range, especially in the presence of rheumatoid factor or cryoglobulins [95,96].

The ISTH-SSC recommended in 2002 that the aCL test should be replaced by anti-β_2GPI and the LA tests [97]. However, the best available evidence indicates that anti-β_2GPI cannot yet be considered a substitute for aCL (Evidence Level II) [21,22,98]; this committee recommends that aCL continue to be a laboratory criterion for APS.

To optimize standardization, new reference samples (monoclonal antibodies, named HCAL and EY2C9) [99] will be distributed from the Center for Disease Control and Prevention to investigators free of charge. They will have to be validated against existing calibrators, and their specificity, avidity and stability over time should be monitored. Because these preparations cannot mirror the heterogeneity present in patient samples [100], firm recommendations cannot be given at this time.

IgA aCL

The IgA aCL are usually detected together with either IgG and/or IgM isotypes in patients with APS (Evidence Level II) [101–103], and agreement among patients grouped according to aCL titers for IgA seems lower than those for the other isotypes [104]. Specificity and standardization considerations for the other aCL isotypes apply also to the IgA aCL assay. In patients with collagen disease, IgA aCL associates with thrombocytopenia, skin ulcers and vasculitis, indicating a patient subgroup at risk for specific clinical manifestations (Evidence Level III) [105], and it is highly prevalent in African–American SLE patients [106]. Hence, this isotype appears to identify patient subgroups rather than adding diagnostic power. The committee consents that IgA aCL cannot be considered as a laboratory criterion for APS.

Anti-β_2GPI

By majority[2], the committee agreed that IgG and IgM anti-β_2GPI should be included as part of the modified Sapporo criteria. Anti-β_2GPI antibodies are an independent risk factor for thrombosis (Evidence Level II) [107,108] and pregnancy complications (Evidence Level I) [109,110], though some studies deny these associations mainly because of methodological differences and lack of standardization [107,108]. Inter-laboratory variation of anti-β_2GPI is better than that found with the aCL assay for both home-made [111] and commercial kits [112] (Evidence Level II). The anti-β_2GPI assay shows higher specificity than aCL for APS diagnosis (Evidence Level II) [21,22,113–115]. In 3–10% of APS patients, anti-β_2GPI may be the only test positive (Evidence Level I) [23,98,116]. The association of anti-β_2GPI with pre-eclampsia and/or eclampsia in unselected pregnant women who tested negative for aCL (Evidence Level I) [109] implies that the inclusion of anti-β_2GPI may also help clarify this pregnancy morbidity.

Methodology and standardization limitations expressed for aCL also apply for anti-β_2GPI [111,112]. Laboratories measuring anti-β_2GPI are encouraged to standardize the types of plates; purity, concentration and source of β_2GPI; and calibrators and units of measurement [18,112]. Validation of monoclonal anti-β_2GPI [99] antibodies and comparison with the existing standards is encouraged. High titers of anti-β_2GPI antibodies are associated with high risk of thrombosis, but it is difficult to define boundaries for medium and high titers at this stage. Until an international consensus is reached, this committee proposes a threshold for positive anti-β_2GPI antibodies > 99th percentile of controls. The possible interference of cryoglobulins and rheumatoid factors should be considered in the interpretation of IgM anti-β_2GPI. Outside the context of clinical studies, testing for anti-β_2GPI can be helpful for APS diagnosis, particularly when aCL and LA are negative and APS is strongly suspected.

IgA anti-β_2GPI and other ELISAs for aPL detection

Data are inadequate for establishing IgA anti-β_2GPI as an independent risk factor for APS in the absence of other anti-β_2GPI isotypes (Evidence Level III) [117]. IgA anti-β_2GPI are the most frequently detected antibodies in patients in specific ethnic groups (Evidence Level II) [118,119]. A significant proportion of IgA anti-β_2GPI-positive tests has no apparent association with any clinical manifestation of APS (Evidence Level IV). Although a few Evidence Level II studies report association of aPE antibodies with thrombosis and fetal loss [120,121], experience with these antibodies is inadequate. Uniform guidelines how to perform the test, units of measurement and control materials do not exist. The committee concludes that it is premature to recommend that tests for an aPL other than IgG and IgM anti-β_2GPI be included in the revized-Sapporo criteria.

