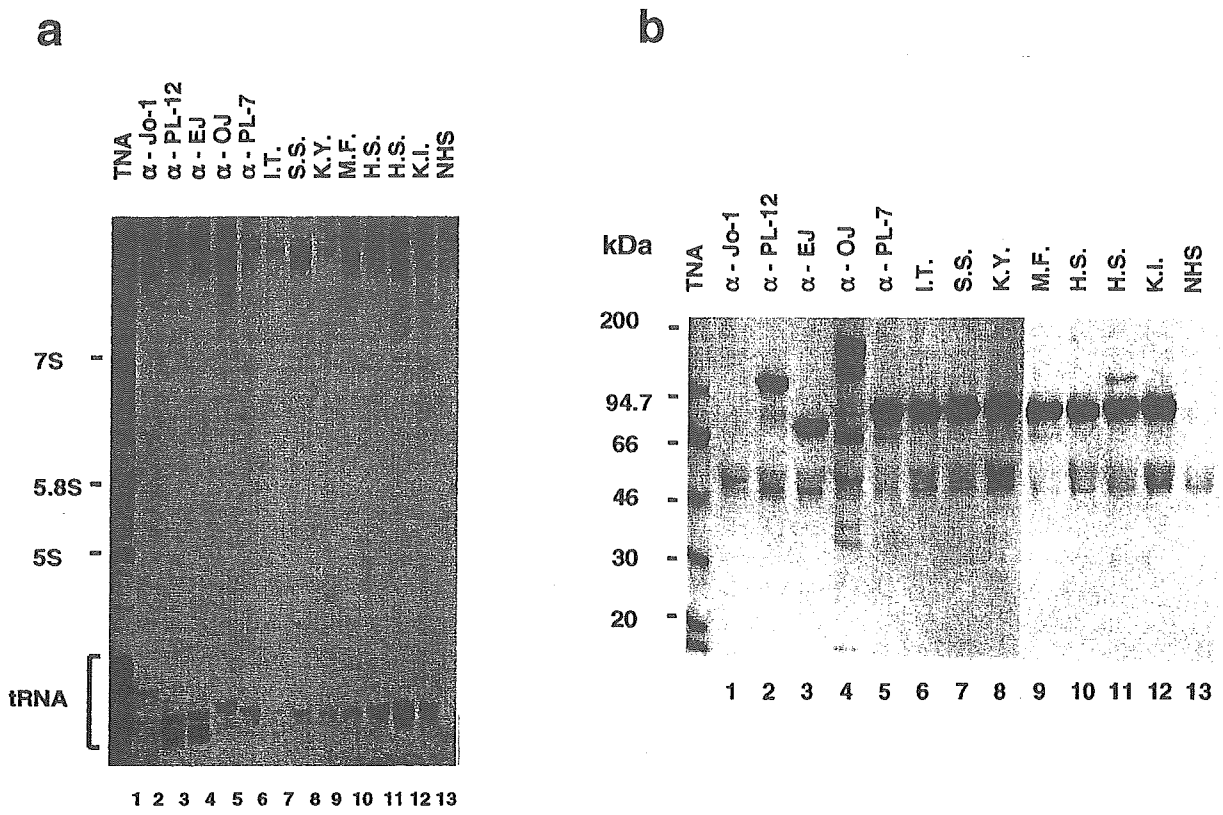

Fig. 1. (**a**) Immunoprecipitation (IPP) of nucleic acids with anti-PL-7 sera and controls. Urea (7 M) and 10% PAGE of phenol-extracted immunoprecipitates from HeLa cell extracts were developed with silver stain. TNA, total nucleic acids, with the 5.8 and 5.0 S small ribosomal RNAs and the tRNA region indicated. Sera used for IPP include: lanes 1-5, the anti-synthetase sera indicated, with antibodies to Jo-1 (histidyl-tRNA synthetase), PL-12 (alanyl-tRNA synthetase), EJ (glycyl-tRNA synthetase), OJ (isoleucyl-tRNA synthetase), PL-7 (threonyl-tRNA synthetase); lanes 6-12, anti-PL-7 sera as indicated; and lane 13, control serum (NHS, normal human serum). The tRNA pattern with anti-PL-7 sera is easily distinguishable from that of the other anti-synthetases.
(**b**) IPP of proteins with anti-PL-7 sera and controls. Autoradiogram of 10% SDS-PAGE of immunoprecipitates from [^{35}S] methionine-labeled HeLa cell extracts. Mr, molecular weight markers of the sizes indicated to the left (kDa). The sera used for IPP are the same as those in (**a**). The same characteristic pattern of 80 kDa protein bands was seen with each of the seven anti-PL-7 sera. The pattern was clearly different from the bands immunoprecipitated by sera against the other anti-synthetases.

Table I. Clinical features of patients with anti-PL-7 antibodies.

Clinical findings	#1	#2	#3	#4	#5	#6	#7
Age/ gender	51/ male	59/ female	32/ female	53/ female	51/ female	64/ female	57/ female
Diagnosis	DM	PM-SSc	PM-SSc	PM-SSc	PM-SSc	IPF	PM-SSc
Fever	(-)	(-)	(+)	(+)	(+)	(+)	(-)
Arthritis	(+)	(+)	(+)	(+)	(+)	(-)	(+)
Muscle weakness	(+)	(+)	(+)	(+)	(+)	(-)	(+)
Raynaud's phenomenon	(-)	(+)	(+)	(+)	(-)	(-)	(+)
Extent of scleroderma	None	Proximal scleroderma	Sclerodactyly alone	Diffuse scleroderma	Diffuse scleroderma	None	Sclerodactyly alone
Digital pitting scar	(-)	(+)	(+)	(+)	(-)	(-)	(+)
Mechanic's hands	(-)	(-)	(-)	(+)	(+)	(-)	(-)
ILD	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Hypergammagloblinemia	(+)	(+)	(-)	(+)	(+)	(-)	(-)
Sjögren's syndrome	(+)	(+)	(+)	(+)	(-)	(-)	(-)
Other autoantibodies	(-)	(-)	Anti-SSA	(-)	(-)	(-)	Anti centromere

PM: polymyositis; DM: dermatomyositis; SSc: systemic sclerosis; ILD: interstitial lung disease.

Table II. Characteristics of myositis in patients with anti-PL-7 antibodies.

Clinical and laboratory findings	#1	#2	#3	#4	#5	#7
DM rash	(+)	(-)	(-)	(-)	(-)	(-)
Maximun CK level (IU/l)	2,830	748	930	1,682	1,663	1,005
EMG findings	Myogenic*	Myogenic	Myogenic	Myogenic	Myogenic	Myogenic
Muscle biopsy	Myopathy	n.d.	n.d.	n.d.	Myopathy	Myopathy
Atrophy	(+)				(+)	(+)
Necrosis with regeneration	(+)				(+)	(+)
Infiltration of lymphocytes	(+)				(+)	(+)
Initial dose of PSL (mg/ day)	60	(-)	40	40	50	30
Duration of treatment (mos.)	159	(-)	44	24	110	93
Efficacy of PSL for myositis	(+)	n.d	(+)	(+)	(+)	(+)
Present status	Death	Alive	Death	Alive	Alive	Alive

*Low amplitude, resting fibrillation, positive sharpe wave (denervatrion potencials) were present. DM: dermatomyositis, CK: creatine kinase, EMG: electromyogram, PSL: prednisolone.

festations were compared between anti-PL-7-positive and negative PM/DM patients (Table III). The frequencies of ILD and sclerodactyly were found to be significantly higher in antibody-positive patients.

Comparison of the clinical features of patients with anti-PL-7 antibodies in the present study and those in the literature

The clinical features of patients with anti-PL-7 antibodies reported in the English-language literature were reviewed (2, 13, 15, 16, 19, 20). A summary of clinical data including our study is shown in Table IV. The frequencies of arthritis, myositis, and Raynaud's phenomenon in our series is similar to those of previously reported patients with anti-PL-7 antibodies. On the other hand, the occurrence of sclerodactyly in our series is greater compared with previous reports from North America and the United Kingdom.

Case 1 (patient #5)

This 51-year-old woman noticed dyspnea on exertion in 1995, after which symptoms progressively worsened. Her general practitioner identified an abnormal lung shadow in the chest radiogram. She was admitted to the Keio University Hospital in October 1995. She had dyspnea on exertion, and muscle weakness predominantly in the proximal muscle. She also had diffuse scleroderma and Raynaud's phenomenon. The CK level was elevated (1,663 IU/l). Myopathic changes detected by EMG mainly in proximal muscles and active necrosis with regeneration seen in a muscle biopsy specimen suggested the presence of myopathy. %VC was 59% and %DLco was 43% on lung function testing, indicating restricted respiratory impairment. A chest radiograph showed bilateral reticular shadow and infiltration. The chest CT revealed interstitial fibrosis and infiltration accompanied by air-bronchogram. A diagnosis of PM/SSc overlap syndrome was established based on proximal muscle weakness, elevated muscle enzymes, typical EMG and muscle biopsy findings and diffuse scleroderma. Treatment with 50 mg/day of PSL was started, resulting in improvement of clinical symptoms including muscle weakness, and dyspnea on exertion, and decrease in CK levels. However, dyspnea worsened again when the dose of PSL was tapered to 11 mg/day. In October 1997, she was re-admitted to our hospital and the dose of PSL was increased to 40 mg/day. %VC improved from the baseline (60%) to the level after treatment (74%). PSL was gradually tapered and she is now taking 10 mg/day of PSL. Although moderate dyspnea on exertion has persisted, she has no muscle weakness and serum CK level is within the normal range.

