Respiratory Medicine (2007) **101**, 1406–1411

respiratoryMEDICINE

Interstitial lung disease associated with amyopathic dermatomyositis: Review of 18 cases ☆

Gen Ideura[a], Masayuki Hanaoka[a,*], Tomonobu Koizumi[a], Keisaku Fujimoto[a], Yasuhiro Shimojima[b], Wataru Ishii[b], Masayuki Matsuda[b], Shuichi Ikeda[b]

[a]*First Department of Medicine, Shinshu University School of Medicine, Matsumoto 390 8621, Japan*
[b]*Third Department of Medicine, Shinshu University School of Medicine, Matsumoto 390 8621, Japan*

Received 28 September 2006; accepted 30 January 2007
Available online 13 March 2007

KEYWORDS
Amyopathic dermatomyositis (ADM);
Interstitial lung disease (ILD);
High-resolution computed tomography (HRCT);
Cyclosporine A (CsA);
Respiratory symptoms

Summary
Interstitial lung disease (ILD) associated with amyopathic dermatomyositis (ADM) is a rare and sometimes fatal condition whose clinical features are not well understood. The goal of this study was to clarify the characteristics of ILD based on its development.
Eighteen patients diagnosed with ILD associated with ADM were assigned to 1 of 2 groups: (1) a rapidly progressing group, which included patients who developed abnormal lung findings within 1 month of being diagnosed with ADM ($n = 9$); or (2) a slowly progressing group, which including patients who developed lung findings greater than 1 month after diagnosis of ADM ($n = 9$).
Serum creatine phosphokinase and C-reactive protein levels were higher in the rapidly progressing group than in the slowly progressing group. Further, arterial pH was higher and PaO_2/F_iO_2 was lower in the rapidly progressing group than in the slowly progressing group. On thoracic high-resolution CT, traction bronchiectasis was present in 4 of the 9 rapidly progressing patients but not in any patients of the slowly progressing group. All 9 slowly progressing patients survived with proper treatment, but only 4 of the 9 rapidly progressing patients survived.
In ADM, appropriate investigations are likely required for the early diagnosis of ILD. Our data suggest that ILD associated with ADM can be classified into 2 clinical subtypes based on the time course of pulmonary involvement. Patients with rapid progression in respiratory symptoms should undergo intensive treatment as soon as possible to promote favorable outcomes.

☆This study was supported partly by a Grant-in-Aid for Scientific Research (C), no. 17590783, from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

*Corresponding author. Tel.: +81 263 37 2631; fax: +81 263 36 3722.
E-mail address: masayuki@hsp.md.shinshu-u.ac.jp (M. Hanaoka).

0954-6111/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2007.01.023

Introduction

Dermatomyositis (DM) is an autoimmune disease that mainly affects the skin and skeletal muscle. However, a rare form of DM with no accompanying muscle symptoms was designated as amyopathic DM (ADM) by Pearson[1] or Euwer and Sontheimerv.[2]

While treatment-resistant interstitial lung disease (ILD) may complicate ADM and result in worse prognoses,[3–8] the pathophysiology and clinical course of ADM-associated ILD remains unclear. Therefore, the goal of this study was to retrospectively analyze clinical data of patients with ADM-associated ILD in order to characterize the clinical features of such condition.

Methods

Patients and diagnostic criteria

This study was performed in accordance with the recommendations of the Helsinki Declaration of 1975,[9] and all investigational protocols were approved by the institutional review board for human studies of Shinshu University.

Eighteen patients with ADM complicated with ILD (5 males, 13 females), ranging in age from 25 to 71 years, were treated at the departments of respiratory medicine or collagen disease in Shinshu University Hospital from 1994 to 2006. Skin biopsies had been performed in all patients, and the pathological findings were consistent with a diagnosis of dermatomyositis. All patients met the diagnostic criteria of ADM as proposed by Euwer and Sontheimer.[2] All patients experienced pulmonary symptoms, including dry cough and shortness of breath, at some point during the course of their disease. Chest X-ray showed findings of ILD, according to the international multidisciplinary consensus classification of idiopathic interstitial pneumonias proposed by the American Thoracic Society and the European Respiratory Society,[10] in all patients. We diagnosed them as ADM-associated ILD based on their clinical course and medical history. We reviewed the patients' records with respect to clinical courses, physical examination, and results of laboratory studies, including serologic tests, bronchoalveolar lavage fluid (BALF) examination, pulmonary function tests, and thoracic computed tomography (CT) scanning. The specific treatments and outcomes of the patients were also reviewed.