Antiprothrombin antibodies

Antiprothrombin antibodies detected by ELISA are a heterogeneous population including antibodies against prothrombin alone (aPT-A) and antibodies to the phosphatidylserine–prothrombin complex (aPS/PT). Data on the clinical associations of aPT-A are contradictory, and they imply low specificity of these antibodies for APS diagnosis (Evidence Level II) [122–127]. A systematic review on antiprothrombin antibodies and risk of thrombosis in APS failed to reveal an association, irrespective of isotype, site and type of event, or presence of SLE [107]. Both the sensitivity and specificity of aPS/PT are higher than those for aPT-A, whereas 95% of patients with aPS/PT are also LA positive, suggesting that aPS/PT can also serve as a confirmatory assay for LA (Evidence Level II); these results, however, only come from one study [128], and concerns regarding aPS/PT arise from multivalent antibody binding; the possibility of measuring antibodies against non-complexed

[2]Consensus was not reached regarding this issue. Two members of the committee considered that existing evidence does not justify inclusion of anti-β_2GPI as a criterion.

phospholipids present in the sample needs to be excluded. Prospective studies examining the association of aPT-A or aPS/PT with APS clinical features are still missing. This committee considers that the inclusion of antiprothrombin antibodies in the classification criteria for APS is premature.

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Conflict of interest statement

No conflicts of interest are declared for this document.

Addendum

Contribution of each author to this manuscript was as follows:
SM: grading of the evidence, synthesis, and writing of the manuscript
MDL: grading of the evidence, manuscript editing
SAK: grading of the evidence, manuscript editing, and authors coordination
The following authors contributed to parts of the manuscript as listed:
TA: thrombocytopenia, antiprothrombin antibodies
DWB: obstetric manifestations
RLB: neurological manifestations
RC: cardiac manifestations
RHWMD: lupus anticoagulant
PGdG: lupus anticoagulant
TK: thrombocytopenia, antiprothrombin antibodies
PLM: renal manifestations
GR: anticardiolipin, anti-β_2GPI
YS: skin manifestations
AT: anticardiolipin, anti-β_2GPI
PGV: renal manifestations.

Appendix: Members Of The Workshop Panel

In addition to the authors, the workshop panel comprised the following individuals:

Marie-Claire Boffa, MD (Hôpital de la Pitié, Paris, France), Benjamin Brenner, MD (Rambam Medical Center, Haifa, Israel), Joab Chapman, MD (Sheba Medical Center, Tel-Hashomer, Israel), Philippe de Moerloose, MD (University Hospital, Geneva, Switzerland), Doruk Erkan, MD (Hospital for Special Surgery, Cornell Medical Center, New York, NY), Thomas Exner, PhD (St. Vincents Hospital, Sydney, Australia), Ricardo R. Forastiero, MD (Favaloro University, Buenos Aires, Argentina), Monica Galli, MD (Ospedali Riuniti, Bergamo, Italy), E. Nigel Harris, MD (Morehouse School of Medicine, Atlanta, GA), Thomas Lecompte, PhD (Université de Nancy, France), Steven R. Levine, MD (The Mount Sinai School of Medicine, New York, NY), Roger A. Levy, MD (Universitario Pedro Ernesto, Rio de Janeiro, Brazil), Gabriella Moroni, MD (Ospedale Maggiore, Milan, Italy), Michelle Petri, MD (John Hopkins University, Baltimore, MD), Silvia Pierangeli, PhD (Morehouse School of Medicine, Atlanta, GA), Jacob H. Rand, PhD (Montefiore Medical Center, New York, NY), Joyce Rauch, MD (McGill University, Montreal, Canada), Veronique Regnault, PhD (INSERM, Nancy, France), Robert A. S. Roubey, MD (The University of North Carolina at Chapel Hill, NC), Marielle Sanmarco, MD (Hopital de la Conception, Marseille, France), Yaniv Sherer, MD (Sheba Medical Center, Tel-Hashomer, Israel), Maria Tektonidou, MD (Department of Pathophysiology, University of Athens, Greece), Pierre Youinou, PhD (Brest University Hospital, Brest, France), and Denis Wahl, MD (INSERM, Nancy, France).

This workshop was chaired by Drs. Ronald Derksen, Steven Krilis, Michael Lockshin, and Spiros Miyakis.

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LETTERS

Methotrexate-induced lung injury in patients with rheumatoid arthritis occurs with peripheral blood lymphocyte count decrease

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Pulsed methotrexate (MTX) treatment, of which the standard dose for Japanese patients with rheumatoid arthritis (RA) approved by the National Health Insurance System is 2–8 mg/week, is still the standard regimen. However, life threatening adverse reactions to this treatment, including lung injury, remain to be elucidated in detail.

We treated 11 patients with RA who developed lung injury during MTX treatment. Their clinical and laboratory features were examined retrospectively, focusing mainly on the changes in peripheral blood lymphocyte count.

The 11 patients (three men, eight women) had a mean (SD) age of 69.8 (7.8) years. All the patients had taken non-steroidal anti-inflammatory drugs, and nine had received steroids with a mean (SD) prednisolone dose of 6.6 (2.9) mg/day.

