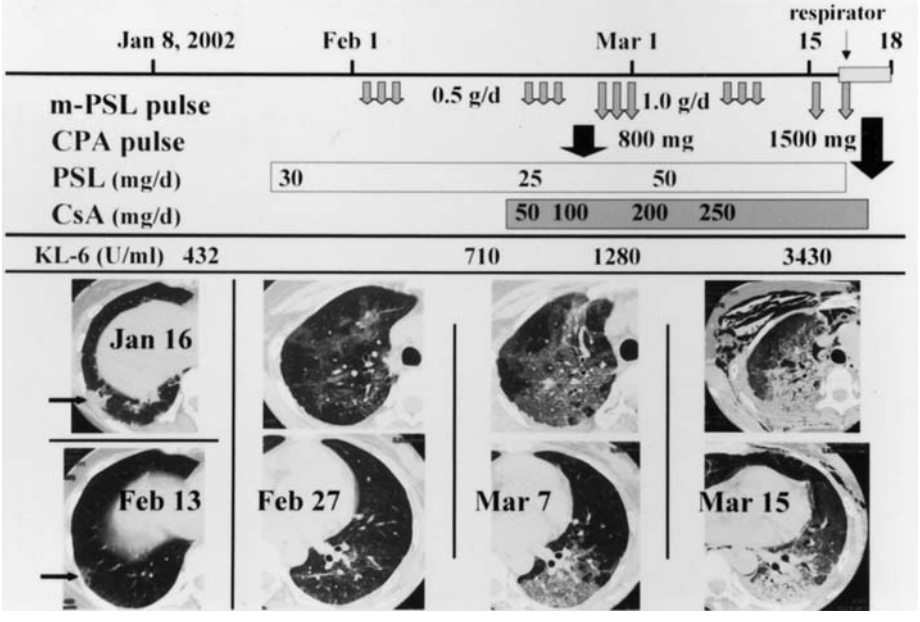

Fig. 1. Clinical course and high-resolution CT (HRCT) image of the chest in patient 2. The initial treatment with oral prednisolone (*PSL*) (30 mg/day) was very effective, and the consolidation pattern on HRCT almost disappeared (*arrow*). After the recurrence, the ground glass (GrGl) shadow of interstitial pneumonia (IP) spread very rapidly, and pneumomediastinum and subcutaneous emphysema appeared on March 9, 2002. *m-PSL*, methylprednisolone; *CPA*, cyclophosphamide; *CsA*, cyclosporine A

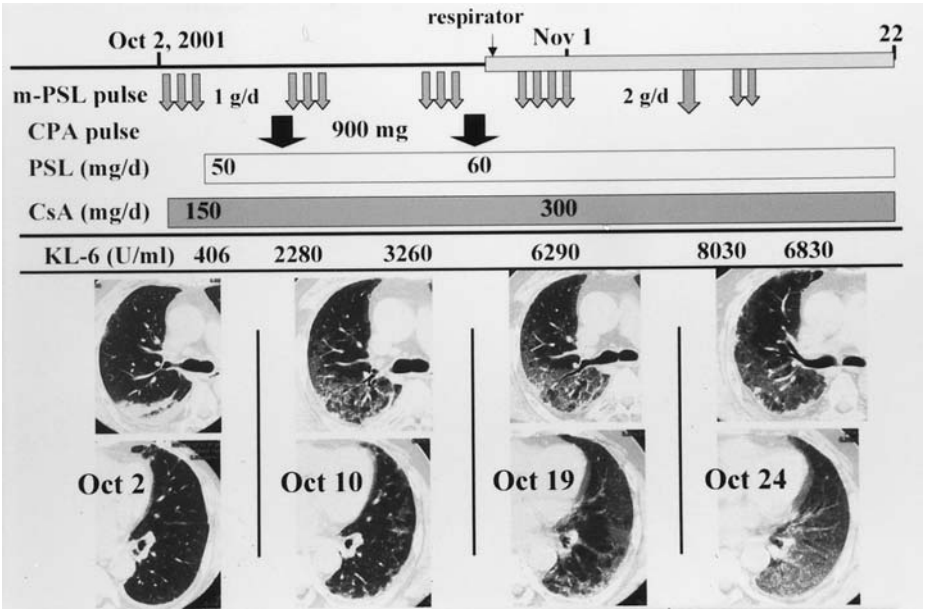

Fig. 2. Clinical course and HRCT image of the chest in patient 5. The IP image deteriorated linearly from the day of admission until the day mechanical ventilation was initiated despite combination therapy