Case 2 (patient #7)

A 57-year-old woman developed dyspnea on exertion and had a non-productive cough in 1994. She was admitted to the Keio University Hospital in November 1994 due to worsening dyspnea. Chest radiography revealed a reticular shadow in both lower lung fields. A chest CT also showed bibasilar interstitial fibrosis. The pulmonary function test showed a decreased %VC (59%) and decreased $\%DL_{CO}$ (35%). A diagnosis of ILD was made, and PSL 40 mg/day was initiated, resulting in improvement of respiratory symptoms. The dose of PSL was tapered and discontinued in November 1995.

In August 1997, she gradually devel-

Table III. Comparison of clinical features in anti-PL-7-positive versus negative PM/DM.

Clinical and laboratory findings	Anti-PL-7(+) (n = 6)	Anti-PL-7(-) (n = 119)	P value
Male / female	1/ 5	36/83	NS
Fever (%)	3 (50)	59 (50)	NS
Arthritis (%)	6 (100)	73 (61)	NS
ILD (%)	6 (100)	52 (44)	$P < 0.05$
Raynaud's phenomenon (%)	4 (67)	35 (29)	NS
Sclerodactyly (%)	5 (83)	17 (14)	$P < 0.005$

* PM/DM: polymyositis/dermatomyositis, ILD: interstitial lung disease.

Table IV. Clinical features of patients with anti-PL-7 antibodies in literature and our study.

	Previous reports from North America and the United Kingdom							Present study	P value
Year/ Author	1984 Mathews	1988 Targoff	1990 Marguerie	1994 Satoh	1995 Mchugh	1999 Wasko	Total	Sato	
No.	5	4	4	1	1	1	16	7	
Male: female	1:4	2:2	1:3	0:1	0:1	1:0	5:11	1:6	n.s.
Arthritis no. (%)	3 (60%)	4 (100%)	4 (100%)	1 (100%)	0	1 (100%)	13 (81)	6 (86)	n.s.
Myositis no. (%)	4 (80%)	4 (100%)	3 (75%)	1 (100%)	0	1 (100%)	13 (81)	6 (86)	n.s.
ILD no. (%)	1 (20%)	3 (75%)	3 (75%)	0	1 (100%)	0	8 (50)	7 (100)	n.s.
RP no. (%)	2 (40%)	1 (25%)	4 (100%)	0	1 (100%)	1 (100%)	9 (56)	4 (57)	n.s.
Sclerodactyly no. (%)	0	0	2 (50%)	0	1 (100%)	0	3 (19)	5 (71)	P < 0.05

ILD: interstitial lung disease, RP: Raynaud's phenomenon

oped muscle weakness and polyarthralgia. In January 1998, the patient was re-admitted. She had sclerodactyly and digital pitting scar as well as muscle weakness and polyarthralgia. Blood tests revealed an elevated CK level (1005 IU/l). The EMG showed myopathic changes. A muscle biopsy revealed chronic inflammatory cell infiltrates in the endomysium, indicating myopathy. The diagnosis of PM-SSc overlap syndrome was made and administration of PSL 30 mg/day was reinstated. The muscle weakness and arthralgia were improved markedly and the CK level normalized in 1998.

Discussion

In the present study, we found 7 patients who had anti-PL-7 autoantibodies among 1,135 patients suspected to have CTD. With regard to clinical symptoms, the features of these patients with anti-PL-7 appeared to reside within the spectrum of the "anti-synthetase syndrome" that has been noted in other patients with anti-ARS antibodies (13). However, it should be noted that the frequency of sclerodactyly in our series was significantly higher than in our PM/DM patients without anti-PL-7 antibodies or anti-PL-7 antibody-positive patients previously reported in the English-language literature. In addition, 2 patients had diffuse scleroderma and one had proximal scleroderma. In fact, 5 of 7 (71%) patients were diagnosed as having PM-SSc overlap syndrome. Anti-PL-7 antibodies are likely to be associated with PM-SSc overlap syndrome in Japanese patients. It is thought that there could be certain racial difference in frequencies of autoantibodies. For instance, anti-PM-Scl antibodies known to be associated with PM-SSc overlap were detected in Caucasian SSc patients but not in Japanese SSc patients (21). Because the number of patients with anti-PL-7 is limited, further studies are required to confirm our hypothesis.

Refractory myositis with anti-ARS antibodies has been reported (22). However the degree of myositis of our cases was relatively mild. Treatment with corticosteroid alone resulted in the resolution of muscle weakness and the normalization of serum CK level successfully in all patients although 2 died from complications unrelated to myositis.

Arthritis and chronic ILD are characteristics of anti-ARS seropositive patients (7, 8) and these features were frequently detected in our series of patients with anti-PL-7 antibodies. It is known that certain patients with PM/DM have ILD preceding the appearance of muscle symptoms (1,8,23). Although patient #6 was diagnosed with IPF at this point, the possibility remains that muscle symptoms may arise in the future. Therefore, continuous careful follow-up observation will be necessary to monitor future muscle involvement.

In conclusion, clinical features detected in 7 Japanese patients with anti-PL-7 antibodies are essentially consistent with anti-ARS syndrome previously reported, such as high frequencies of arthritis, chronic ILD and relatively mild PM/DM for which corticosteroid therapy is effective. An additional clinical manifestation unique to anti-PL-7-positive patients is concomitant scleroderma, and anti-PL-7 are likely to be associated with PM-SSc overlap syndrome in Japanese patients. The detection of anti-PL-7 antibodies may be useful in the diagnosis and disease classification of patients with connective tissue diseases.

Acknowledgement

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□ CASE REPORT □

Long-term Clinical Course of a Patient with Anti PL-12 Antibody Accompanied by Interstitial Pneumonia and Severe Pulmonary Hypertension

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Abstract

We report a case of a patient with anti PL-12 antibody accompanied by interstitial pneumonia and severe pulmonary hypertension. At first presentation, hyperkeratotic skin lesions were found, although the diagnosis of CVD was not conclusive. Lung histology showed diffuse fibrosing interstitial pneumonia predominantly in the subpleural regions. During the seven-year follow-up period, severe pulmonary hypertension developed, although the progression of lung fibrosis was relatively limited. Anti-PL12 antibody was detected, and therefore the patient was diagnosed as having antisynthetase syndrome. Lung histology and pulmonary arteriogram suggested that vascular involvement of the disease contributed to the development of severe pulmonary hypertension.

(Internal Medicine 44: 319–325, 2005)

Key words: antisynthetase syndrome, interstitial pneumonia, pulmonary hypertension

Introduction

Collagen vascular disease (CVD) is considered to be a major cause of interstitial pneumonia, and assessment of comorbid CVD is necessary for the evaluation of patients with interstitial pneumonia (1). The presentation of interstitial pneumonia precedes other organ involvement in some patients with CVD (2), and the diagnosis is challenging in such patients. In such situations, the detection of a specific autoantibody is sometimes helpful for the diagnosis of CVD.

The antisynthetases are the most widely recognized myositis-specific autoantibodies. They are directed at aminoacyl-tRNA synthetases (ARS), cytoplasmic enzymes that catalyze the binding of amino acids to their cognate tRNAs for incorporation into growing polypeptide chains. Among the antisynthetases, anti-Jo-1 antibody (anti-histidyl-tRNA synthetase antibody) was the first to be discovered (3), followed by anti-PL-7 (4), anti-PL-12 (5), anti-EJ, anti-OJ (6), and anti-KS (7) antibodies. In patients with polymyositis/dermatomyositis (PM/DM) carrying the antisynthetases, an increased frequency of interstitial lung disease (50–100% versus 10%) and arthritis (60–100% versus 30%) compared to patients without the antibody has been reported (8). Other characteristic clinical features include Raynaud's phenomenon, fever, and hyperkeratotic skin lesions called mechanic's hand (9, 10). The disease characterized by positive antisynthetase, accompanied by some of these clinical features is called antisynthetase syndrome.

Anti-PL-12 antibody (anti-alanyl-tRNA synthetase antibody) is one of the antisynthetases; an association of anti-PL-12 antibody with a high frequency of interstitial lung disease, myosistis, arthritis, skin rash, Raynaud's phenomenon, and fever has been reported (11–14), although the number of patients described in such reports was limited.

Pulmonary hypertension is a life-threatening complication of patients with interstitial pneumonia. However the incidence of pulmonary hypertension in patients with antisynthetases is unknown.

Here, we report a patient with anti PL-12 antibody complicated by interstitial pneumonia and severe pulmonary hypertension.