All of them responded well to MTX, when evaluated by American College of Rheumatology 20 core set.[1] The dose of MTX had been increased from 2.8 (1.4) to 7.1 (3.4) mg/week during 15.4 (17.8) months. At the onset of respiratory distress with a fever, plain chest radiography and/or computed tomography showed ground-glass opacities, mainly from the middle to upper central lung fields; the findings differed from those of rheumatoid pneumonitis which usually involves the periphery and results in structural derangement. The bronchoalveolar lavage fluid of five patients contained CD4+ T cells (70.7 (15.1)% of the total cells). No micro-organism was detected either in lavage fluid or sputum in any of the patients. Hypoxaemia was severe, with a mean (SD) Pao_2 of 47.1 (15.2) mm Hg. Serum C reactive protein (CRP) level was as high as 233 (136) mg/l, and serum β_2-microglobulin level was 4.94 (1.83) mg/l (normal range 0.8–1.7). Three patients underwent mechanical ventilation, and six received pulsed steroid treatment; a patient who received both of these treatments died 1 month later. After recovery in 10 patients, the opacities in chest radiography/computed tomography completely disappeared, and Pao_2 and serum CRP and β_2-microglobulin levels returned to normal.

The peripheral blood lymphocyte count was followed throughout from the start of MTX treatment to after the recovery from lung injury, and the counts at the start of MTX treatment, at arthritis remission, at the onset of lung injury, and after the recovery from lung injury were compared with each other (fig 1). The count did not change from the start of MTX treatment (1.91 (0.83)$\times 10^9$/l) to arthritis remission (1.77 (0.69)$\times 10^9$/l, $p = 0.293$), then decreased in all of the patients at the lung injury onset (0.56 (0.45)$\times 10^9$/l, $p<0.0001$ *v* arthritis remission; $p<0.0001$ *v* MTX treatment start), and re-increased to preinjury level in 10 patients who recovered (1.96 (1.06)$\times 10^9$/l, $p = 0.0002$ *v* lung injury onset; $p = 0.738$ *v* arthritis remission; $p = 0.880$ *v* MTX treatment start). In the patient who did not recover, the lymphocyte count did not re-increase after MTX administration was stopped. Other blood cell count changes did not correlate with the event.

The new finding in this study was the significant decrease in peripheral blood lymphocyte count concurrent with the lung injury. This observation was in agreement with our previous study that the lymphocyte count did not change during RA remission, but decreased only when various adverse reactions to MTX occurred.[2] Along with this, the increase in lymphocyte count in bronchoalveolar lavage fluid, particularly in the count of CD4+ T cells, in this study and in previous reports,[3 4] suggests that lymphocytes may participate in the injury. A high serum level of β_2-microglobulin at injury onset might be relevant to the changes of lymphocytes.

We conclude that a peripheral blood lymphocyte count decrease in a responder, concurrent with respiratory distress and fever after receiving MTX dose, strongly suggests MTX-induced lung injury, and an increase again to the preinjury level predicts recovery from the injury.

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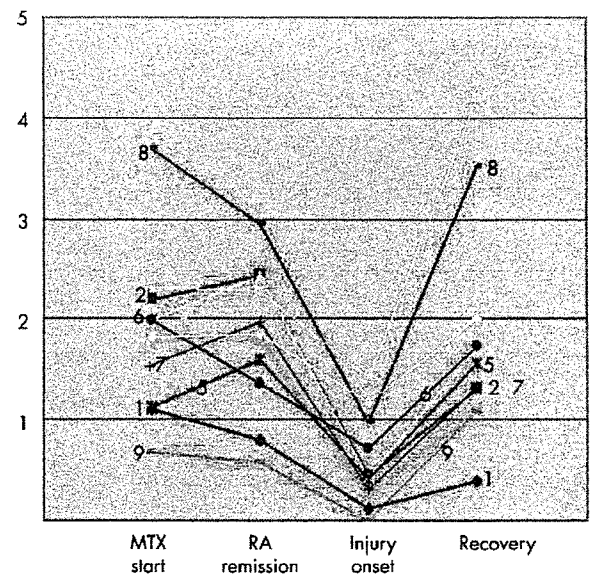

Figure 1 Peripheral blood lymphocyte count (10^9/l) at the start of methotrexate treatment, at arthritis remission, at lung injury onset, and after recovery from lung injury. The numbers refer to the individual patients. Patient 2 eventually died.