Clinical assessments

Eighteen patients diagnosed with ILD associated with ADM were assigned to 1 of 2 groups: (1) a rapidly progressing group, which included patients who developed abnormal lung findings within 1 month of being diagnosed with ADM ($n = 9$); or (2) a slowly progressing group, which including patients who developed lung findings greater than 1 month after diagnosis of ADM ($n = 9$).

The following clinical parameters were compared between the groups: age; gender; skin symptoms; biochemical markers in peripheral blood including anti-Jo-1 antibody, creatine phosphokinase (CPK) and Krebs von den Lungen 6 (KL-6); arterial blood gas parameters; BALF findings; pulmonary function tests; thoracic high-resolution (HR) CT findings before treatment; treatments; and clinical course. Standard laboratory methods were used for the biochemical laboratory tests and blood gas analysis. Hematoxylin-eosin staining was used for cellular examination of BALF.

Statistical analysis

Continuous data are expressed as mean $\pm$ standard error of the mean (SEM), and categorical data are expressed as positive "+" or negative "−". The unpaired Student's t-test was used to analyze continuous variables, and the χ^2 test was used to analyze categorical data. A $P<0.05$ was regarded as statistically significant.

Results

Clinical course of the rapidly and slowly progressing groups

As shown in Table 1, the 9 patients in the rapidly progressing group consisted of 4 males and 5 females (mean age 50.4 years). By contrast, the 9 patients in the slowly progressing group consisted of 1 male and 8 females (mean age, 44.9 years). The mean age was not significantly different when comparing the 2 groups.

The mean interval between the onset of respiratory symptoms, such as dry cough and shortness of breath, and the diagnosis of ADM was 16 ± 2 days (range, 9–25 days) in the rapidly progressing group and 128 ± 43 days (range, 45–210 days) in the slowly progressing group (Table 1).

Skin manifestations

The Gottron's sign was observed in all patients (Table 1). Seven of the 9 patients in both groups were positive for heliotrope rash. Furthermore, skin ulcers were observed in 7 of 9 patients (77.8%) in the rapidly progressing group, while they were observed in only 3 of 9 patients (33.3%) in the slowly progressing group.

Laboratory examinations

Anti-Jo-1 antibody titers were negative in all 18 patients (Table 1). The rapidly progressing group was characterized by significantly increased levels of CPK and C-reactive protein (CRP) when compared with the slowly progressing group (Table 2, CPK: 287.2 ± 57.0 vs. 92.1 ± 25.0 U/l; $P = 0.0132$, CRP: 2.75 ± 0.79 vs. 0.58 ± 0.18 mg/dl; $P = 0.0227$).

Results of arterial blood gas analysis at admission are summarized in Table 2. Since some patients had received oxygen at their previous medical facilities due to respiratory failure, the ratio of PaO_2 to F_IO_2 (PaO_2/F_IO_2) was used as a measure of hypoxemia. The rapidly progressing group had a significantly higher arterial pH (7.464 ± 0.011) and lower PaO_2/F_IO_2 (252.8 ± 25.3 Torr) on admission when compared with the slowly progressing group (7.418 ± 0.011; $P = 0.0096$, 359.4 ± 14.2 Torr; $P = 0.0020$, respectively).

Although there was no significant difference in the BALF findings when comparing the 2 groups, the percentage of

Table 1 Overview of the 18 cases of amyopathic dermatomyositis (ADM) complicated with interstitial lung disease.

