Combination Therapy with Corticosteroids, Cyclosporin A, and Intravenous Pulse Cyclophosphamide for Acute/Subacute Interstitial Pneumonia in Patients with Dermatomyositis

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ABSTRACT. ***Objective.*** Acute/subacute interstitial pneumonia (A/SIP) in patients with polymyositis/dermatomyositis (PM/DM) is frequently fatal within months despite high dose prednisolone (PSL) therapy. Our objective was to improve the survival rate of patients with A/SIP associated with PM/DM; and to characterize patients with PM/DM who are at high risk of developing A/SIP.

Methods. We conducted a pilot trial of combined immunosuppressive therapy with high dose PSL, 10–30 mg/kg of intravenous pulse cyclophosphamide (IVCYC) every 3–4 weeks, and 2–4 mg/kg/day of cyclosporin A (CSA) for patients with A/SIP. A/SIP was diagnosed based on a history of rapidly worsening respiratory symptoms, progressive radiological findings or hypoxemia, and compatible findings in high resolution computed tomography images.

Results. Before December 2000, 12 patients with DM among 83 PM/DM patients developed A/SIP, and 9 patients died despite treatment using high dose PSL with or without a choice of CSA, cyclophosphamide, or azathioprine. Thereafter, 10 patients with DM among 27 PM/DM patients developed A/SIP, and they were given combination therapy with PSL, CSA, and IVCYC. Five patients survived and are doing well for more than 2 years, although the remaining 5 patients died of respiratory failure within 3 months. DM patients with A/SIP showed the following characteristic features: mild myositis, palmar papule, fever, and negative or low titer of antinuclear antibody.

Conclusion. Immediate institution of intensified immunosuppressive therapy should be considered for patients with A/SIP complicating DM. However, even early recognition of A/SIP and immediate commencement of a regimen including CSA and IVCYC in addition to high dose PSL may not be sufficient for some of those patients. (J Rheumatol 2005;32:1719–26)

Key Indexing Terms:
PALMAR PAPULE POLYMYOSITIS DERMATOMYOSITIS PNEUMOMEDIASTINUM

Polymyositis/dermatomyositis (PM/DM) is a disease of autoimmune origin, predominantly affecting the proximal girdle muscles[1,2]. The presence of the pathognomonic rashes, namely the heliotrope rash and Gottron's papules, distinguishes DM from PM[1-3]. PM and DM share overlapping systemic features, including Raynaud's phenomenon, polyarthritis, dysphagia, cardiac dysfunction, and interstitial pneumonia (IP).

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IP is an important factor adversely influencing the prognosis of patients with PM/DM, and is related to the presence of some autoantibodies against aminoacyl transfer ribonucleic acid (tRNA) synthetases such as the anti-Jo-1 antibody[4]. Some patients with PM/DM, especially with amyopathic DM (ADM), develop acute or subacute interstitial pneumonia (A/SIP), with rapid worsening within a month (acute) or within 2–3 months (subacute)[5]. The prognosis of patients with ADM who develop A/SIP is extremely poor, and they usually do not respond to the corticosteroid treatment, including high dose prednisolone (PSL) and pulse corticosteroid therapy, cyclosporin A (CSA), and cyclophosphamide (CYC), and often die of respiratory failure within a few months[5-7]. Indeed, the condition has been estimated to be fatal in about 70% of the patients despite therapy of high dose corticosteroid plus CSA[8].

We reviewed patients with PM/DM who had visited our department until November 2000. Then we prospectively investigated the efficacy of an intensified immunosuppressive therapy regimen consisting of a combination of high

dose PSL, CSA, and intravenous pulse CYC (IVCYC). Finally, we examined the clinical features of PM/DM patients who developed A/SIP, in order to clarify the characteristic features of those patients who are at high risk of developing A/SIP, for early recognition of A/SIP and immediate institution of intensive therapy.

MATERIALS AND METHODS

Patients. A total of 110 consecutive patients with a diagnosis of PM (n = 35 including 5 men) or DM (n = 75, 24 men) were enrolled for this study. All were seen at our department, either as inpatients or outpatients, between 1985 and 2002. Patients were evaluated according to the criteria of Bohan and Peter[1], and cases with both definite and probable PM/DM were included in the study. To include patients with "hypomyopathic" DM or ADM, patients exhibiting biopsy-confirmed hallmark cutaneous manifestations of classic DM, including the heliotrope rash and Gottron's papules/signs, were enrolled according to the criteria proposed by Sontheimer[3].