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Analyses of ADAMTS13 activity and its inhibitor in patients with thrombotic thrombocytopenic purpura secondary to connective tissue diseases: Observations in a single hospital

Sirs,

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disorder characterized by generalized platelet thrombi in arterioles and capillaries (1, 2). A severe decrease of a disintegrin and metalloprotease with thrombospondin type I motif 13 (ADAMTS13) activity and positive ADAMTS13 inhibitor have been considered to be characteristic features of classical TTP (3, 4). TTP has been described as a rare but severe complication associated with connective tissue diseases (CTDs) (5). In this study, we examined whether patients with TTP secondary to CTDs have a decreased ADAMTS13 activity and ADAMTS13 inhibitor.

Among the number of 1056 patients with CTDs hospitalized in Department of Allergy and Immunological Diseases, Tokyo Metropolitan Komagome Hospital from 1978 to 2004, 12 patients were diagnosed as having TTP with four or five of the pentad of TTP (Table I). The incidences of TTP secondary to CTDs were estimated as follows: 12 of 1056 patients (1.14%) as a whole, 3 of 53 (5.66%) in systemic sclerosis, 2 of 66 (3.03%) in vasculitic syndrome, 5 of 222 (2.25%) in systemic lupus erythematosus, 1 of 65 (1.54%) in myositis, and 2 of 132 (1.52%) in primary Sjögren's syndrome. All the patients were female, and none of them was pregnant. Ten patients had active CTDs. Anti-phospholipid antibody was detected in none of the nine patients examined. None of them received cyclosporine, antimalarial, ticlopidine, and clopidogrel before the development of TTP. In one patient, TTP developed at the diagnosis of CTD, and in 11 patients 0.2 to 16 years (median 1 year) after the diagnosis of CTDs. The mortality rates were 58% overall, and 88% and 0% in patients with and without neurological disorders, respectively.

Among the eight patients whose ADAMTS13 activity was measured (6, 7), three had a moderately decreased (3 to 25%), two a mildly decreased (25 to 50%), and three a normal activity (more than 50%); the ADAMTS13 inhibitor was detected at a low titer in only one patients. In five of the eight patients tested, unusually-large von Willebrand factor (VWF) multimers were clearly detected, and plasma VWF antigen levels were markedly high, ranging from 440% to 1400%.

In the present study, none of our patients had a severely decreased ADAMTS13 activity, indicating that the pathogenesis of TTP secondary to CTDs is not necessarily the same as that of classical TTP. Mannucci *et al.* (8) reported that patients with systemic lupus erythematosus and systemic sclerosis had low but detectable levels of ADAMTS13 without inhibitor, although they had no sign or symptom of TTP. On the other hand, Matsumoto *et al.* (9) reported that 10 of 43 patients with TTP secondary to CTDs had a severely decreased ADMATS13 activity and its inhibitor was detected in 13 of 27 patients tested. From these findings, it appears that a severely decreased ADAMTS13 activity caused by its inhibitor is involved in some patients with TTP secondary to CTDs, but a mildly to moderately decreased ADAMTS13 level can be a finding in CTD patients with or without TTP.

Particularly interesting was the result that unusually-large VWF multimers were detected in five of eight patients tested. In cases of CTDs, the damage of the endothe-

Table 1. Clinical features and measurement of ADAMTS13 activity, its inhibitor, ULVWFM, and VWF Ag in patients with TTP secondary to CTDs..

		Underlying CTDs									
Patient No.	Sex/age (years)	Disease	Activity	Positive autoantibody*	Treatment	TTP treatment	Outcome	ADAMTS13 activity (%)	Inhibitor (BU/mL)	ULVWFM	VWF Ag (%)
1	F / 28	SLE	None	ANA, DNA	PSL 5 mg/day	PE, mPSL 64mg/day dipyridamole, aspirin	Recovered	NA	NA	NA	NA
2	F / 55	SSc, PM	+	ANA, DNA, Scl-70, RF	PSL 1.4 mg/kg, d-PC	PE, dipyridamole, aspirin	Died	NA	NA	NA	NA
3	F / 67	SjS	NA	ANA, RF	Non	PI	Died	NA	NA	NA	NA
4	F / 50	MPA	+	MPO-ANCA, PR3-ANCA	PSL 1.2 mg/kg, CPA	PI	Recovered	NA	NA	NA	NA
5	F / 74	SjS	+	ANA, RF, MPO-ANCA, PR3-ANCA	None	PI, PSL 0.8mg/kg	Died	70	< 0.5	None	440
6	F / 83	SSc	+	ANA	None	PE, dipyridamole, VCR PSL 1.2mg/kg	Died	20	< 0.5	+	500
7	F / 68	GS, MPA	+	RF, MPO-ANCA, GBM	PSL 1.2 mg/kg, CPA	PE	Died	48	< 0.5	None	720
8	F / 42	SLE, SjS	+	ANA- ds-DNA	PSL 0.8 mg/kg	PE	Recovered	17	< 0.5	+	560
9	F / 25	SLE, SjS	+	ANA, ds-DNA, RNP	PSL 1.2 mg/kg	PE	Died	26	< 0.5	+	1400
10	F / 48	SLE	+	ANA, RNP, Sm, SS-A, SS-B	PSL 1.2 mg/kg	PI	Recovered	66	< 0.5	+	560
11	F / 33	SLE	+	ANA, ds-DNA, SS-A	PSL 1.2 mg/kg	PE, PI	Recovered	51	< 0.5	+	680
12	F / 72	SSc	+	ANA, Scl-70, SS-A	PSL 0.6 mg/kg	ACE inhibitor	Died	10	0.5	None	1000