Patient number	Age (years)	Sex	Time interval (days)*	Skin manifestations			Anti-Jo-1 antibody	Thoracic CT					Treatments			Therapeutic outcome
				Gottron's sign	Heliotrope rash	Skin ulcer		SCS	CABB	GGO	HC	TB	Corticosteroid	CsA	Other therapy	
Rapidly progressing group																
1	39	F	14	+	−	−	−	+	+	+	−	+	+	+	−	Improvement
2	25	M	21	+	−	+	−	+	+	+	−	−	+	+	IVIG	Improvement
3	65	F	27	+	+	+	−	+	+	+	−	−	+	+	IVIG PE	Death
4	46	M	10	+	+	+	−	+	+	+	−	+	+	+	−	Death
5	53	F	15	+	+	+	−	+	+	+	−	−	+	+	IVIG CPA	Death
6	71	F	9	+	+	+	−	+	+	+	−	+	+	+	−	Improvement
7	53	F	10	+	+	−	−	+	+	+	−	−	+	+	−	Improvement
8	46	M	14	+	+	+	−	+	+	+	−	+	+	−	−	Death
9	56	M	25	+	+	+	−	+	+	+	−	−	+	+	PE	Death
Slowly progressing group																
10	42	M	180	+	+	−	−	+	+	+	−	−	+	−	CPA	Improvement
11	59	F	90	+	−	−	−	+	+	+	+	−	−	−	−	No change
12	34	F	210	+	+	−	−	+	+	+	−	−	+	+	−	Improvement
13	46	F	60	+	+	+	−	+	+	+	−	−	+	+	−	Improvement
14	42	F	90	+	+	+	−	+	+	+	−	−	+	+	−	Improvement
15	38	F	45	+	−	−	−	+	+	+	−	−	+	−	−	Improvement
16	53	F	210	+	+	−	−	+	+	+	−	−	+	−	−	Improvement
17	32	F	180	+	+	−	−	+	+	+	−	−	+	+	−	Improvement
18	58	F	90	+	+	+	−	+	+	+	−	−	+	+	−	Improvement

SCS, subpleural curvilinear shadows; CABB, consolidation around bronchovascular bundles; GGO, ground-glass opacities; HC, honey-comb change; TB, traction bronchiectasis; CsA, cyclosporine A; F, female; M, male; IVIG, intravenous high-dose immunoglobulin; PE, plasma exchange; CPA, cyclophosphamide; +, positive; −, negative.

*Time interval indicates the interval between the onset of respiratory symptoms (such as dry cough and shortness of breath) and the diagnosis of ADM.

Table 2 Laboratory findings, cellular fractions of bronchoalveolar lavage fluid and pulmonary functions in the two groups.

	Rapidly progressing group	Slowly progressing group	*P* value*
Peripheral blood			
WBC (/μl)	6094±668	5942±626	0.8714
BUN (mg/dl)	11.0±1.5	12.6±1.8	0.5009
Creatinine (mg/dl)	0.59±0.04	0.52±0.05	0.2514
AST (U/l)	76.0±12.8	52.5±16.2	0.2670
ALT (U/l)	66.8±24.2	29.6±5.8	0.1790
LDH (U/l)	502.6±83.9	312.4±50.5	0.0795
CPK (U/ml)	287.2±57.0	92.1±25.0	0.0132
CRP (mg/dl)	2.75±0.79	0.58±0.18	0.0227
KL-6 (U/ml)	1243.9±335.1	771.9±95.7	0.2253
Arterial blood gas			
pH	7.464±0.011	7.418±0.011	0.0096
PaO_2/F_iO_2 (Torr)	252.8±25.3	359.4±14.2	0.0020
$PaCO_2$ (Torr)	33.9±1.3	36.4±1.3	0.1984
HCO_3^- (mEq/l)	23.9±0.7	23.4±1.3	0.7471
Bronchoalveolar lavage fluid			
Macrophages (%)	51.1±12.2	47.9±9.6	0.8378
Neutrophils (%)	27.0±12.5	6.6±3.7	0.1009
Lymphocytes (%)	18.4±6.9	43.1±9.5	0.0799
Eosinophils (%)	3.9±3.2	2.5±1.8	0.6890
CD4/CD8	1.30±0.38	1.25±0.38	0.9316
Pulmonary function			
VC, % pred	66.3±9.2	82.2±8.5	0.1646
FEV_1, % pred	88.3±2.7	78.7±3.7	0.7545
RV, % pred	144.6±21.9	93.0±9.4	0.0354
DL_{CO}, % pred	50.5±3.1	59.9±4.2	0.2013

Values are means±SEM. WBC, white blood cell count; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; CRP, C-reactive protein; KL-6, Krebs von den Lungen-6; % pred, percentage of predicted value; VC, vital capacity; FEV_1, forced expiratory volume in 1 s; RV, residual volume; DL_{CO}, diffusion capacity for carbon monoxide.

*Comparisons between the rapidly and slowly progressing groups by unpaired Student's *t*-test.

neutrophils was higher and the percentage of lymphocytes was lower in the rapidly progressing group than in the slowly progressing group (Table 2).