Diagnosis of A/SIP. A/SIP was diagnosed based on (1) a history of worsening respiratory symptoms within 3 months; and (2) worsening chest radiograph or computerized tomography (CT) findings, or decrease in the level of PaO_2 within 3 months; and (3) findings in high resolution CT (HRCT) images of the lungs compatible with nonspecific interstitial pneumonia (NSIP), diffuse alveolar damage (DAD), or organizing pneumonia (OP)[9].

Treatment. In December 2000, we started a prospective pilot study of a combination immunosuppressive therapy regimen consisting of high dose corticosteroids (> 0.5 mg/kg/day PSL), 10–30 mg/kg IVCYC every 3–4 weeks, and 2–4 mg/kg/day CSA (to achieve a trough level of 150–250 ng/ml) for patients who had A/SIP associated with DM, only if HRCT of the lungs suggested NSIP or DAD. On the other hand, when the chest HRCT suggested OP associated with PM/DM, 0.5 mg/kg/day of PSL alone was typically started. The dose of PSL was tapered by 10% weekly after 2–3 weeks of treatment at the initial dose. The dose of IVCYC was adjusted to achieve a peripheral blood total leukocyte count nadir not less than 2000/μl.

Statistical analysis. For group comparisons using binary data, Fisher's exact test was used. Comparisons based on continuous data were by Mann-Whitney U test. The results were regarded as significant when the p value was < 0.05.

RESULTS

A/SIP complicating DM was associated with death within months of the diagnosis despite conventional immunosuppressive therapies. First, we investigated the prevalence of A/SIP in patients with PM/DM. Until November 2000, we had seen 83 patients with PM/DM, and surprisingly, all the patients with A/SIP in our series had a diagnosis of DM. Twelve patients with DM developed A/SIP, and 9 (75%) patients died of respiratory failure within months. Then we reviewed the response of those patients with A/SIP to immunosuppressive therapy. Most of them failed to respond to the treatment using high dose PSL with or without one of the following immunosuppressant drugs: CSA, CYC (oral or intravenous), azathioprine, and mizoribine (an inhibitor of inosine monophosphate dehydrogenase; Figure 1). PSL alone, PSL plus CSA, or PSL plus CYC was effective in only one patient each. Thus, DM patients with complicating A/SIP showed an extremely unfavorable course, and the disease was often fatal despite the treatment with immunosuppressive agents, either singly or sequentially, immediately after establishment of the diagnosis. Therefore, in December 2000, we decided to treat patients with PM/DM who developed A/SIP with a combination of PSL, CSA, and IVCYC.

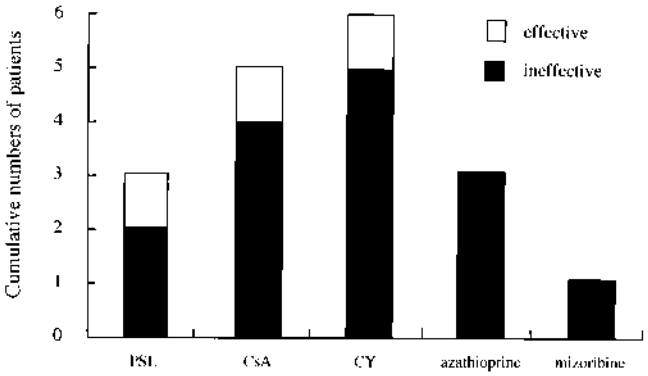

Figure 1. Lack of efficacy of PSL with or without another immunosuppressive drug administered singly in DM patients with A/SIP. Until November 2000, 12 DM patients who developed A/SIP had been treated with high dose PSL alone, or PSL in combination with another immunosuppressive agent administered singly, including CSA, CYC, azathioprine, or mizoribine. Some patients who showed no response to the first drug were given a second drug, thus the total cumulative number of patients reached 18.