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Table 1. Laboratory Tests on Admission

<CBC>		<Arterial blood gas (room air)>	
White blood cells	$10.9\times10^9/l$	pH	7.435
Red blood cells	$4.82\times10^{12}/l$	PaO_2	78.6 mmHg
Hemoglobin	15.8 g/dl	$PaCO_2$	41.4 mmHg
Platelets	$263\times10^9/l$	HCO_3^-	27.5 mmol/l
ESR	38.2 mm/h	<Bronchoalveolar lavage (right B^{3b})>	
<Serology>		Fluid recovery	57/100 ml
CRP (<0.3)	2.2 mg/dl	Recovered cell count	2.68×10^5/ml
RAHA (<×40)	×1,280	Macrophage	80.0%
Antinuclear antibody	<×40	Lymphocyte	10.7%
Anti -dsDNA antibody	negative	Neutrophil	9.3%
Anti-RNP antibody	negative	CD4/CD8 ratio	0.34
Anti-Scl-70 antibody	negative	<Pulmonary function tests>	
Anti-Jo-1 antibody	negative	VC	1.91 *l*
Anti-SSA antibody	negative	%VC (predicted)	70.5%
Anti-SSB antibody	negative	$FEV_{1.0}$	1.51 *l*
<Biochemistry>		$FEV_{1.0}$/FVC	77.4%
LDH (240–460)	318 IU/*l*	%DLco	78.7%
CPK (20–110)	16 IU/*l*		
ALD (1.7–5.7)	3.7 IU/*l*		
TP (6.5–8.3)	7.4 g/dl		
γglobulin (10.8–19.4)	26.3%		

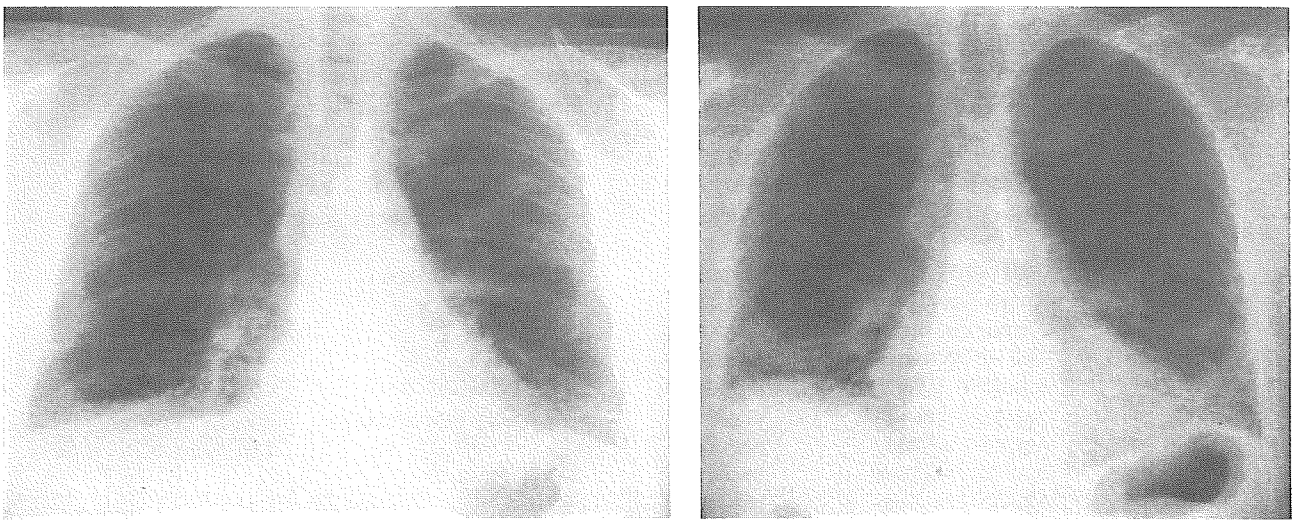
ESR: erythrocyte sedimentation ratio, RAHA: rheumatoid arthritis hemagglutinin, dsDNA: double-strand DNA, RNP: ribonucleoprotein, LDH: lactate dehydrogenase, CPK: creatine phosphokinase, ALD: aldolase, TP: total protein, VC: vital capacity, FEV: forced expiratory volume, FVC: forced vital capacity, DLco: diffusing capacity for carbon monoxide.

Case Report

In August 1994, a 44-year-old Japanese man underwent a pulmonary function test as part of his annual medical check-up, and he was found to have a reduced vital capacity (%VC 73%). However, he did not visit a hospital because of the absence of symptoms. In April 1996, he noticed xerosis of the fingertips, and on August 1996, he was first found to have abnormal opacities on chest X-ray. Two months later, he suffered from cough, and in March 1997, he visited a hospital because of dyspnea on exertion (Fletcher-Hugh-Jones II°) and exacerbation of the cough. At this time, chest computed tomography revealed reticular and ground glass opacities at the level of the bilateral lung bases, and his pulmonary lesion was diagnosed as interstitial pneumonia. He was subsequently admitted to our hospital in May 1997 for further investigations and treatment of interstitial pneumonia.

Physical examination revealed a body temperature of 36.6 °C, blood pressure of 104/62 mmHg, and pulse rate of 94/min with a regular rhythm. Though hyperkeratosis of the fingers was found, it was not specific for any CVD. There was no other skin lesion such as Gottron's sign or Heliotrope rash. Finger clubbing and Raynaud's phenomenon were not apparent. In the lung auscultation, fine crackles were audible in the bilateral lower lungs. Heart auscultation, abdominal and neurological examinations were normal. There was no superficial lymph node swelling. The patient had no history of smoking or previous illnesses. The laboratory tests (Table 1) showed elevation of WBC (10,900/μl), CRP (2.2 mg/dl), and erythrocyte sedimentation ratio (38.2 mm/h). Rheumatoid factor was significantly elevated to ×1,280 (normal range: <×40), although antinuclear antibody and autoantibodies for CVD were negative.

Arterial blood gas measurement revealed mild hypoxia (PaO_2 78.6 mmHg). A pulmonary function test showed mild reduction of vital capacity (%VC 70.5%). Bronchoalveolar lavage fluid showed an increased total cell recovery (2.68×10^5/ml), without an increase of lymphocyte ratio (lymphocytes 10.7%), and a slight increase in the neutrophil ratio (neutrophils 9.3%). The pathologic findings obtained from transbronchial lung biopsy were not diagnostic. The electrocardiogram revealed no abnormality. The findings on chest X-ray at admission (Fig. 1A) showed a reduced volume of the bilateral lower lungs with mild reticular shadows. Chest computed tomography showed ground glass opacities and reticular shadows at the bilateral lung bases, while other areas of the lung fields were almost clear (Fig. 2A). In September 1997, a videoscope-assisted lung biopsy was performed, and three specimens were sampled from the left S1+2, the left B8, and the left B9 regions. Lung tissues from the 3 biopsy sites showed fibrotic changes with loss of normal alveolar structure, predominantly in the subpleural and periacinar regions. The fibrotic lesions showed gradual changes from fibrosis with loss of normal alveolar structures, to thickened



A B

Figure 1. Chest X-ray (A, April 1997 (on admission); B, May 2004). A: On admission, reduced volume of bilateral lungs, and elevation of diaphragm was observed. B: During the follow-up period of seven years, linear and reticular shadows developed in the bilateral lower lungs, however, the lesions were minimal in the upper and middle lung fields.

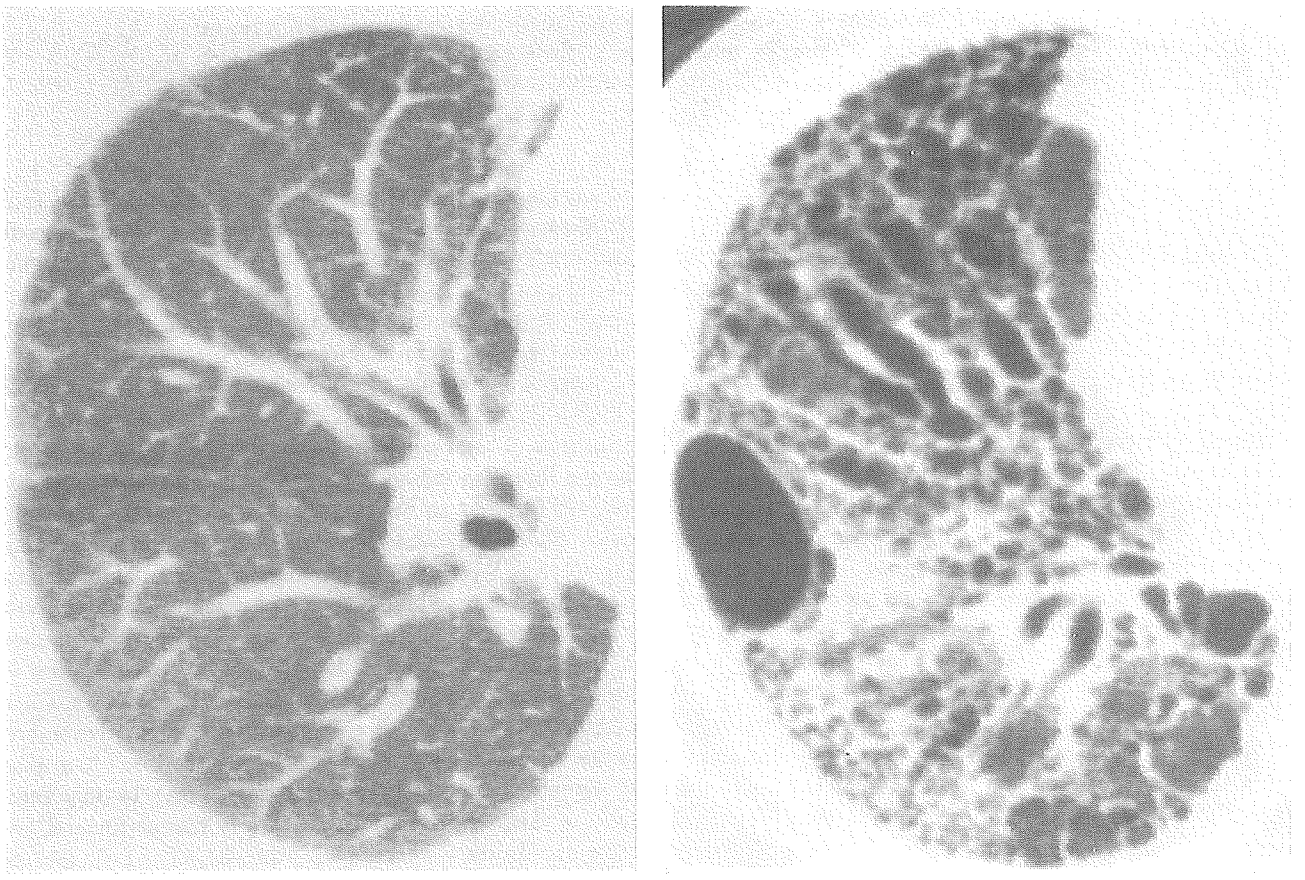


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Figure 2. Chest computed tomography (A, Right lower lobe, April 1997; B, Right lower lobe, May 2004). During the follow-up period, ground glass opacity accompanied by traction-bronchiectasis developed along the broncho-vascular bundles, and subpleural bullae were also found.