Pulmonary function testing

The rapidly progressing group was characterized by a significantly increased percentage of predicted residual volume (%RV) when compared with the slowly progressing group (Table 2, 144.6±21.9 vs. 93.0±9.4; $P = 0.0354$). Moreover, the percentage of predicted vital capacity (%VC) was abnormally low in the rapidly progressing group when compared with normal values (80–120%). Both groups showed an abnormally low percentage of predicted diffusion capacity for carbon monoxide (%DL_{CO}) with a normal percentage of predicted normal forced expiratory volume in 1 s (%FEV_1).

Thoracic HRCT findings

As shown in Table 1, traction bronchiectasis was noted in 4 of 9 patients (44.4%) of the rapidly progressing group, but in none of the patients of the slowly progressing group. Ground glass opacity, subpleural curvilinear shadows and consolidation around the bronchovascular bundles were seen in all patients of both groups. Honeycomb change was noted in only 1 case of the slowly progressing group and in none of the patients of the rapidly progressing group. A representative thoracic HRCT image obtained from a patient of the rapidly progressing group is presented in Fig. 1.

Treatment and outcomes

In the rapidly progressing group, corticosteroid was given with cyclosporine A (CsA) to all patients with the exception of 1 patient who experienced respiratory failure and died soon after the onset of pulmonary symptoms (patient 8, Table 1). Since ILD activity could not be completely suppressed by corticosteroid and CsA, 4 of the 9 rapidly progressing patients also received intravenous high-dose immunoglobulin (IVIG) (patients 2, 3, and 5) and/or plasma exchange (PE) (patients 3 and 9) and cyclophosphamide (CPA) treatment (patient 5). However, only 4 of these 9 rapidly progressing patients (44.4%) survived, and the

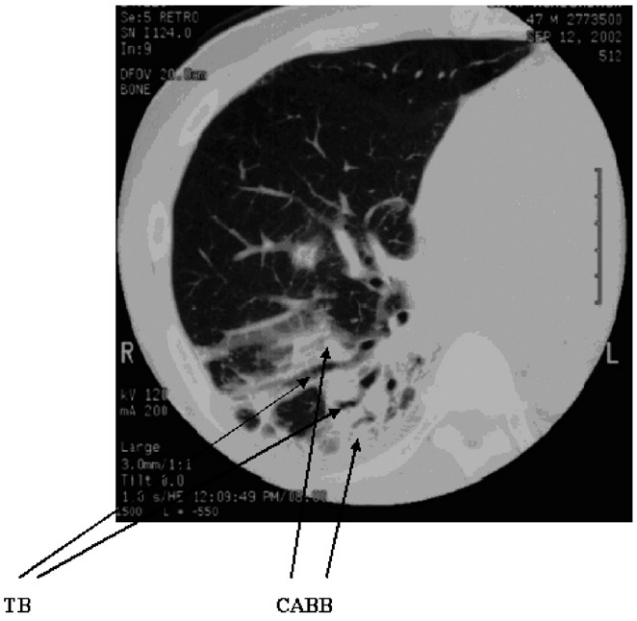

Figure 1 High-resolution CT scanning in patient no. 4 of the rapidly progressing group. Traction bronchiectasis (TB) and consolidation around bronchovascular bundles (CABB) is present in the dorsal subpleural area.

remainder died due to respiratory failure within 1 month after the diagnosis of ILD.

In the slowly progressing group, corticosteroid therapy was used in 8 patients, and CsA was sequentially administered to 5 of these 8 patients (Table 1). Patient 10 received CPA instead of CsA because of a history of an allergic reaction to CsA. Another patient (patient 11) was followed without treatment, since her pulmonary symptoms developed much later and her mild fibrosis was stable on serial chest X-rays. All patients in the slowly progressing group survived.

In patients treated with CsA, the daily dose was initiated at 5 mg/kg/day and then carefully adjusted in order to keep the plasma trough concentration between 100 and 150 ng/ml. When the trough concentration either exceeded 200 ng/ml or was between 150 and 200 ng/ml on 2 successive occasions, the daily dose was reduced by 50 mg at a time. No CsA-related adverse effects were seen in any of these patients during treatment.

Discussion

ADM is a rare form of dermatomyositis that typically manifests with characteristic cutaneous lesions without muscle involvement.[1,2] In general, lung involvement is uncommon, and the prognosis is favorable.[2,11,12] However, recent reports have described several cases of fatal ILD associated with ADM.[3–8] In the present study, the mortality rate of ADM complicated with ILD was 27.8% (5 of the 18 patients), indicating that ILD is an important prognostic factor for patients with ADM. In the rapidly progressing group, cutaneous rashes and respiratory symptoms appeared almost simultaneously (16 ± 2 days), and 4 of the 9 patients died due to respiratory failure within 1 month after the diagnosis of ILD. These data suggest that rapid diagnosis and initiation of treatment is critical in patients with rapidly progressing disease and that differentiation of the disease state based on the temporal course of pulmonary involvement is a clinical relevant characterization.