Only half of the DM patients with A/SIP who were administered combination therapy with PSL, CSA, and IVCYC survived. From December 2000 to December 2002, 27 patients with PM/DM were recruited to our hospital. Among them, A/SIP was diagnosed in 10 patients, and again exclusively in patients with DM. All their initial HRCT findings for IP suggested DAD (Patients 3 and 7 in Table 1) or NSIP, hence all of them were treated with the combination therapy regimen of PSL, CSA, and IVCYC. Corticosteroid pulse therapy was performed when the development or worsening of A/SIP was observed under treatment with high dose corticosteroids. The responses to the combination therapy regimen are summarized in Table 1. Since the introduction of this combination regimen, the survival rate of DM patients with A/SIP seemed to have improved to 50%. Only one patient (Patient 7) showed both apparent muscle weakness and an elevated serum CK concentration to above twice the value of the upper limit. There were no significant differences between the patients who survived and those who eventually died in terms of the levels of serum CK, lactate dehydrogenase, or KL-6, or in terms of the dose of IVCYC, the serum trough level of CSA, or the time interval between the onset of A/SIP and the start of treatment. However, the patients who eventually died showed a decreased PaO_2 (necessitating the use of oxygen in Patients 7 and 9) at the start of the therapy, tended to develop pneumomediastinum (60% in dead vs 20% in surviving patients), and died within a few months of the diagnosis despite repeated pulses of steroid therapy. All sera from those 10 patients were examined for the presence of antinuclear antibodies (ANA) by

Table 1. Comparison of clinical features between surviving and dead patients with DM and A/SIP.

Patient	Age/Sex	Muscle Weakness	Pneumo-mediastinum	CK, IU/l	PaO_2, Torr	LDH, IU/l	KL-6, U/ml	PSL, mg/day	Steroid Pulse	Maximum IVCYC, mg	CSA Trough, ng/ml	A/SIP Therapy*, days	Outcome**, Days
Surviving													
1	55 M	+	+	235	90.6	230	2710	60	–	750	98–244	8	> 1206
2	33 F	–	–	987	94.0	436	308	60	+	1500	101–178	5	> 1058
3	45 F	+	–	219	86.1	267	885	50	+	1000	119–449	11	> 797
4	34 M	–	–	81	88.3	208	465	60	–	1500	113–227	43	> 788
5	68 F	–	–	133	79.6	238	580	30	–	1000	86–201	45	> 763
Dead													
6	50 F	+	–	103	63.0	419	1160	60	+	1000	40–59	8	55
7	29 F	+	+	1052	10†	1450	4900	100	+	750	86–121	13	48
8	66 F	–	–	411	72.2	296	773	60	+	1000	18–391	34	53
9	58 F	–	+	298	3†	491	803	50	+	1000	75–293	19	52
10	47 F	+	+	338	84.4	306	431	45	+	900	151–348	4	67

* Duration from onset of A/SIP to start of combination therapy. ** Duration from start of combination therapy to outcome. † Oxygen supplementation with 10 l/min and 3 l/min, respectively.

both immunofluorescence and RNA-immunoprecipitation tests, which resulted in negative tests for all the patients.

Representative radiographic changes of A/SIP in the chest CT during treatment with the combination regimen of PSL, CSA, and IVCYC. Patient 7 did not show apparent lung disease at the time of diagnosis of DM (Figure 2A). However, soon after the start of treatment with PSL 60 mg/day, she developed a subpleural consolidation, which developed into diffuse ground-glass opacities within 9 days. With a diagnosis of A/SIP, CSA and IVCYC as well as corticosteroid pulse therapy were immediately added to PSL; however, despite this treatment, she died of respiratory failure within a month. Patient 3 also showed no evidence of IP at the time of diagnosis of DM; however, later, during treatment with PSL 50 mg/day, she developed linear opacities in the lung fields bilaterally (Figure 2B). Despite immediate addition of CSA and IVCYC as well as corticosteroid pulse therapy to the therapeutic regimen, ground-glass opacities appeared in the CT. This patient did not develop pneumomediastinum, and the ground-glass opacities gradually changed to reticular or linear opacities, and marked resolution of the chest CT abnormalities was observed within a few months. Patient 9 showed reticular opacities and a subpleural consolidation in June 2002 (Figure 2C). Although combination therapy with PSL, CSA, and IVCYC was immediately started, the changes of interstitial lung disease showed marked aggravation, and she died of respiratory failure in August 2002 despite repeated pulses of steroid therapy. Patient 10 showed reticular opacities and a subpleural consolidation in her chest CT in November 2002 (Figure 2D). Despite immediate institution of treatment with PSL, CSA, and IVCYC, progressive reticular opacities developed as well as pneumomediastinum, and she died of respiratory failure in January 2003 despite repeated pulses of steroid therapy.