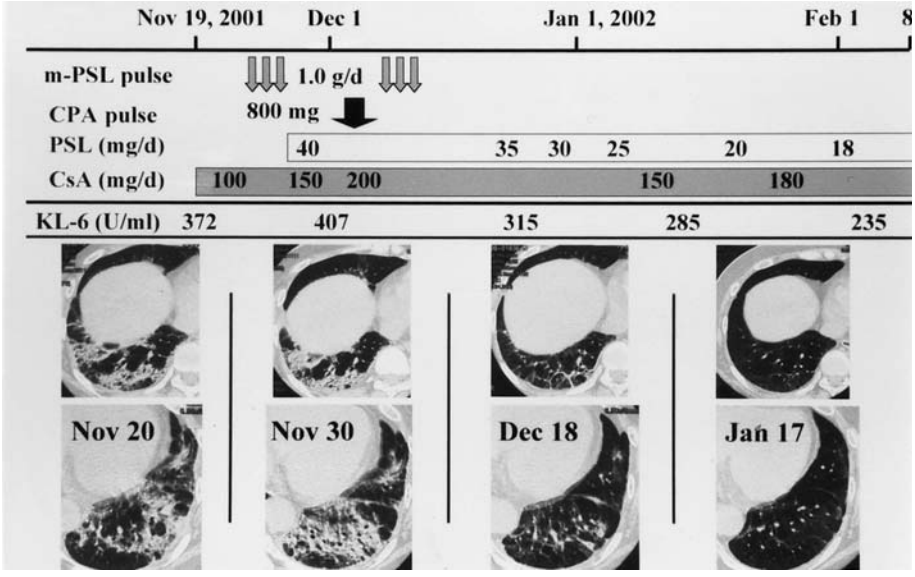

Fig. 3. Clinical course and HRCT image of the chest in patient 9. The consolidation pattern of IP had almost disappeared after only 2 months of the initial treatment

CsA (100 mg/day) improved her clinical condition and laboratory data (CPK 107 IU/l, aldolase 19 IU/l), and the diffuse GrGl shadow disappeared completely.

Patient 9 had finger erythema on October 3, 2001, and suffered from a dry cough on October 13. On November 2, the patient had exertional dyspnea, which later worsened. On November 19, she consulted our hospital and was admitted immediately with a diagnosis of DM with IP. Although her PO_2 was within the normal range (85 mmHg) and IP on HRCT showed a Cp/s pattern, we started a combination therapy for fear of an exacerbation of the IP, as shown in Fig. 3. By mid-December, the dry cough had disappeared completely, and the IP shadow on HRCT improved gradually. Her KL-6 level was within the normal range during her clinical course. The patient was discharged on February 8, 2002.

With regard to other collagen diseases, one of 9 PM cases with subacute IP was treated successfully with a combination therapy of m-PSL pulse therapy and oral CsA. Three of 28 SSc cases had been complicated with AIP and had survived, which was attributed to a combination therapy of m-PSL pulse therapy, CPA pulse therapy, and CsA. One of 61 SLE cases had AIP (lupus pneumonitis) and died despite the combination therapy. Two of 642 RA cases with AIP died despite m-PSL pulse therapy and CPA pulse therapy, but 2 other cases with AIP survived with the same therapy. One case with subacute IP was treated successfully with the combination therapy of m-PSL pulse therapy, CPA pulse

therapy, and oral CsA. All cases with drug-induced AIP recovered completely after m-PSL pulse therapy or oral PSL only (see Table 1).

Discussion

In 1979, Pearson reported the cases of 12 patients with typical skin features of DM, but with little sign of myositis, and named such cases amyopathic DM (ADM).[11] Fudman and Schnitzer[6] also reported cases of DM with AIP without CPK elevation, and their prognosis was very poor. Euwer and Sontheimer[8,9] termed such patients ADM and defined the criteria for ADM. Histological diagnoses of IP were classified into four main types, as follows: 1, diffuse alveolar damage (DAD); 2, bronchiolitis obliterance organizing pneumonia (BOOP); 3, nonspecific interstitial pneumonia (NSIP); 4, usual interstitial pneumonia (UIP).[12,13] Patients with DAD generally have a poor prognosis, and AIP is thought to be closely related to DAD. NSIP is classified into 3 types, namely, NSIP 1, 2, and 3. The prognosis for patients with NSIP2 is comparatively better than for those with NSIP3 under adequate therapy. We diagnosed 6 patients with ADM because of low CPK, low aldolase, and typical skin features without any sign of myositis. Of these patients, 2 with subacute IP are still alive, but all 4 patients with AIP died despite combination therapy (see Table 2). This means that the prognosis for ADM patients with AIP is very poor, and this has been shown in all other reports.[6] Furthermore, we obtained histopathological data for 5 patients whose diagnoses of IP were DAD (patients 2 and 5), NSIP3 (patient 1), and NSIP2 (patients 7 and 9). All 3 patients with DAD or NSIP3 were ADM, and died in a short period. Toyoshima et al.[14] reported 4 ADM cases, all of whom died despite having received high-dose corticosteroid and immunosuppressive therapy, and their IP were all DAD. Radiological findings demonstrated that all cases of AIP and subacute IP showed a GrGl pattern and a Cp/s pattern, respectively, on HRCT. With the exception of patient 6, all those with AIP died.