The progression of systemic stress and inflammation might result in the significant increases of serum CPK and CRP in the rapidly progressing group. The elevated BALF neutrophil level in the rapidly progressing patients may be a reflection of acute inflammatory destruction of the lung tissues and have been shown to be associated with treatment resistance and poor prognosis.[13] The abnormal values of %VC, %RV and $\%DL_{CO}$ in pulmonary function examination also suggest advanced lung involvement in this group. By contrast, the elevation in BALF lymphocyte counts in the slowly progressing patients may be a reflection of chronic inflammatory changes that correlate with a relatively stable clinical course.[14] To summarize, these data suggest that elevated CRP and pulmonary function test abnormalities, such as decreases in VC and DL_{CO} or an increase in RV, correlate with the severity of the ILD associated with ADM.

Ground glass opacity, subpleural curvilinear shadow, and consolidation around bronchovascular bundles are common findings of ILD associated with dermatomyositis/polymyositis.[15,16] In the present study, the frequency of traction bronchiectasis was high (44.4%) in the rapidly progressing group, while no traction bronchiectasis was observed in the slowly progressing group. Therefore, the presence of traction bronchiectasis on thoracic CT may be a prognostic factor in patients with ADM and ILD. This is consistent with a previous report, in which traction bronchiectasis was more frequent in non-survivors with acute interstitial pneumonia than in survivors.[17] Likewise, another report on cryptogenic fibrosing alveolitis demonstrated that severe traction bronchiectasis was associated with more extensive disease and physiological impairments than cryptogenic fibrosing alveolitis with no or mild traction bronchiectasis.[18] However, it is difficult to distinguish rapidly progressing group from slowly progressing group using HRCT findings other than traction bronchiectasis. Therefore, a combination of appropriate lung investigations is likely required for the early diagnosis of ILD.

Impairments in the immune response may contribute to the pathogenesis of ADM. Indeed, the number of CD4-positive T cells in the peripheral blood is increased in patients with ADM, and clonal expansion of Th1 cells in the skin and affected visceral organs, including the lung, may occur in affected patients.[19] In the present study, most patients with ADM-associated ILD were treated with oral CsA immunomodulatory therapy along with corticosteroid, since this treatment strongly and reversibly suppresses T-cell activity. Another advantage of CsA is that the therapeutic effects appear within 1 month, whereas the effects of other immunosuppressive agents usually require at least 2–3 months.[20,21] Several studies have reported that CsA has a good therapeutic effect in patients with ADM-associated ILD. Four of the 5 patients with ADM-associated ILD resistant to corticosteroid therapy, including 3 rapidly progressing patients, showed improvement following the additional administration of CsA.[22] Our previous case report also clearly demonstrated the efficacy of sequential treatment of CsA with corticosteroid.[23] In the present study, 9 of the 13

patients (69.2%) showed improvement following the combination therapy of corticosteroid and CsA. In particular, all survivors in the rapidly progressing group received corticosteroid and CsA and no serious complications ascribable to CsA were observed during treatment. These data suggest that CsA is an important therapeutic option for this condition, and early initiation of treatment including CsA may result in better outcomes in rapidly progressing patients.

In summary, the clinical course of ILD associated with ADM can be distinguished by the time interval to the development of pulmonary symptoms. Specifically, patients with a pulmonary involvement interval shorter than 1 month are likely to experience rapid destructive damage to both lungs and have a poor prognosis. Characterization of biochemical markers, such as CRP in serum, detection of severe hypoxemia and traction bronchiectasis may also be predictors of rapid progression and poor prognosis. Patients with rapid lung involvement should undergo intensive treatment, such as concurrent corticosteroid and CsA treatment, as soon as possible in order to promote favorable outcomes. Further studies with larger patient populations are required to confirm results from the present study.

Acknowledgement

The authors would like to thank Dr. Keishi Kubo for his support throghout the study.