Clinical characteristics of DM patients with A/SIP. Finally, in order to clarify the clinical characteristics of DM patients with A/SIP for early recognition of patients at high risk of developing fatal lung disease, the clinical characteristics of 22 patients with DM who developed A/SIP were compared with those of 53 DM patients with chronic IP or no IP (Table 2). More than half the patients with A/SIP showed only a modest increase in the serum CK level (less than twice the value of the upper limit), and these patients tended to show negative electromyography or muscle biopsy findings for myositis. Thus, DM patients who developed A/SIP had a tendency to have modest myositis, compared to other DM patients with chronic IP or no IP. Patients with A/SIP more frequently showed the heliotrope rash and, interestingly, palmar papules were observed almost exclusively in these patients (Figure 3). These DM patients with A/SIP also had fever and a negative test for ANA.

DISCUSSION

We describe a subgroup of DM patients with an extremely poor prognosis because of the development of A/SIP. Further, we conducted, for the first time, a pilot prospective study of an intensified immunosuppressive therapy regimen consisting of PSL, CSA, and IVCYC for these patients.

About 50% of Japanese patients with PM/DM develop IP during the course of their disease[4], whereas only around 30% of Caucasian patients with this disease have been reported to develop IP[9,10]. Further, a disproportionately large number of cases of fatal A/SIP among Japanese patients without muscle weakness has been reported from Japan; 16 out of 27 patients (59%) died due to IP[5], although there is a tendency recently that only successfully treated cases have been reported, thus raising the apparent survival rate.