ADAMTS: a disintegrin and metalloprotease with thrombospondin type I motif; TTP: thrombotic thrombocytopenic purpura; CTDs: connective tissue diseases; ULVWFM: unusually-large von Willebrand factor multimers; VWF Ag: von Willebrand factor antigen; F: female; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; PM: polymyositis; SjS: Sjögren's syndrome; MPA: microscopic polyangiitis; GS: Goodpasture's syndrome; NA: not available; ANA: anti-nuclear antibody; RF: rheumatoid factor; MPO: myeloperoxidase; ANCA: antineutrophil cytoplasmic antibody; PR3: proteinase-3; GBM: glomerular basement membrane; PSL: prednisolone; d-PC: d-penicillamine; CPA: cyclophosphamide; PE: plasma exchange; mPSL: methylprednisolone; PI: plasma infusion; VCR: vincristine; ACE: angiotensin converting enzyme

*ANA was measured by immunofluorescent antibody technique, RF by nephelometry, and other autoantibodies by enzyme-linked immunoassay.

lium of capillaries caused by angiitis, the deposition of immune complexes, or certain drugs may result in a defective utilization of ADAMTS13 and the subsequent accumulation of unusually-large VWF multimers in the circulation. Since a markedly high level of plasma VWF antigen observed in our study appears to reflect a proportional increase in plasma unusually-large VWF multimers, it is conceivable that a decreased enzyme-to-substrate (ADAMTS13/unusually-large VWF multimers) ratio results in an accumulation of undigested unusually-large VWF multimers, leading to TTP.

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特集 多発性筋炎・皮膚筋炎の診断と治療の問題点

悪性腫瘍の合併とその臨床的特徴*

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Key Words：polymyositis, dermatomyositis, malignancy, paraneoplastic syndrome

はじめに

横紋筋(骨格筋)に炎症を起こす原因不明の慢性炎症性疾患を特発性炎症性ミオパチーといい，膠原病・リウマチ性疾患の中で，皮膚筋炎(dermatomyositis)および多発性筋炎(polymyositis)，封入体筋炎(inclusion body myositis)が代表的である．古典的には，BohanとPeterの分類が有名である(表1)．この分類では悪性腫瘍を合併する筋炎として分けられているが，皮膚筋炎および多発性筋炎は悪性腫瘍の合併が多くみられることが知られている．しかし，その理由などはまだ明らかではない．筋炎の発症に前後して悪性腫瘍の合併が判明した症例は悪性腫瘍随伴症候群(paraneoplastic syndrome)と呼ばれることがあり，悪性腫瘍の直接的な浸潤による症状ではなく，悪性腫瘍に随伴する免疫異常と考えられている[1)2)]．

炎症性筋疾患の臨床像

筋症状を有する疾患としてリウマチ性多発筋痛症(polymyalgia rheumatica)，線維筋痛症候群，重症筋無力症などがあるが，筋肉に炎症を起こす疾患である皮膚筋炎，多発性筋炎，封入体筋炎は病態，病因などが区別されている．リウマチ性多発筋痛症や封入体筋炎の発症年齢は50歳以上の高齢であるのに対し，皮膚筋炎，多発性筋炎では二峰性を示し，10～15歳の小児期と45～60歳の成人にみられる．

表1 Bohan & Peterの分類

Group I	原発性特発性多発性筋炎
II	原発性特発性皮膚筋炎
III	悪性腫瘍に伴う多発性筋炎/皮膚筋炎
IV	小児の多発性筋炎/皮膚筋炎
V	他の膠原病に伴う多発性筋炎/皮膚筋炎(重複症候群)

組織免疫学的所見で皮膚筋炎と多発性筋炎は異なっている．皮膚筋炎では，B細胞とCD4陽性T細胞(ヘルパーT細胞)が血管周囲に浸潤することで炎症をひき起こし，血管閉塞による支配領域の筋細胞の壊死が特徴である．血管壁への免疫グロブリンや補体の沈着を認めることから液性因子が関与する血管障害，血管炎と虚血性変化が筋障害の機序と考えられている．

一方，多発性筋炎においては炎症の誘起にMHCクラスIが重要な役割を担っている．未知の遺伝的素因や何らかのウイルス感染が契機となり，筋細胞表面にMHCクラスIを介した抗原提示が

* The association and the clinical characteristic of malignancy with polymyositis and dermatomyositis.