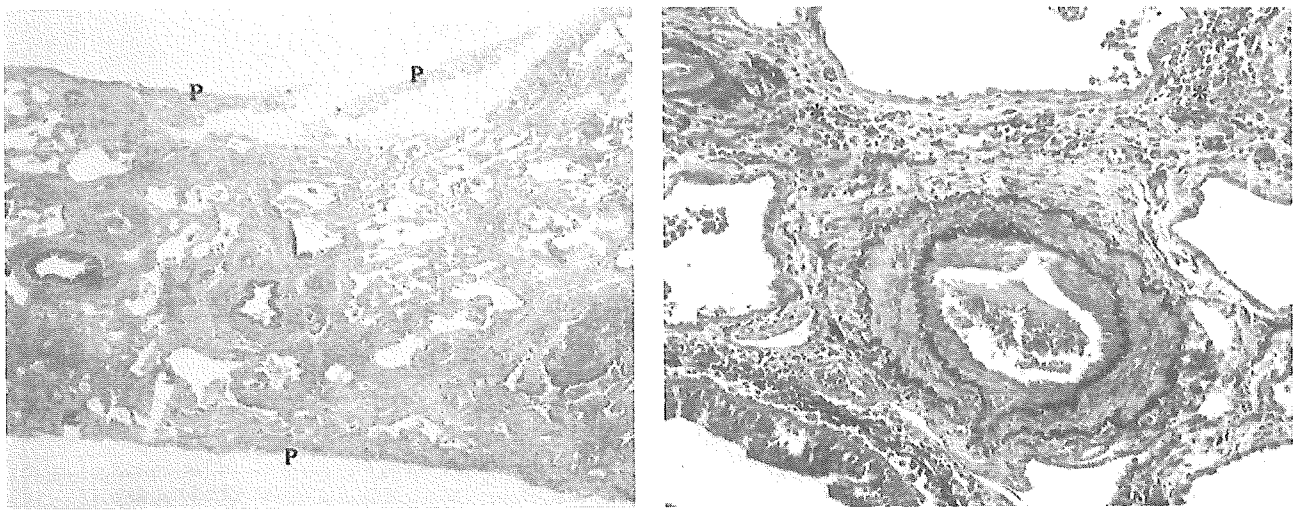
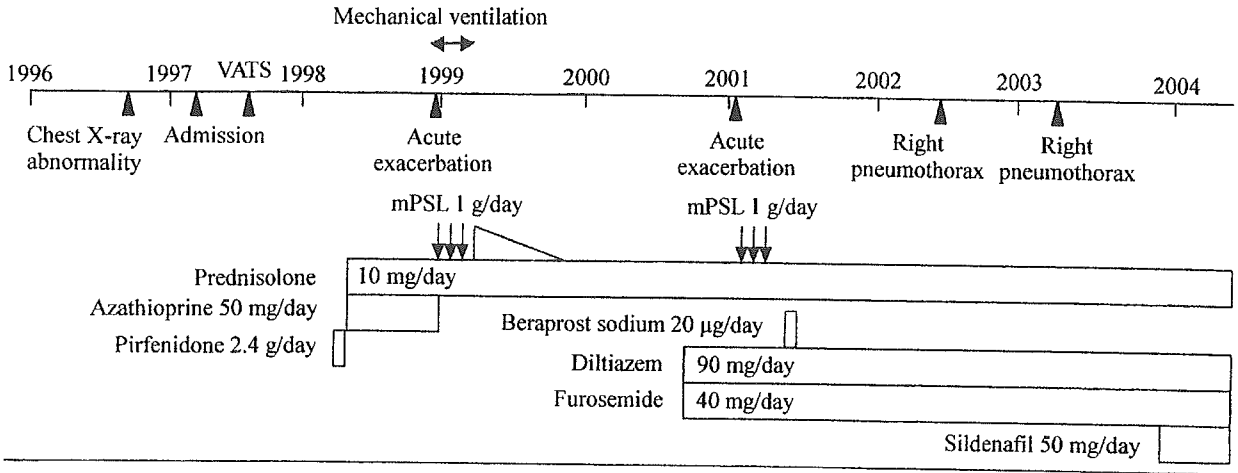


Figure 3. Histopathologic findings in the lung obtained by video-assisted thoracoscopic surgery. (A) Predominantly subpleural/periacinar fibrosis is seen diffusely with loss of normal alveolar structure (P: visceral pleura) (left S1+2, HE stain, ×2). (B) A higher magnification of the left half of (A). The muscular pulmonary artery shows thickening of intimal and medial layers, causing mild luminal stenosis. Adjacent alveolar tissue (*) shows fibrosis with loss of normal alveolar elastic framework (left S1+2, EvG stain, ×10).

and then to normal alveolar walls. Aeration of alveolar regions was about 25% of normal, while the ratio of normal to total alveolar walls in the lung specimen was about 3%. Fibroblastic foci and lymphoid follicles were not marked. These findings are summarized as nonspecific interstitial pneumonia (NSIP), mixed cellular and fibrosing pattern (Fig. 3A). Muscular pulmonary arteries showed mild luminal stenosis (Fig. 3B). The patient was followed in our hospital without treatment until March 1998, by which time vital capacity was decreased to 43.6% and supplemental oxygen treatment was necessary, due to the development of hypoxemia (Table 2). At this time, pirfenidone was prescribed for the treatment of pulmonary fibrosis, but discontinued due to the side effect of fever. Low-dose prednisolone (10 mg/day) in combination with azathioprine was then started. During this period, pulmonary arterial pressure measured using a Swan-Ganz catheter was normal. In December 1998, acute exacerbation of the interstitial pneumonia occurred, and mechanical ventilation was needed to rescue the patient. After three months of steroid treatment including pulse therapy, the patient recovered. In August 2000, right ventricular overload was detected by echocardiogram, and therefore treatment with calcium channel blocker and diuretics was started. On the occasion of a second acute exacerbation in January 2001, severe pulmonary hypertension with right ventricular heart failure was noted. However, after treatment with dopamine and diuretics, the patient recovered again, and the extent of subsequent pulmonary hypertension assessed by echocardiogram was mild. Prostacyclin (beraprost sodium) was also administered, but discontinued due to the side effect of flushing. During the clinical course, pulmonary fibrosis with traction bronchiectasis and the formation of subpleural bullae progressed (Fig. 2B), and the patient suffered twice from right lung pneumothorax; in each case this was successfully treated by application of an autologous blood patch. However, the involved area was limited to both lower lung fields (Fig. 1B), and the progression of lung fibrosis was relatively mild. In November 2003, the dyspnea got worse, and the estimated systolic pulmonary arterial pressure (PAP) measured by cardiac echogram was increased to 83 mmHg. Swan-Ganz catheterization was performed again, which showed that mean PAP was 56 mmHg. At the same time, the response of PAP to the administration of sildenafil was examined, and the mean PAP decreased to 36 mmHg; thus treatment with sildenafil was started soon afterward. In November 2003, antisynthetase antibody was measured by the immunoprecipitation method as described previously (15), and the patient was found to be positive for anti PL-12 antibody. Three months after the administration of sildenafil, the mean PAP had decreased to 40 mmHg, and hypoxemia had improved. Pulmonary arteriography was performed in February 2004, which showed no apparent thrombosis; however, narrowing of the pulmonary arteries of both lower lobes was observed (Fig. 4). Despite the relatively mild development of lung fibrosis, since the progression of pulmonary hypertension is critical, the patient is now undergoing registration as a candidate for lung transplantation.

Table 2. Clinical Course of the Patient



F-H-J	II°			III°				IV°		
PA pressure (systolic)			28			80→44**	Mild**		93	65
PA pressure (mean)			18						56	40
%VC	70.5	54.7	43.6		31.0		33.1			38.1
Oxygen dose*	none		1 *l*/min				1.5 *l*/min		3 *l*/min	
PaO_2*	78.6		77.8				78.4		60.2	75.2
$PaCO_2$*	41.4		38.9				46.8		55.2	53.4
KL-6 (U/ml)						1,150	1,230	1,240		849
ANP/BNP (pg/ml)				89/53	17/–	18/<5	186/346	51/27	36/13	–/809	207/273

*Under the administration of oxygen (Torr). **Systolic PA pressure estimated by echocardiogram. Normal value: KL-6 <500 U/ml, ANP 8.0–32.2 pg/ml, BNP <18.5 pg/ml.

Discussion

We encountered a patient with anti-PL-12 antibody accompanied by interstitial pneumonia and severe pulmonary hypertension. At first presentation, skin lesions and marked elevation of rheumatoid arthritis hemagglutinin (RAHA) were found.