In DM patients, DAD, NSIP, and OP have been found

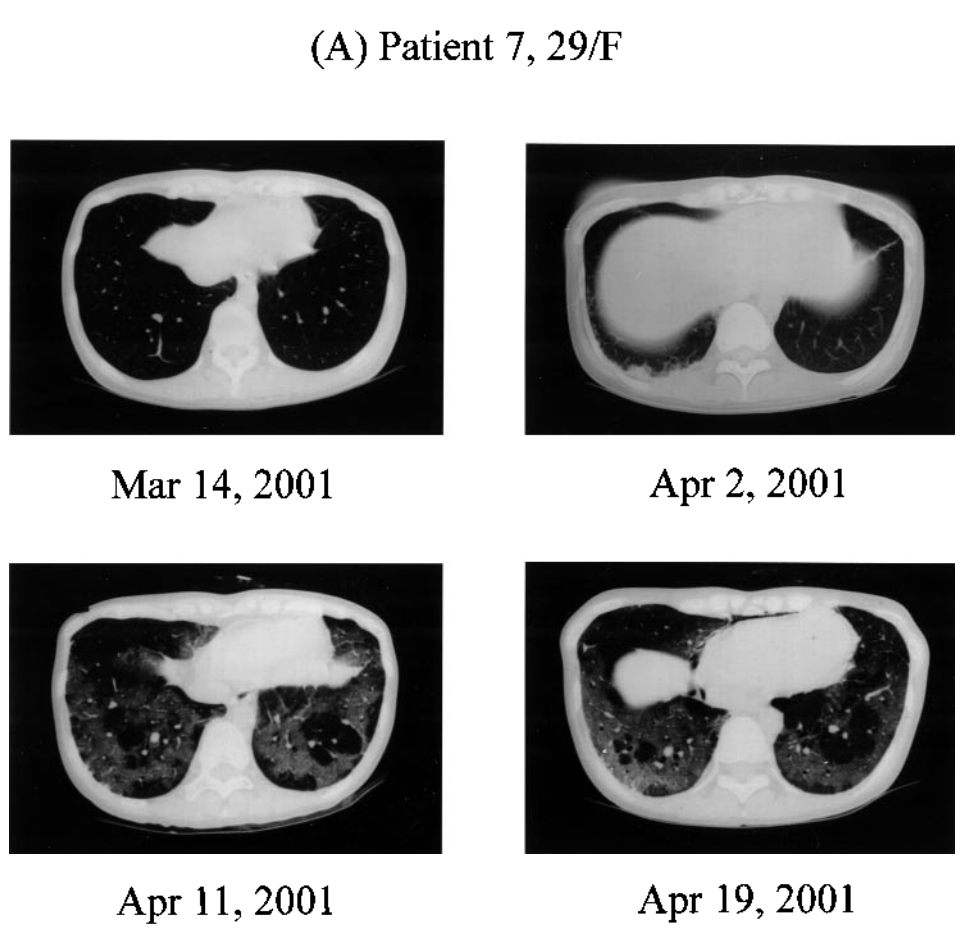

Figure 2. Progression or resolution of chest CT findings in DM patients with A/SIP during PSL + CSA + IVCYC therapy. Paired images from different axial levels are shown sequentially in B. A, B, C, and D correspond to Patients 7, 3, 9, and 10, respectively (see Table 2).

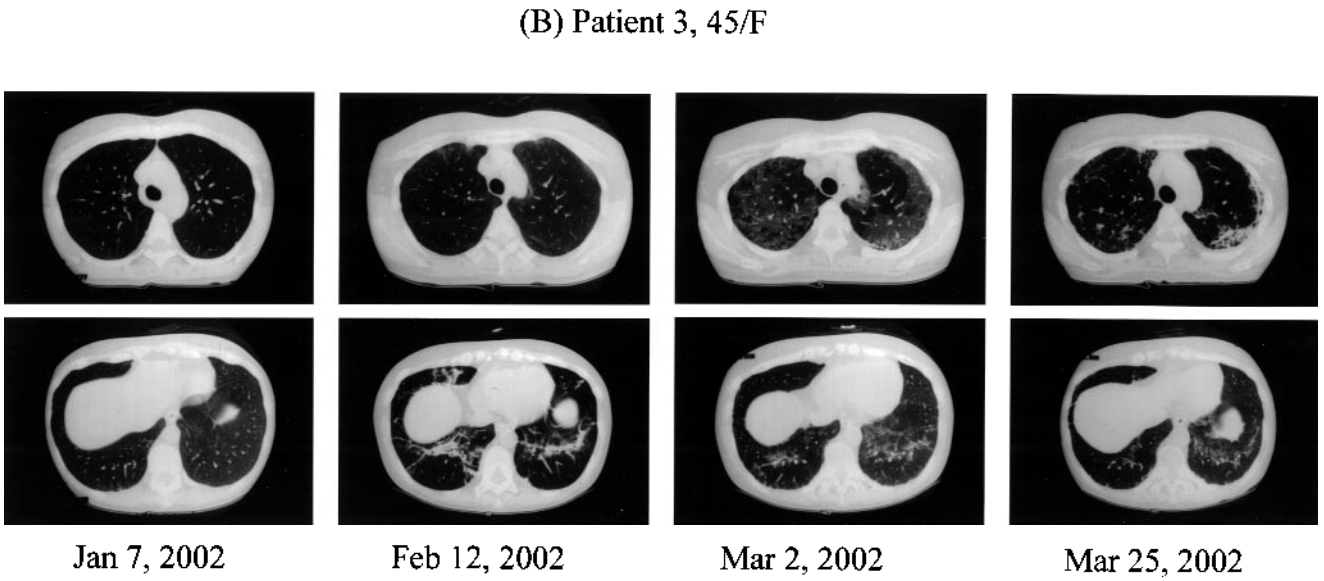

Figure 2B. Patient 3; paired images from different axial levels are shown sequentially.