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起こり，CD8陽性T細胞(細胞障害性T細胞)がその筋細胞を異物とみなし筋細胞の破壊がひき起こされ，筋細胞の壊死がみられるのが特徴である．封入体筋炎は筋線維萎縮，筋内膜の線維化があり，核内，細胞質内に封入体がみられ，アミロイド蛋白が証明される．

以上より，皮膚筋炎，多発性筋炎は皮膚病変の有無だけではなく，近年では別の疾患であると考えられており，悪性腫瘍との関連も多少異なっていると考えられる．

筋炎と悪性腫瘍

悪性腫瘍に起因して筋症状を発現することがあり，通常1年以内程度のことが多く[1)3)4)]，悪性腫瘍関連筋炎と言われている．とくに，腫瘍の合併は多発性筋炎より皮膚筋炎で多く，10～30%にみられる[5)]．男女比は，多発性筋炎ではあまり差がないが，皮膚筋炎では男性で多く，とくに50歳以上に多い[4)]．小児では，皮膚筋炎がほとんどであるが，悪性腫瘍の合併はきわめて稀である．

悪性腫瘍の発現は筋症状の発現に先行することも，筋症状が先行することもある．筋炎の診断前に発現した悪性腫瘍は皮膚筋炎では2年以内が多いが，多発性筋炎では5年以上前のことが多くみられる．多発性筋炎では筋炎の診断後5年以上で悪性腫瘍発現の危険性が少なくなるが，皮膚筋炎では診断後5年以上経っても危険性はまだ高いままである[3)]．

腫瘍の摘出などによる治療により筋炎症状が軽快し，悪性腫瘍の再発により筋炎症状の再燃をみることがあり，paraneoplastic syndromeが示唆される．また，悪性腫瘍を合併した筋炎はしばしばステロイド治療に抵抗性を示す．

悪性腫瘍を合併した皮膚筋炎は，しばしば筋原性酵素の上昇がみられなかったり，抗Jo-1抗体などの特異抗体が陰性であったりすることが多い．皮膚症状として指尖の血管炎，皮膚壊疽，瘙痒を伴った多形皮膚萎縮は，しばしば悪性腫瘍の合併が示唆される．また，皮膚筋炎の発症形式では，亜急性より急性発症の症例で悪性腫瘍の合併が多くみられる．

筋炎の所見が乏しく，間質性肺炎の合併頻度が高い，いわゆるamyopathic dermatomyositisでも同様に悪性腫瘍の合併がみられると報告されている[6)]．

原発部位

悪性腫瘍の原発部位あるいは種類は，一般の発現と同様にみられる．皮膚筋炎では卵巣癌，肺癌，膵癌，胃癌，大腸癌，直腸癌，非ホジキンリンパ腫，多発性筋炎では非ホジキンリンパ腫，肺癌，膀胱癌が多くみられた[3)7)]．男性では呼吸器系の癌が多いのに対し，女性では生殖器系の癌が多くみられている．卵巣癌は一般女性の1%であるのに対し，皮膚筋炎では13%にみられ，40歳以上の患者では21%であった[8)]．Paraneoplastic syndromeは腎癌[9)]，肺癌，大腸癌[10)]に多いという報告がある．

1994～2004年に順天堂医院膠原病・リウマチ内科に入院した患者での調査で，他の膠原病に比べ同様に筋炎，とくに皮膚筋炎での悪性腫瘍の合併が多くみられた．原発部位では，上記以外に皮膚筋炎で食道癌，上咽頭癌，乳癌，胸腺癌，膀胱癌がみられ，多発性筋炎で大腸癌，胆嚢癌，頬粘膜癌，甲状腺癌，膵癌，乳癌，子宮癌，白血病がみられた．

免疫抑制剤との関係

ステロイド剤抵抗例，再発例ではメトトレキサートやアザチオプリン，間質性肺炎合併例ではシクロスポリンやシクロフォスファミドの大量静注療法などの免疫抑制剤を使用することがあるが，それらによる悪性腫瘍の発現との関連はまだ明らかではない．しかし，免疫抑制剤の使用が多くなるとともに，メトトレキサートによる間質性肺炎やシクロフォスファミドによる出血性膀胱炎などが知られていることより，肺癌，膀胱癌といった二次的な悪性腫瘍の発現の増加も今後は注意を要すると考えられる．