The findings on chest radiography and lung histology were not typical for idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP), suggesting the existence of underlying CVD, although the diagnosis of CVD was not conclusive. During the follow-up period, the patient was suspected to have antisynthetase syndrome, and the antisynthetase was measured in November 2003 for the first time. Anti-PL-12 antibody was detected, thus the patient was diagnosed with antisynthetase syndrome. The clinical features of the patient such as young age, concurrent skin lesions, and long duration of the disease were mostly compatible with those in previous reports of antisynthetase syndromes. Retrospectively, the hyperkeratotic skin lesions found on both hands at the presentation seemed compatible with mechanic's hand (9, 10). However, Raynaud's phenomenon, arthritis, and clinical signs of myositis were not found in this case. Previous reports demonstrated that some patients with anti-PL-12 antibody show interstitial pneumonia without clinical evidence of myositis (11, 16–18). Friedman et al reported 10 cases with interstitial pneumonia and positive anti-ARS antibodies without clinical evidence of myositis (16). Among them, 6 cases had anti-PL12 antibodies, and myositis was not apparent during the average follow-up period of 3.7 years. Hirakata et al reported that none of 6 Japanese patients with anti-PL-12 antibodies fulfilled the criteria for myositis (17). In the present case also, there were no clinical symptoms of PM/DM, and both serum creatine phosphokinase (CPK) and aldolase were negative during the follow-up period of seven years. The patient is now being closely observed to assess whether clinical signs of myositis will appear or not.

On admission, the chest X-ray findings showed volume loss in the bilateral lower lungs, and marked elevation of the diaphragm similar to "shrinking lung", which is characteristic of CVD such as PM/DM (19). Chest computed tomography showed ground-glass opacities, while honeycombing was not apparent during the development of lung fibrosis.

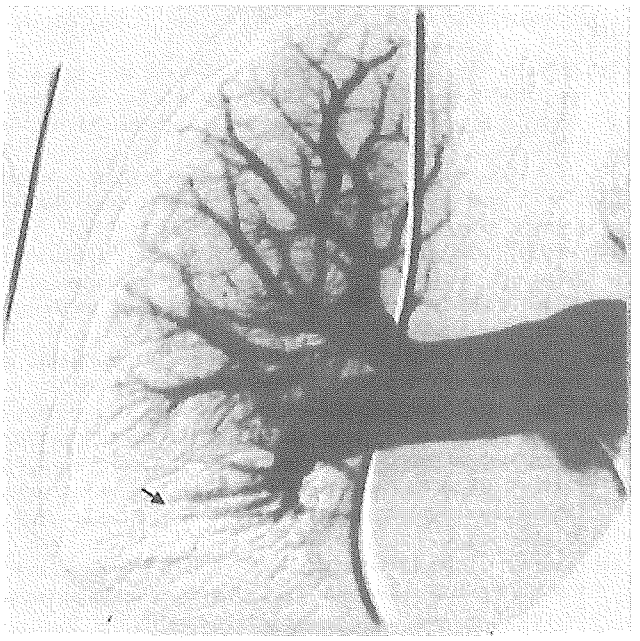


Figure 4. Pulmonary arteriogram (three months after the administration of sildenafil). No apparent thrombosis was found, however, narrowing of the pulmonary arteries was found in the area where lung fibrosis was severe (arrow).

These findings were compatible with NSIP as confirmed by the lung histology (1).

In general, a favorable response to corticosteroid or other immunosuppressive therapy can be expected in patients with interstitial pneumonia and anti-ARS antibodies (10, 16, 20). Hirakata et al followed 35 patients with PM/DM, and found that anti-ARS antibodies were negative in all 5 patients who showed acute exacerbation of interstitial pneumonia, leading to death in 4 cases. Conversely, anti-ARS antibodies were positive with a high frequency in patients who showed a chronic disease course (20). In the present case, the patient recovered twice from acute exacerbation and survived for 10 years from the onset of the disease.

Regarding pulmonary hypertension, few cases have been reported in patients with anti-ARS antibodies. Among 10 cases with anti PL-12 antibodies reported by Targoff and Arnett (11), 2 cases died of severe interstitial pneumonia, and 1 showed pulmonary hypertension. In the present case, the initial lung histology showed mild to moderate intimal proliferation in the muscular pulmonary arteries. Furthermore, pulmonary arteriography performed after the exacerbation of pulmonary hypertension showed narrowing of the pulmonary arteries in the areas of lung fibrosis. These findings suggest that not only the hypoxic vasoconstriction due to the lung fibrosis, but also the vascular lesion directly contributed to the development of severe pulmonary hypertension. Pronk and Swaak reported that intimal proliferation, narrowing of the vessel lumen, and intimal fibrosis were found in the lung histology of patients with CVD accompanied by pulmonary hypertension without lung fibrosis (21). Similar pathologic events might have occurred in the vasculature in this case, during the development of pulmonary hypertension.

In the present case, echocardiography was useful for serial non-invasive evaluation of pulmonary hypertension. Oudiz and Ginzton showed a high correlation between catheterization and echocardiography in estimating the pulmonary arterial pressure, when performed simultaneously (22). As shown in Table 2, ANP (atrial natriuretic peptide, normal value: 8.0–32.2 pg/ml) and BNP (brain natriuretic peptide, normal value: <18.5 pg/ml) levels correlated with the severity of pulmonary hypertension. Wiedemann et al have reported that ANP correlated with pulmonary vascular resistance in patients with primary and non-primary pulmonary hypertension (23). Based on this evidence, we recommend serial evaluation of pulmonary hypertension by echocardiography and measurement of ANP/BNP levels in patients at high risk for development of pulmonary hypertension.

In conclusion, the measurement of anti-ARS antibodies is recommended in cases with interstitial pneumonia, especially when underlying CVD is suspected. The possibility that patients with anti-ARS antibodies might develop pulmonary hypertension should be taken into consideration, even when the progression of lung fibrosis is not significant. Echocardiography and the measurement of ANP/BNP levels can be useful as non-invasive methods for serial evaluation of the severity of pulmonary hypertension.

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Autoantibodies to a 140-kd Polypeptide, CADM-140, in Japanese Patients With Clinically Amyopathic Dermatomyositis

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Objective. **To identify novel autoantibodies specific for dermatomyositis (DM), especially those specific for clinically amyopathic DM (C-ADM).**

Methods. **Autoantibodies were analyzed by immunoprecipitation in 298 serum samples from patients with various connective tissue diseases (CTDs) or idiopathic pulmonary fibrosis (IPF). Antigen specificity of the sera was further examined by immunoblotting and indirect immunofluorescence (IF). The disease specificity and clinical features associated with the antibody of interest were determined.**

Results. **Eight sera recognized a polypeptide of ~140 kd (CADM-140 autoantigen) by immunoprecipitation and immunoblotting. Immunoreactivity was detected in the cytoplasm, and indirect IF revealed a granular or reticular pattern. Anti–CADM-140 antibodies were detected in 8 of 42 patients with DM, but not in patients with other CTDs or IPF. Interestingly, all 8 patients with anti–CADM-140 antibodies had C-ADM. Among 42 patients with DM, those with anti–CADM-140 autoantibodies had significantly more rapidly progressive interstitial lung disease (ILD) when compared with patients without anti–CADM-140 autoantibodies (50% versus 6%; $P = 0.008$).**

Conclusion. **These results indicate that the presence of anti–CADM-140 autoantibodies may be a novel marker for C-ADM. Further attention should be directed to the detection of rapidly progressive ILD in those patients with anti–CADM-140 autoantibodies.**

Polymyositis (PM)/dermatomyositis (DM) is a chronic inflammatory disorder that culminates in injury to the skin and muscle and, sometimes, is associated with interstitial lung disease (ILD) and/or neoplasia (1,2). A number of autoantibodies are associated with myositis, including those specific for aminoacyl–transfer RNA synthetase (anti-ARS) (3), signal recognition particle (anti-SRP) (4), and Mi-2 (5). These autoantibodies have proven to be clinically useful in the diagnosis and classification of these diseases and are predictive of responses to treatment.

It has been known for some time that certain patients may have the typical skin manifestations of DM but no evidence of myositis, a condition known as amyopathic DM. Recently, Sontheimer proposed the existence of a unique subgroup of patients with DM who have the clinical cutaneous features of DM but no evidence of clinical myositis symptoms for at least 2 years after the onset of skin manifestations (referred to as clinically amyopathic DM [C-ADM]) (6). In other words, C-ADM includes patients with amyopathic DM and patients with hypomyopathic DM (patients with subclinical signs of myositis and DM skin manifestations). Some patients with C-ADM, especially those in Japan (7), have been noted to develop rapidly progressive ILD. This condition in many of these patients is resistant to treatment, and fatal outcomes have been observed.

Because of the severity of ILD accompanying C-ADM, a marker autoantibody would be useful for early diagnosis and treatment monitoring. Potential marker autoantibodies have been described by Targoff et al, who, in a preliminary study, described specificity for a 95-kd Se protein, as well as an unidentified 155-kd protein (8). However, a full survey of the autoantibodies

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associated with C-ADM has not been performed. In the present study, we examined the sera from 15 Japanese patients with C-ADM to identify additional autoantibodies associated with this disease.

PATIENTS AND METHODS

Patients and sera. Serum samples were obtained from 255 randomly selected Japanese adult patients with connective tissue diseases (CTDs) who were being followed up in clinics at Keio University in Tokyo and collaborating medical centers. These sera were obtained, prior to therapy, from a cohort of 61 patients with PM, 42 with DM (including 15 with C-ADM), 50 with rheumatoid arthritis, 46 with systemic lupus erythematosus, 27 with mixed CTD/overlap syndrome, 22 with systemic sclerosis, and 7 with Sjögren's syndrome. Sera from 43 patients with idiopathic pulmonary fibrosis (IPF) and 16 normal human sera were used as control sera. The diagnosis of C-ADM was based on diagnostic criteria proposed by Sontheimer (6), i.e., DM patients with no clinical muscle symptoms for more than 2 years after the onset of skin manifestations.

The patients were diagnosed as having ILD according to the results of chest radiography, chest computed tomography (CT), and pulmonary function testing, which included the percent predicted values for forced vital capacity and diffusing capacity for carbon monoxide. A subset of patients with rapidly progressive ILD was defined as those presenting with progressive dyspnea and progressive hypoxemia, and a worsening of interstitial change on the chest radiograph within 1 month from the onset of respiratory symptoms.