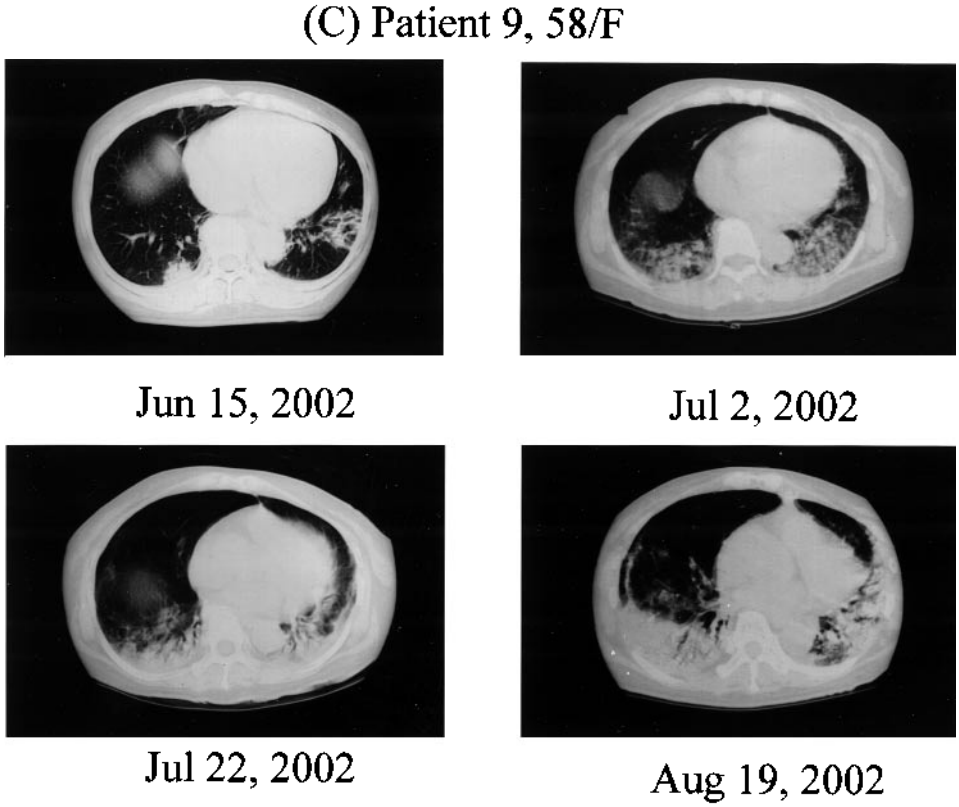

Figure 2C. Chest CT findings, Patient 9.