On the other hand, all the patients with subacute IP survived. This suggests that patients showing a GrGl pattern on HRCT have a very poor prognosis compared with those showing a Cp/s pattern. There have been very few reports of ADM with IP that review the histopathological and radiological data (HRCT) simultaneously. Therefore, our present study of ADM, where both histopathological and HRCT findings were evaluated, is expected to be of great interest and value. We presume that four factors might be important indices for the poor prognosis of DM patients with IP. These are acute progression, amyopathy, or hypomyopathy in the physical aspect, DAD or NSIP3 in the histological aspect, and a GrGl pattern in the radiological aspect.

The incidence of ILD complicated with pneumomediastinum in interstitial pneumonitis was reported to be 7.4%.[15] The three main pathological mechanisms of pneumomediastinal development have been described as: (1) soft tissue infections by gas-forming microorganisms; (2) disruption of cutaneous or mucosal barriers; (3) rupture of the alveoli due to a marked increase in intraalveolar pressure or a decrease in peribronchovascular interstitial pressure, or both.[16] In cases of DM with IP, pneumomediastinum is often recurrent and resistant to therapy, and causes respiratory failure. Two types of pneumomediastinum have been described in patients with DM, namely, that associated with rapidly progressive IP with or without vasculitis, and a poor prognosis, and that characterized by chronic or recurrent pneumomediastinum with or without IP.[17–20] Up to 1998, 33 cases of DM with pneumomediastinum had been reported in Japan.[21] Of these patients, 18 died, giving a mortality rate of 56%. These reports clarified the poor prognosis of DM with pneumomediastinum. The mechanism of pneumomediastinum is the rupture of the alveoli surrounding capillary arteries, and a leakage of air flow to the mediastinum.[22] Furthermore, steroids cause tissue fragility and delay tissue healing.[23] Kono et al.[24] reported 4 DM cases complicated with pneumomediastinum, and 3 of them were associated with cutaneous vasculopathy. They speculated that the main cause of pneumomediastinum was the focal bronchial wall necrosis caused by vasculopathy. In our study, the appearance (patients 1, 3, and 4) or exacerbation (patient 2) of pneumomediastinum occurred just after mechanical ventilation was started, which meant that it was induced by the increased intraalveolar pressure. Only patient 4 showed mild cutaneous ulceration on her left elbow due to vasculopathy, and therefore a definite relation between vasculopathy and pneumomediastinum could not be found. All 4 patients with pneumomediastinum died within 40 days from IP onset. This suggested that the existence of pneumomediastinum might be a fifth index for the poor prognosis of DM with IP, in addition to acute progression, physically amyopathic or hypomyopathic, a histopathological diagnosis of DAD or NSIP3, and a GrGl pattern on HRCT.

The most standard treatment for PM/DM with IP is m-PSL pulse therapy and oral PSL, and the second is oral CsA.[3,4] The first clinical trial of CsA in PM/DM with IP was performed by Gruhn and Diaz-Buxo in 1987.[3] Pugh et al.[25] have also reported successful treatment with CsA in a case of steroid-resistant DM with ILD. In Japan, the effectiveness of CsA on PM/DM with IP was first reported in the annual report of the Ministry of Health and Welfare Autoimmune Diseases Research Committee in 1997.[26] The efficacy of CsA was almost 68% in AIP and 50% in chronic IP. The trough level of CsA was recommended to be between 100 and 200 ng/ml. Nawata et al.[27] reported that corticosteroid-resistant IP cases mainly developed in PM/DM without CPK elevation at the onset of IP, and that CsA was effective in such cases, and the survival of the patients was prolonged. With regard to the effect of CPA, useful reports of CPA pulse therapy are few.[28–30] The precise mode of action of CPA pulse therapy on ILD associated with PM/DM is unknown, but Al-Janadi et al.[29] have reported that the use of CPA during the cellular phase of ILD might prevent progression to irreversible interstitial fibrosis and pulmonary insufficiency. Therefore, in this study, we started

a combination therapy of m-PSL pulse therapy, CPA pulse therapy, oral CsA, and PSL from the beginning, when the condition of the patients was serious, or when they had been diagnosed with ADM or hypomyopathic DM with a pulmonary manifestation. Despite the early start of the combination therapy for AIP, 5 out of 6 cases died within 50 days of IP onset. These data suggested that there should be a specific group of DM with AIP, a fulminant group, which is very refractory to any therapy. Yamasaki et al.[31] reported 14 cases of DM with acute or subacute IP, and 6 cases died within 3 months despite a combination therapy of oral CsA, PSL and CPA pulse therapy. The reason for this resistance to therapy was suggested to be a rather rapid progression of pulmonary injury. On the other hand, CsA was used in all cases and was effective in a case of AIP with severe myositis, and in all the cases with subacute IP. These data suggest that use of CsA is very effective in cases of DM with AIP and subacute IP with the exception of the so-called fulminant group.

In summary, we have described 3 groups of DM patients with different IP progression. Of these, group 3 (the subacute group) had a comparatively good prognosis, whereas group 1 (the recurrent group) and group 2 (the acute progressive group) had very poor prognoses. From this standpoint, an earlier diagnosis and the rapid establishment of a more effective combination therapy for DM with AIP are hoped for.

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