Immunoprecipitation. The immunoprecipitation assay was performed using extracts of the leukemia cell line, K562, as previously described (9). A total of 10 μl of patient serum was mixed with 2 mg of polypeptide A–Sepharose CL-4B (Pharmacia Biotech AB, Uppsala, Sweden) in 500 μl of immunoprecipitation buffer (10 m*M* Tris HCl, pH 8.0, 500 m*M* NaCl, 0.1% Nonidet P40) and incubated for 2 hours at 4°C, and then washed 3 times with immunoprecipitation buffer.

For polypeptide studies, antibody-coated Sepharose beads were mixed with 100 μl of ^{35}S-methionine–labeled K562 cell extracts derived from 2×10^5 cells, and rotated at 4°C for 2 hours. After 6 washes, the Sepharose beads were resuspended in sodium dodecyl sulfate (SDS) sample buffer and the polypeptides were fractionated by 6% SDS–polyacrylamide electrophoresis gels. Radiolabeled polypeptide components were analyzed by autoradiography.

For analysis of RNA, the antigen-bound Sepharose beads were incubated with 100 μl of K562 cell extracts (6×10^6 cell equivalents per sample) for 2 hours at 4°C. To extract bound RNA, 30 μl of 3.0*M* sodium acetate, 30 μl of 10% SDS, 2 μl of carrier yeast transfer RNA (10 mg/ml; Sigma, St. Louis, MO), and 300 μl of phenol:chloroform:isoamyl alcohol (50:50:1, containing 0.1% 8-hydroxyquinoline) were added. After ethanol precipitation, the RNA was resolved using a 7*M* urea–10% polyacrylamide gel, which was subsequently silver-stained (Bio-Rad, Hercules, CA).

Immunoblotting. Immunoblotting analysis was performed using K562 cell extracts in a modification of the procedure described by Towbin et al (10).

Immunodepletion. A 10-μl aliquot of the prototype serum of autoantibodies to the 140-kd polypeptide was mixed with 2 mg of Sepharose beads and incubated for 2 hours at 4°C, followed by 3 washes with immunoprecipitation buffer. Another serum that recognized the 140-kd polypeptide was added in a dose-dependent manner (0 μl, 10 μl, 25 μl, and 50 μl) and then incubated. After 3 washes, immunoprecipitation for polypeptide analysis was performed as described above.

Indirect immunofluorescence (IF). Indirect IF was performed using HEp-2 cells and fluorescein-labeled anti-human immunoglobulin (Inova Diagnostics, San Diego, CA).

Clinical studies. The patients whose sera immunoprecipitated a 140-kd polypeptide were examined for their clinical symptoms, clinical course, muscle enzyme levels (creatine kinase [CK] and aldolase), results on chest radiographic and CT scans, and findings of skin pathology. An assessment of muscle weakness was performed using a manual muscle test (11). Some patients were also examined by electromyogram and muscle magnetic resonance imaging (MRI), and by pathologic analysis of the muscle.

Statistical analysis. The 2 groups of DM patients with or without autoantibodies to the 140-kd polypeptide were compared. The results of comparisons between groups were analyzed using the chi-square test, with Yates' correction where appropriate.

RESULTS

Detection of anti–140-kd polypeptide antibodies in patients with C-ADM. We screened 298 patient sera and 16 normal human sera by immunoprecipitation. Sera from 8 (19%) of 42 patients with DM immunoprecipitated a polypeptide of ~140 kd from ^{35}S-methionine–labeled K562 cell extracts (Figure 1A, lanes 1–8). All 8 patients were diagnosed as having C-ADM, a subtype of DM. In the analysis of RNA specificity, these sera did not immunoprecipitate any nucleic acid band, except for 1 patient's serum, which precipitated hYRNA of SSA/Ro components.

The C-ADM sera that immunoprecipitated the 140-kd polypeptide were also used to immunoblot K562 cell extracts. These sera from C-ADM patients displayed a similar reaction on immunoblot, with a polypeptide band of similar molecular weight (results not shown).

For identification of novel autoantibodies recognizing the 140-kd molecule, the polypeptide immunoprecipitated by the prototype serum was compared with antigens of similar molecular weight recognized by other known autoantibodies (Figure 1B). The protein recognized by the prototype serum migrated slightly faster than the 140-kd protein recognized by anti-MJ antibody (Figure 1B, lane 2) and faster than that recognized by anti–RNA helicase A antibody (Figure 1B, lane 3), but more slowly than the 120-kd protein precipitated by

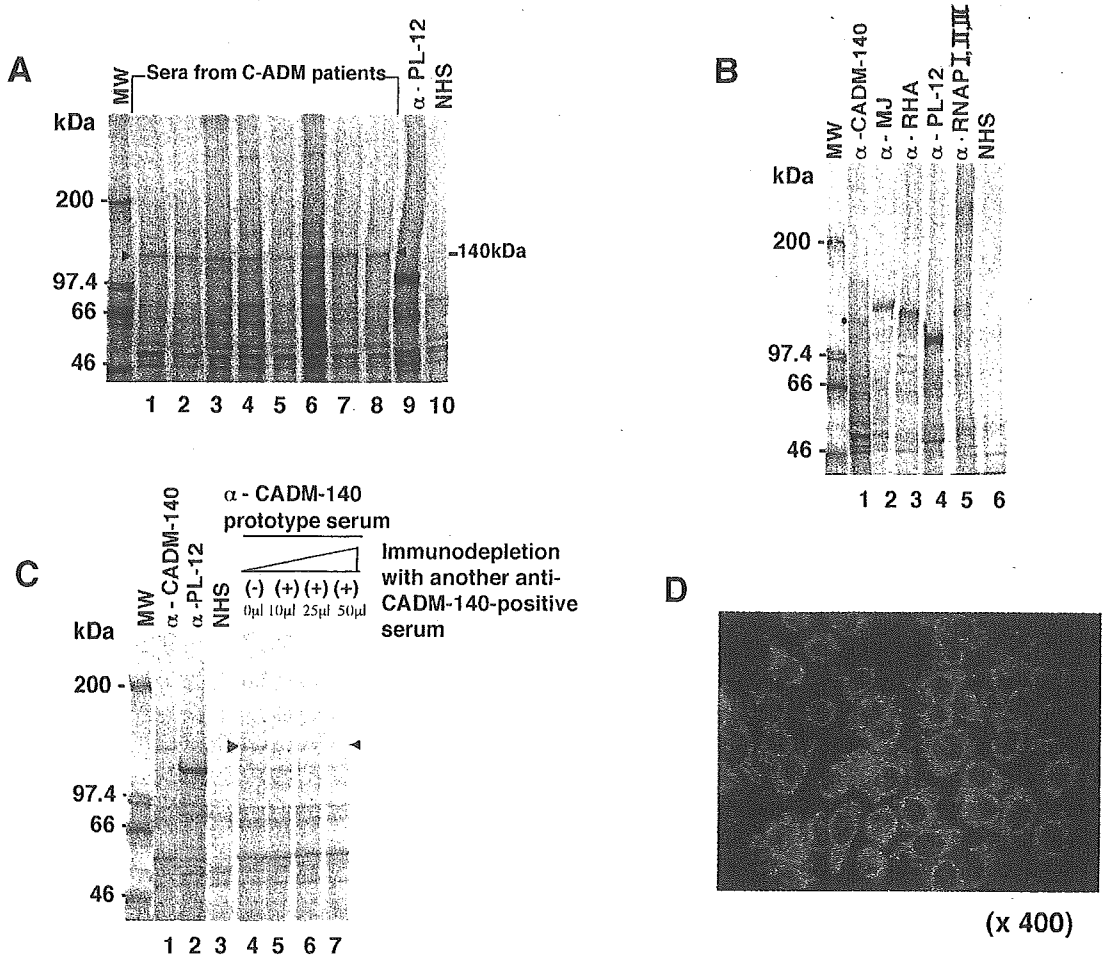

Figure 1. A, Immunoprecipitation of polypeptides with sera from patients with clinically amyopathic dermatomyositis (C-ADM), using ^{35}S-methionine–labeled K562 cell extracts. Lanes 1–8, Sera from C-ADM patients; lane 9, anti–PL-12 serum; lane 10, control normal human serum (NHS). A 140-kd protein was recognized by 8 sera from C-ADM patients (lanes 1–8). **B,** Immunoprecipitation of polypeptides by the prototype serum and by other known autoantibodies. Lane 1, The prototype anti–CADM-140 serum; lane 2, anti-MJ serum; lane 3, anti–RNA helicase A (RHA) serum; lane 4, anti–PL-12 (alanyl–transfer RNA synthetase) serum; lane 5, anti–RNA polymerase I, II, and III (RNAP I, II, and III) serum; lane 6, control NHS. Anti–CADM-140 serum immunoprecipitated an ~140-kd polypeptide that was easily distinguished from that of other known antibodies. **C,** Immunodepletion studies. Sera used for immunoprecipitation were as follows: lane 1, anti–CADM-140; lane 2, anti–PL-12; lane 3, control NHS; lanes 4–7, immunoprecipitation with anti–CADM-140 serum after absorption by another anti–CADM-140–positive serum in a dose-dependent manner. **Arrows** in **A** and **C** denote the 140-kd polypeptide. The sizes of the molecular weight markers are indicated to the left in **A–C. D,** Immunofluorescence pattern of HEp-2 cells stained with anti–CADM-140 serum. A granular or reticular cytoplasmic staining pattern on HEp-2 cells was observed. (Original magnification × 400.)

anti–PL-12 antibody (Figure 1B, lane 4). These results clearly indicate that the 140-kd polypeptide immunoprecipitated by the prototype serum was different from the proteins immunoprecipitated by these other known antibodies. We designated this new autoantibody specificity as anti–CADM-140.