References

1. Person CM. Polymyositis and dermatomyositis. In: McCarty DJ, editor. *Arthritis and allied conditions: a text book of rheumatology*. 9th ed. Philadelphia: Lea & Febiger; 1979. p. 742–61.
2. Euwer RL, Sontheimer RD. Amyopathic dermatomyositis: a review. *J Invest Dermatol* 1993;**100**:124S–7S.
3. Krain LS. Dermatomyositis in six patients without initial muscle involvement. *Arch Dermatol* 1975;**111**:241–5.
4. Fernandes L, Goodwill CJ. Dermatomyositis without apparent myositis, complicated by fibrosing alveolitis. *J R Soc Med* 1979;**72**:777–9.
5. Fudman EJ, Schnitzer TJ. Dermatomyositis without creatine kinase elevation. A poor prognostic sign. *Am J Med* 1986;**80**: 329–32.
6. Takizawa H, Shiga J, Morii Y, Miyachi S, Nishiwaki M, Miyamoto T. Interstitial lung disease in dermatomyositis: clinicopathological study. *J Rheumatol* 1987;**14**:102–7.
7. Gerami P, Schope JM, McDonald L, Walling HW, Sontheimer RD. A systematic review of adult-onset clinically amyopathic dermatomyositis (dermatomyositis sine myositis): a missing link within the spectrum of the idiopathic inflammatory myopathies. *J Am Acad Dermatol* 2006;**54**:597–613.
8. Kang EH, Lee EB, Shin KC, et al. Interstitial lung disease in patients with polymyositis, dermatomyositis and amyopathic dermatomyositis. *Rheumatology (Oxford)* 2005;**44**:1282–6.
9. World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. *JAMA* 1997;**277**:925–6.
10. American Thoracic Society/European Respiratory Society. International multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Resir Crit Care Med* 2002;**165**:277–304.
11. El-Azhary RA, Pakzad SY. Amyopathic dermatomyositis: retrospective review of 37 cases. *J Am Acad Dermatol* 2002;**46**: 560–5.
12. Caproni M, Cardinali C, Parodi A, et al. Amyopathic dermatomyositis. A review by the Italian group of immunodermatology. *Arch Dermatol* 2002;**138**:23–7.
13. Rudd RM, Haslam PL, Turner-Warwick M. Cryptogenic fibrosing alveolitis. Relationships of pulmonary physiology and bronchoalveolar lavage to response to treatment and prognosis. *Am Rev Respir Dis* 1981;**124**:1–8.
14. Watters LC, Schwarz MI, Cherniack RM, et al. Idiopathic pulmonary fibrosis. Pretreatment bronchoalveolar lavage cellular constituents and their relationships with lung histopathology and clinical response to therapy. *Am Rev Respir Dis* 1987;**135**:696–704.
15. Ikezoe J, Johkoh T, Kohno N, Takeuchi N, Ichikado K, Nakamura H. High-resolution CT findings of lung disease in patients with polymyositis and dermatomyositis. *J Thorac Imag* 1996;**11**: 250–9.
16. Bonnefoy O, Ferretti G, Calaque O, et al. Serial chest CT findings in interstitial lung disease associated with polymyositis–dermatomyositis. *Eur J Radiol* 2004;**49**:235–44.
17. Ichikado K, Suga M, Muller NL, et al. Acute interstitial pneumonia: comparison of high-resolution computed tomography findings between survivors and nonsurvivors. *Am J Respir Crit Care Med* 2002;**165**:1551–6.
18. Desai SR, Wells AU, Rubens MB, du Bois RM, Hansell DM. Traction bronchiectasis in cryptogenic fibrosing alveolitis: associated computed tomographic features and physiological significance. *Eur Radiol* 2003;**13**:1801–8.
19. Ejstrup L. Severe dermatomyositis treated with cyclosporin A. *Ann Rheum Dis* 1986;**45**:612–3.
20. Nunes JP, Resende C, Delgado L. Severe acute form of adult dermatomyositis treated with cyclosporin. *Int J Dermatol* 1992;**31**:517–9.
21. Amato AA, Griggs RC. Treatment of idiopathic inflammatory myopathies. *Curr Opin Neurol* 2003;**16**:569–75.
22. Tokano Y, Ogasawara H, Ando S, et al. Cyclosporin a therapy for interstitial pneumonitis associated with rheumatic disease. *Mod Rheumatol* 2002;**12**:305–10.
23. Shimojima Y, Ishii W, Kato T, et al. Intractable skin necrosis and interstitial pneumonia in amyopathic dermatomyositis, successfully treated with cyclosporin A. *Intern Med* 2003;**42**:1253–8.