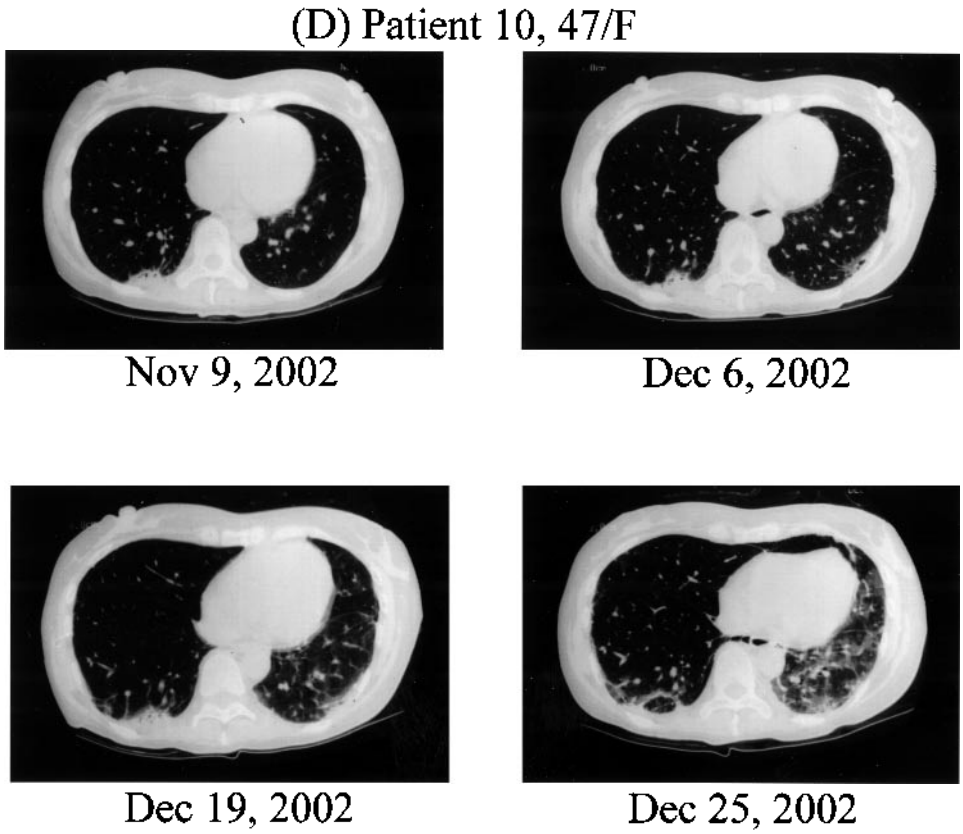

Figure 2D. Chest CT findings, Patient 10.

Table 2. Comparison of clinical features between DM patients with A/SIP and either chronic or no IP. Data are percentages, except serum CK.

	A/SIP, % (n = 22)	Chronic or No IP, % (n = 53)	p
Male	27	30	NS
Muscle weakness	74	76	NS
Serum CK ≥ 2 × upper limit	41	86	< 0.001
Serum CK, IU/l	429	4109	NS
Positive EMG	55	91	< 0.01
Positive muscle biopsy	32	81	< 0.001
Heliotrope rash	68	36	< 0.05
Gottron's papule/sign	91	76	NS
Palmar papule	64	4	< 0.0001
Fever ≥ 38°C	59	34	< 0.05
ANA ≥ × 160	41	73	< 0.05
Anti-Jo-1 positive	0	10	NS

NS: not significant.

during histologic examination for A/SIP[4,7,9-11]. Among these histologic patterns, patients with OP, and also a majority with NSIP, typically show a favorable response to corticosteroids[5,7,12]. In contrast, DAD usually shows exacerbation during immunosuppressive therapy, and is often fatal[6–8,13,14]. Recently, Kuroda, *et al* described 10 Japanese DM patients with A/SIP. Histopathological diagnosis was made in 5 patients: the diagnoses were DAD in 2 patients, who died, and NSIP in 3 patients including 2 survivors[7]. In our series of patients, transbronchial lung biopsy was performed in Patient 3; unfortunately, nondiagnostic samples were obtained. The remaining patients refused consent for lung biopsy procedures and autopsy results were obtained only from Patient 9, which revealed DAD.

Thus, we conducted serial HRCT of the chest once or twice a month in order (1) to confirm the diagnosis; (2) to clarify the mode of IP progression; and (3) to rule out opportunistic infections. We also regularly performed tests for monitoring the serum level of ß-D-glucan, bacterial cultures of the sputum, and polymerase chain reaction for the detection of *Pneumocystis carinii* in the sputum and to determine the copy number of cytomegalovirus in whole blood. Among 10 patients described here, none developed any opportunistic infections. The serial chest HRCT findings in the patients who died (Patients 7, 9, and 10; Figure 2) clearly showed steady progression of the IP despite immunosuppressive therapy, resulting in a fatal outcome; and based on the CT findings, the possible histologic patterns in these cases were consistently deduced to be NSIP or DAD. Importantly, the chest CT findings at the time of starting the combined immunosuppressive therapy were typically not so severe, even in patients who eventually died of respiratory failure within a few months. Therefore, the initial CT findings do not seem to be predictive of the prognosis.

In this study, we identified some characteristic clinical features of DM patients who developed A/SIP: (1) milder myositis, in terms of either the absence of muscle weakness or a serum CK level less than twice the upper limit value; (2) presence of the characteristic rashes of DM, including the heliotrope rash and Gottron's papules/signs; (3) presence of