間質性肺炎との合併

皮膚筋炎，多発性筋炎では間質性肺炎の合併は30～60%にみられるが，悪性腫瘍合併例は間質性肺炎の合併はむしろ少ないと言われている．とくに，悪性腫瘍を合併した皮膚筋炎は多発性筋炎より間質性肺炎の合併が少ない傾向にある．

悪性腫瘍合併例の予後

悪性腫瘍合併例で，死亡原因が筋炎に起因するものが10%，循環器系によるものが26%に対し，40%で主因が悪性腫瘍によるものであった[11]．

おわりに

膠原病・リウマチ性疾患の中で，炎症性筋疾患，とくに皮膚筋炎において悪性腫瘍の合併が多いことが知られている．とくに高齢者では，筋症状発症後しばらくは悪性腫瘍の合併が多くみられ，筋炎の治療と平行して悪性腫瘍の検索が必須である．

悪性腫瘍の検査としては，血液検査，単純X線などの一般検査以外に，便鮮血，CT，超音波，婦人科検査，さらにはMRI，ガリウムシンチグラフィーなどの全身的検索が必要である．多くの場合は，問診および臨床症状の注意深い観察と，一般検査，スクリーニング検査で発見されるが，稀に各種精密検査を行っても原発部位が明らかでないこともある．筋炎症状が治療によっても軽快しない難治例や再燃例では，悪性腫瘍の合併も考慮し，十分精査する必要がある．

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Recent Advances in the Treatment of Interstitial Lung Disease in Patients with Polymyositis/Dermatomyositis

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Abstract: Interstitial lung disease (ILD) develops in 30-50% of patients with polymyositis/dermatomyositis (PM/DM) and negatively affects their prognosis. The progression of PM/DM-ILD may be acute, subacute, chronic, or chronic becoming acute. The histopathological classification of PM/DM-ILD includes non-specific interstitial pneumonia (NSIP), organizing pneumonia (OP), diffuse alveolar damage (DAD), and usual interstitial pneumonia (UIP) or mixed variations. Some patients with acute/subacute interstitial pneumonia (A/SIP), typically with lung histology of OP or cellular NSIP, respond favorably to corticosteroid treatment, while others do not. Japanese patients with DM, especially those with clinically amyopathic DM (C-ADM) and palmar papules, seem to be at a greater risk of developing fulminant A/SIP with DAD histology resulting in pneumomediastinum and fatal outcome in a few months. An aggressive combination regimen including cyclosporine A (or tacrolimus) and cyclophosphamide should be immediately added to corticosteroid treatment for such patients. Sequential follow-up examination using high-resolution computed tomography (HRCT) of the chest and careful monitoring for bacterial and viral infections are essential. However, intensive immunosuppression alone may not be sufficient to control fulminant A/SIP, and other therapeutic targets, such as fibroblasts, should be considered.

Key Words: Clinically amyopathic dermatomyositis, diffuse alveolar damage, cyclosporine A, cyclophosphamide

INTRODUCTION – PROGNOSIS OF PM/DM

Polymyositis/dermatomyositis (PM/DM) is a systemic autoimmune disease which predominantly affects the proximal girdle muscles [1,2]. The presence of pathognomonic skin rashes, namely heliotrope rash and Gottron's papules, distinguishes DM from PM [1,2], and a minimal set of hallmark cutaneous manifestations of DM has been proposed recently [3].

The differences between PM and DM are more extensive than the simple presence or absence of diagnostic skin involvements. For example, the frequency and severity of vital organ involvement and other complications such as malignancies differ between PM and DM, influencing patients' prognosis. In a series by Marie *et al.* [4], mortality was observed in 5 out of 41 patients with PM and 12 out of 36 patients with DM. Strikingly, cancer was the main cause of death in DM (8 out of 12 patients) while none of 5 patients with PM died from cancer.

Moreover, interstitial lung disease (ILD) associated with PM (PM-ILD) and DM (DM-ILD) also exhibits clinical differences. A recent report from Japan suggested that patients with DM-ILD had significantly higher percentages of lymphocytes and eosinophils in their bronchoalveolar lavage (BAL) samples than patients with PM-ILD [5]. Also, DM-ILD was more refractory to corticosteroid therapy than PM-ILD, resulting in a poorer prognosis that may be partly related to histological differences. Diffuse alveolar damage (DAD) was exclusively found in 3 patients with DM at autopsy, while non-specific interstitial pneumonia (NSIP) was found in 4 out of 5 biopsy samples from patients with PM-ILD and 3 out of 5 biopsy samples from patients with DM-ILD [5]. Another report by Dankó *et al.* [6] demonstrated an apparently more favorable cumulative survival rate in patients with PM-ILD than in patients with DM-ILD.