The prototype serum depleted extracts of the 140-kd polypeptide in a dose-dependent manner (Figure 1C, lanes 4–7), and the polypeptide recognized by the prototype serum was no longer immunoprecipitated in these extracts (Figure 1C, lane 7). In contrast, the depletion of radiolabeled K562 cell extracts with the use of autoantibodies of different immunologic specificities did not affect the levels of the anti–CADM-140–specific antigen (results not shown). When sera positive for anti–CADM-140 antibodies were assessed in indirect IF studies, a granular or reticular cytoplasmic staining pattern was observed (Figure 1D).

Table 1. The frequencies of myositis-specific, myositis-associated, and anti–CADM-140 antibodies in patients with connective tissue diseases and IPF*

Autoantibodies	PM (n = 61)	DM (n = 42)		RA (n = 50)	SLE (n = 46)	MCTD/OL (n = 27)	Systemic sclerosis (n = 22)	Sjögren's syndrome (n = 7)	IPF (n = 43)
		Classic DM (n = 27)	C-ADM (n = 15)						
Myositis-specific									
Anti-ARS (anti-Jo-1)	10 (16)	6 (22)	0	0	0	0	0	0	0
Anti-ARS (non–anti-Jo-1)	10 (16)	2 (7)	0	0	0	1 (4)	0	0	4 (9)
Anti-SRP	5 (8)	0	0	0	0	0	0	0	0
Anti–Mi-2	0	2 (7)	0	0	0	0	0	0	0
Myositis-associated									
Anti-SSA/Ro	3 (5)	3 (11)	2 (14)	8 (16)	15 (33)	6 (22)	1 (5)	5 (71)	1 (2)
Anti–U1 RNP	2 (3)	2 (7)	0	1 (2)	18 (39)	23 (85)	2 (9)	0	0
Anti–CADM-140	0	0	8 (53)	0	0	0	0	0	0

* Values are the number (%) of patients. Anti-PM/Scl and other myositis-associated autoantibodies were not detected in any of the sera tested. PM = polymyositis; DM = dermatomyositis; C-ADM = clinically amyopathic dermatomyositis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; MCTD/OL = mixed connective tissue disease/overlap syndrome; IPF = idiopathic pulmonary fibrosis; anti-ARS = anti–aminoacyl–transfer RNA synthetase; anti-SRP = anti–signal recognition particle.

Disease specificity of the anti–CADM-140 antibodies. The frequencies of myositis-specific antibodies, myositis-associated antibodies, and anti–CADM-140 antibodies are summarized in Table 1. Myositis-specific antibodies are found in most patients with myositis, whereas myositis-associated antibodies are frequently found in patients without myositis (12). Among the patients with CTDs or IPF, myositis-specific antibodies (33 with anti-ARS, 5 with anti-SRP, 2 with anti–Mi-2) and myositis-associated antibodies (44 with anti-SSA/Ro, 48 with anti–U1 RNP, none with anti-PM/Scl or other myositis-associated antibodies) were detected. Anti–CADM-140 autoantibodies were found in 19% of sera from patients with DM (especially in 53% with the C-ADM subtype), but were not detected in patients with other CTDs or IPF.

Clinical features of C-ADM patients with anti–CADM-140. Clinical findings were compared between DM patients (including those with C-ADM) with anti–CADM-140 autoantibodies and those without anti–CADM-140 autoantibodies (Table 2). There were no significant differences in the frequencies of skin symptoms. However, the frequency of rapidly progressive ILD was significantly increased in anti–CADM-140–positive patients compared with that in anti–CADM-140–negative patients (50% versus 6%; $P = 0.008$). No myositis-specific antibodies were found in patients with anti–CADM-140; nevertheless, there was no significant

Table 2. Comparison of clinical features in anti–CADM-140–positive versus anti–CADM-140–negative patients with dermatomyositis

Feature	Anti–CADM-140–positive (n = 8)	Anti–CADM-140–negative (n = 34)	*P*
Age at onset, mean ± SD years	44.5 ± 12.7	46.5 ± 15.7	NS
No. male/no. female	2/6	8/26	NS
Gottron's sign or papules	75	88	NS
Heliotrope rash	50	53	NS
Muscle weakness	0	76	0.02
Elevation of CK	25	74	0.03
Fever	25	50	NS
Raynaud's phenomenon	13	24	NS
Arthritis	50	71	NS
Rapidly progressive ILD	50	6	0.008
Malignancy	0	18	NS
MSAs	0	29	NS
MAAs	13	18	NS

* Except where indicated otherwise, values are the percent of patients. NS = not significant; CK = creatine kinase; ILD = interstitial lung disease; MSAs = myositis-specific autoantibodies; MAAs = myositis-associated autoantibodies.

difference in the frequency of these autoantibodies in comparison with the anti–CADM-140–negative group.

None of the 8 patients with anti–CADM-140–positive sera were treated with steroids or other immunosuppressive medications prior to being assessed for C-ADM. All of these patients had Gottron's sign or papules, or periorbital heliotrope erythema and skin biopsy specimens yielding results compatible with DM. None of these patients had muscle weakness. CK levels were in the normal range in 6 patients (75%) and slightly elevated in the remaining 2 patients. Of the 6 patients assessed for the muscle enzyme aldolase, levels were normal in 2 patients. Of the 2 patients who underwent muscle MRI, neither showed findings compatible with a diagnosis of myopathy. Four patients had a muscle biopsy, and 2 of the muscle specimens exhibited mild infiltration of inflammatory cells, but there was no evidence of necrosis of muscle fibers, variation in fiber size, regeneration, or phagocytosis. Of the 7 patients with ILD (88%), 4 developed rapidly progressive disease.

DISCUSSION

We have identified novel autoantibodies (anti–CADM-140 autoantibodies) to an ~140-kd polypeptide in patients with DM. Anti–CADM-140 antibodies were detected specifically in patients with DM, especially those with C-ADM. In addition, anti–CADM-140 antibodies were associated with rapidly progressive ILD.

It has been reported that amyopathic DM may be accompanied by rapidly progressive ILD, especially in Japanese patients and other Asian patients (7). In contrast, rapidly progressive ILD was shown to be rare in patients with amyopathic DM in a North American population (13). In our series, 5 of 15 patients with C-ADM (33%) (4 of whom had anti–CADM-140 antibodies) had rapidly progressive ILD during their clinical course. Rapidly progressive ILD was more frequent in our series compared with that reported previously in North American populations (13). Although the number of patients that we studied was very limited, it remains possible that racial differences are the reason for this discrepancy, because other clinical studies of Japanese patients also demonstrated findings similar to ours (7).

Furthermore, in a recent preliminary report, using immunoprecipitation and immunoblotting of HeLa cell extracts, Targoff et al documented the presence of antibodies to a 155-kd protein and/or Se protein in patients with C-ADM (8). Thirteen of 18 C-ADM sera possessed an anti–155-kd polypeptide antibody, and 6 also immunoprecipitated a 95-kd polypeptide (anti-Se antibody). In contrast, Oddis et al identified the anti-MJ antibody, which was also found to recognize a 140-kd polypeptide, in patients with juvenile DM (14,15). We have been able to conclude that anti–CADM-140 is distinctively different from anti-MJ, because the molecular weights of the immunoprecipitated polypeptides are different. Moreover, the clinical features of anti-MJ are quite different from those associated with anti–CADM-140. Anti-MJ is detected mainly in juvenile DM, has been observed in the US and Argentina, and is clinically characterized by severe DM with a chronic and polycyclic course, sometimes accompanied by vasculitis (14). In order to elucidate the racial differences in the frequency of these antibodies, the examination of a larger number of patients from several different populations is required.

Our results have thus demonstrated the presence of anti–CADM-140 autoantibodies in patients with C-ADM, and these were found to be associated with rapidly progressive ILD. Further studies of this novel autoantibody specificity may provide insight into the pathogenic mechanisms of C-ADM accompanied by rapidly progressive ILD.

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CONCISE COMMUNICATION

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Association between autoantibodies to the Ku protein and DPB1*

The Ku protein, a heterodimer consisting of 70-kd (p70) and 80-kd (p80) polypeptide subunits, binds free ends of double-stranded DNA (dsDNA). Once associated with DNA it creates a binding site for the catalytic subunit of the holoenzyme known as DNA-dependent protein kinase. This enzyme is essential for repairing dsDNA breaks that occur during radiation injury and V(D)J recombination (1).

Autoantibodies to the Ku protein were identified originally in 9 individuals among a randomly selected group of 330 Japanese patients (3%) with various connective tissue diseases studied with a classic immunodiffusion assay. Six of the patients who tested positive for autoantibodies came from a subgroup of 11 individuals (55%) with polymyositis–scleroderma (PM–scleroderma) overlap syndrome (2).

A somewhat different picture of anti-Ku autoantibodies emerged from studies of patients in the US. Reeves observed anti-Ku autoantibodies in the sera of 39% of patients with systemic lupus erythematosus (SLE), 55% of patients with mixed connective tissue disease, and 40% of patients with scleroderma, using an enzyme-linked immunosorbent assay (3). These antibodies also appear to be much more common among African American patients than white patients with SLE (4). Using immunoprecipitation assays, Francoeur et al observed anti-Ku antibodies in 10% of patients with SLE and in no samples obtained from patients with scleroderma (5). These observations suggest that anti-Ku antibodies have unique clinical associations in different racial groups, but further studies applying the same assay systems to different populations simultaneously will be required to confirm this speculation.