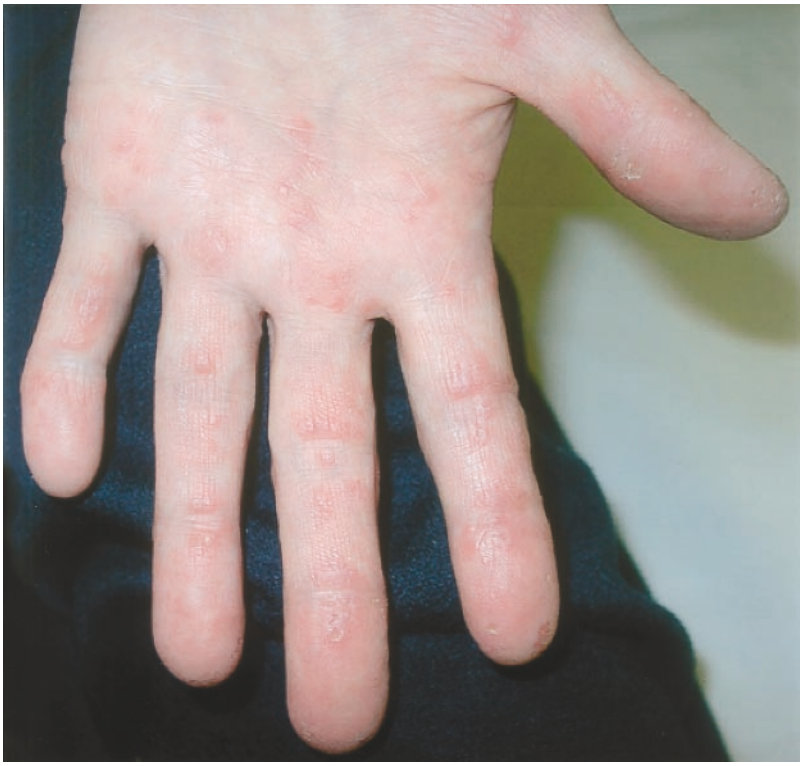

Figure 3. Palmar papules, Patient 10.

palmar papules; (4) presence of fever; and (5) negative tests for serum ANA, anti-Jo-1, and other autoantibodies. Among these 5 features, the association between palmar papules and the risk of development of A/SIP was the most striking. This is a painful papule, raising the possibility of the presence of cutaneous vasculitis. Unfortunately, however, skin biopsy samples from that lesion were not obtained in our patients. Instead, skin samples were always obtained from Gottron's papule on knuckles or elbows in order to confim the diagnosis of DM. Those biopsy samples always revealed perivascular lymphocytic infiltration, but they did not show evidence of vasculitis. However, it is also noteworthy that cutaneous vasculopathy has been reported to be associated with pneumomediastinum[15,16], which was observed in only one patient who survived, but in 3 out of the 5 patients who died in our series. Thus, palmar papule is likely to be an indicator not only of the presence or development of A/SIP, but also of the potential development of pneumomediastinum and a fatal outcome. Muscle histopathology in patients with A/SIP usually reveals mild myositis, and vasculitis was never observed in their muscle specimens.

The efficacy of CSA in patients of PM/DM with IP has been reported, and those reports indicate that CSA should be used early in the course of IP to obtain a favorable response[17-22]. However, the prognosis of a subset of patients with A/SIP complicating DM, especially those with DAD in ADM, is still very poor, despite immunosuppressive therapy with a single agent such as CSA or IVCYC at a standard dose (10–30 mg/kg)[6-8]. IVCYC is also the drug of choice for treatment of various lung diseases including IP associated with PM/DM[23]. The rationale for the combined use of CSA and IVCYC is based on the fact that CSA is a selective T cell inhibitor, whereas IVCYC mainly suppresses B cell functions[24]. Our aim was to improve the survival rate of the patients with DM and A/SIP, rather than to determine which immunosuppressive agent might be more effective. Adverse events were observed exclusively in surviving patients, mostly after a few months of the therapy: nasal septal perforation, subcutaneous abscess, and submucosal dissection of the esophagus in Patient 1; herpes zoster infection in Patient 2; diverticular hemorrhage in the ascending colon in Patient 3; and peripancreatic abscess in Patient 4.

With the use of the combination therapy regimen including PSL, CSA, and IVCYC, the survival rate of patients with A/SIP associated with DM seems to have improved from 25% in the era of conventional therapy to 50%. Nonetheless, it is more important that half of such patients still died of respiratory failure within a few months, despite immediate institution of an aggressive combination therapy. Furthermore, it is of considerable interest that A/SIP tended to develop about the same time as the onset of DM, and has not relapsed in surviving patients followed for more than 2 years (Table 1).

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