In the last several years, it has become clear that autoantibodies to nucleoproteins are antigen driven and require T helper cell support. Therefore, variations of autoantibody correlations in different patient groups seem likely to reflect racial differences in distribution of major histocompatability complex (MHC) phenotypes and the pattern of peptide antigens that are presented to T cells. We have now explored this idea through a genotypic analysis of all patients with anti-Ku autoantibodies at our institution in Japan.

A total of 750 Japanese patients were screened for autoantibodies in a radioimmunoprecipitation assay (6), and 21 were found to have anti-Ku autoantibodies. The presence of these antibodies was confirmed in an immunoblot assay using extracts of HeLa cells. The clinical diagnosis was established from a review of the medical record (Table 1). None of these patients had familial relationships. Clinically, 13 patients had PM or overlap syndromes with myositis (5 had PM–scleroderma, 4 had PM–scleroderma–SLE overlap, 2 had PM–SLE overlap, and 2 had PM), 5 had SLE, 2 had autoimmune hepatitis, and 1 had scleroderma according to established classification criteria (7–10). Forty-six healthy unrelated Japanese individuals served as control subjects. The HLA class II (DRB1, DQA1, DQB1, and DPB1) alleles were identified from restriction fragment length polymorphisms of polymerase chain reaction–amplified genomic DNA (11).

The HLA class II genotypes of all 21 patients are shown in Table 1. DRB1*0901 (62% of subjects versus 28% of controls; $P = 0.009$, odds ratio [OR] = 4.1), DQA1*0302 (62% versus 59%), and DQB1*0303 (62% versus 30%) were elevated in the study group, but none of these associations were statistically significant. However, DPB1*0501 was present in all patients with anti-Ku autoantibodies, compared with 59% of control subjects. This association was significant ($P = 0.0016$, OR 30) and remained significant ($P = 0.03$) when corrected for the number of alleles examined. Thirteen of the 21 patients (62%) with anti-Ku antibodies had myositis. Ten of these individuals (77%) had the class II haplotype of DRB1*0901-DQA1*0302-DQB1*0303, compared with 38% of anti-Ku–positive patients without myositis and 28% of controls ($P = 0.004$, OR 8.5). Four patients were homozygous for DRB1*0901, DQA1*0302, and DQB1*0303, but we found no indication of more severe disease in this group.

Studies of HLA associations with anti-Ku autoantibodies are limited. Yaneva and Arnett reported that the HLA class II antigen DQw1 was present in 17 of 19 anti-Ku positive patients (89%), compared with its frequency in local white (58%) and African American (61%) controls ($P = 0.01$, relative risk 5.8) (12). Although this allele occurs at increased frequency in patients with SLE, it is not associated with myositis and scleroderma. In the present study, the most striking finding is the universal occurrence of DPB1*0501 in 21 consecutive patients with anti-Ku autoantibodies. The DRB1*0901-DQA1*0302-DQB1*0303 haplotype also correlates with myositis in this patient cohort. Both DPB1*0501 and the DRB1*0901-DQA1*0302-DQB1*0303 haplotype are more common in the Japanese population than in the white population (13). It should be noted that DPB1*0501 is also a risk factor for Graves' disease in Japan (14). These findings suggest that there is a common immunogenetic background for Graves' disease and the anti-Ku autoimmune response. Therefore, these associations help to rationalize the earlier findings that anti-Ku autoantibodies are more clearly associated with myositis among the Japanese population.

Among the patients studied here, 9 had PM–scleroderma overlap syndrome with anti-Ku antibodies but none had the anti–PM-Scl, specificity. In the US population, ~10% of patients with this syndrome develop anti–PM-Scl. We have examined >100 patients with this overlap syndrome, but none have had anti–PM-Scl, nor have any of the >3,000 patients screened in our clinical diagnostic laboratory. Therefore we believe this autoantibody is rare among Japanese individuals. An explanation may be that anti–PM-Scl antibodies have been linked with DR3, a phenotype that is uncommon in the Japanese population (13). In any case, the MHC phenotype appears to exert a stronger influence over expression of specific autoantibodies than over the emergence of individual autoimmune syndromes. Further studies including analysis of MHC-restricted T cell responses could provide important clues for understanding mechanisms of onset of the PM–scleroderma overlap syndrome and the expression of anti-Ku antibodies.

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Table 1. HLA class II genes in Japanese patients with anti-Ku autoantibodies*

Patient no.	Diagnosis	DRB1*	DQA1*	DQB1*	DPB1*
1	PM/SSc	0405/1101	0303/0505	0401/0301	0501/0402
2	PM/SSc	0901/080302	0302/0103	0303/0601	0501/0202
3	PM/SSc	0901/080302	0302/0103	0303/0601	0501/0201
4	PM/SSc	0901/0405	0302/0303	0303/0401	0201/0501
5	PM/SSc	0901/0901	0302/0302	0303/0303	0501/0402
6	PM/SSc/SLE	0901/0901	0302/0302	0303/0303	0501/0402
7	PM/SSc/SLE	0901/1401	0302/0104	0303/0503	0501/0201
8	PM/SSc/SLE	0901/1502	0302/0103	0303/0601	0501/0901
9	PM/SSc/SLE	0901/0901	0302/0302	0303/0303	0501/0201
10	PM/SLE	0901/0901	0302/0302	0303/0303	0501/0201
11	PM/SLE	0405/0405	0303/0303	0401/0401	0501/0301
12	PM	0901/0802	0302/030101	0303/0302	0501/4101
13	PM	0405/1502	0303/0103	0401/0601	0501/0901
14	SLE	0901/1501	0302/0102	0303/0602	0501/0501
15	SLE	1501/0802	0401/0102	0302/0602	0201/0501
16	SLE	0405/080302	0303/0103	0401/0601	0501/0501
17	SLE	0901/080302	0302/0103	0303/0601	0501/0201
18	SLE	080302/1302	0103/0102	0601/0604	0501/0401
19	SSc	0405/0405	0303/0303	0401/0401	0501/0201
20	AIH	0802/0802	030101/030101	0302/0302	0201/0501
21	AIH	0901/0802	0302/030101	0303/0302	0501/0501

* PM = polymyositis; SSc = systemic sclerosis (scleroderma); SLE = systemic lupus erythematosus; AIH = autoimmune hepatitis.

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CASE REPORT

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Sensorimotor polyneuropathy as an initial clinical manifestation of sarcoidosis

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Abstract A 45 year-old Japanese woman developed numbness and tingling of both hands and feet. Electrophysiological examination revealed sensorimotor polyneuropathy. She was diagnosed as suffering from sarcoidosis on the basis of the pathological findings from dermal biopsy. Steroid therapy effectively improved the clinical symptoms. Although sarcoid neuropathy is rare, this case suggests sensorimotor polyneuropathy is an important symptom of sarcoidosis and can represent the initial clinical manifestation of the disease.

Key words Axonal degeneration · Electromyography (EMG) · Sarcoidosis · Sensorimotor polyneuropathy

Introduction

Sarcoidosis is a disorder of unknown cause, which affects multiple organs with formation of granulomatous lesions and causes many different clinical manifestations including neurological signs. Among its various manifestations, sarcoid neuropathy is a rare complication of sarcoidosis. Here, we report a Japanese patient with sarcoidosis who showed progressive gait disturbance due to sensorimotor polyneuropathy.

Case report

A 45-year-old Japanese woman developed numbness and tingling of both hands and feet in March 2000. Magnetic resonance imaging of the spine was performed at another hospital and no major abnormality was observed. In April, she began to have painful legs with difficulty in walking. She was referred to our outpatient clinic for further examination in June 2000. At the time of admission, she had fever at 37°C and had pain in her lower extremities. She was a housewife with no alcohol habit and had never been exposed to any toxic chemical materials. On physical examination, there was slight edematous erythema in her feet. However, there was no facial erythema, xerostomia, scleroderma, muscle atrophy, or subcutaneous nodules. Neurological examination revealed symmetric muscle weakness in the plantar extensors and flexors, iliopsoas, hamstrings, and gastrocnemius muscles graded as 3–4/5, as well as painful paresthesia. Cutaneous sensation was impaired in glove and stocking distribution to the ankles and wrists. Brachioradialis and Achilles tendon reflexes were absent. However, there were no cranial nerve abnormalities.

Laboratory findings (Table 1) showed an erythrocyte sedimentation rate (ESR) of 39 mm/h; there was a normal urinalysis and blood count with no eosinophilia. Liver and renal functions were normal. The serum creatine kinase, calcium, vitamin B_{12}, and folic acid values were within the normal range. Serum angiotensin-converting enzyme (ACE) was 23.6 IU/l (normal 7.7–29.4 IU/l), but lysozyme was elevated to 12.5 μg/ml (normal 4.2–11.5 μg/ml). Hypergammaglobulinemia was found and C-reactive protein was slightly elevated to 0.24 mg/dl. Cryoglobulin, antineutrophil cytoplasmic autoantibodies (PR-3 ANCA, MPO-ANCA), and immune complexes were within normal limits. Anti-dsDNA, anti-SS-A, anti-SS-B, anti-RNP, anti-Jo-1 antibodies, and the tuberculin skin test were all negative.

In nerve conduction studies in June 2000 (Table 2), distal motor latencies were prolonged in the median and ulnar nerves. Compound muscle action potentials (CMAPs) were very low in amplitude in the tibial and peroneal nerves, and temporal dispersion and conduction block were not detected. Sensory nerve action potentials (SNAPs) of the median nerve were also low in amplitude. However, motor and sensory conduction velocities were relatively preserved

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