A concept of amyopathic DM (ADM) [3,7,8] was described a while ago, followed by its extended concept "clinically amyopathic DM (C-ADM)" [3,8]. C-ADM refers to patients with DM-specific skin disease but no clinical evidence of myositis with (hypomyopathic DM) or without (ADM) subclinical evidences of myositis on laboratory, electrophysiologic, or radiographic evaluation [3]. For patients having features of C-ADM for less than 6 months, the term premyopathic DM may be adequate [8,9]. In addition to the above-mentioned papers reporting poor prognosis of patients with DM *vs.* PM, several recent studies suggested particularly poor prognosis of patients with C-ADM. Our own observation agrees with these findings. We examined the survival of 110 patients with PM/DM who were treated at our department between 1985 and 2002 (Fig. 1). The overall 5-year-survival rate of patients with PM/DM was 68%. The rapidly deteriorating clinical course of patients with C-ADM (including those with "premyopathic DM" [8]) was most striking: nearly half (6 out of 14) of the patients with C-ADM died within 6 months of diagnosis due to respiratory failure caused by acute or subacute interstitial pneumonia (A/SIP), which consistently progressed despite aggressive treatment. More importantly, the outcome of patients with C-ADM who survived for more than 6 months was excellent. Among 13 patients with malignancy-associated PM/DM, lung cancer was the cause of death in 4 patients and gastric, pharyngeal, colon, bladder, and ovarian cancer was the cause of death in 1 patient each. ILD and infection was the cause of death in 4 cases each out of 32 patients with classical DM

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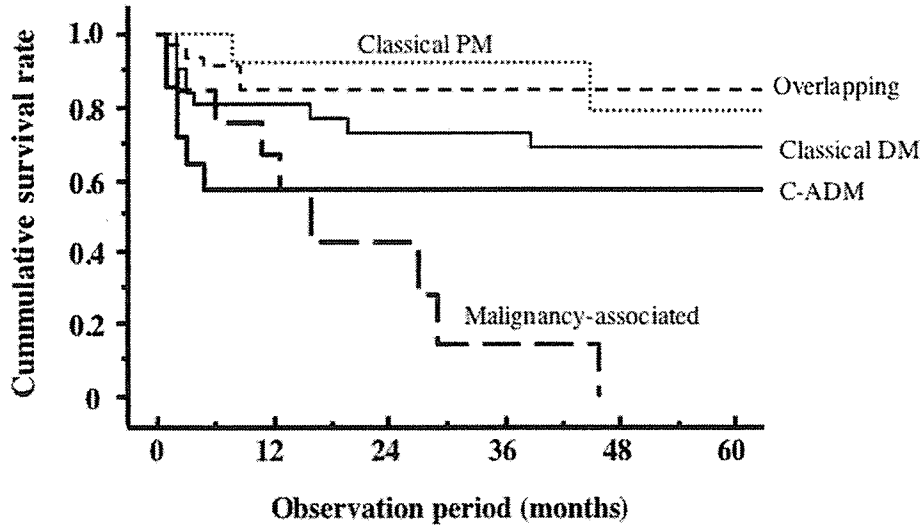

Fig. (1). Cumulative survival rate after diagnosis of PM/DM.

Patients with PM/DM were classified as follows. First, 13 patients with malignancy (2 patients with PM and 11 with DM; a thick broken line) were extracted. Then, 33 patients (15 patients with PM and 18 with DM) with an overlapping diagnosis of systemic lupus erythematosus, systemic sclerosis (scleroderma), or rheumatoid arthritis were classified (a thin broken line). C-ADM patients were enrolled accordi the criteria proposed by Sontheimer (a thick solid line) (3). Patients diagnosed as having mixed connective tissue disease were not in in the study because most of these patients only had modest myopathy, while the manifestations of systemic lupus erythemato scleroderma were more prevalent. Classical PM (n=18) and classical DM (n=32) are represented as a fine dotted line and a thin soli respectively.

and 3 cases each out of 33 patients with overlap syndrome. Obviously, the risk of fatal infections increases with the development of ILD, which consequently requires aggressive immunosuppressive therapy. Nevertheless, infection was not considered as the primary cause of death in any of the patients with C-ADM. Thus, ILD is an important factor that adversely influences the prognosis of patients with PM/DM, especially those with DM.

RACIAL DIFFERENCES

Japanese patients with DM appear to be at a greater risk of developing ILD than DM patients from other ethnic groups. Indeed, about 50% of Japanese patients with PM/DM develop ILD during the course of their disease [10] whereas only ~30% of Caucasian patients with PM/DM develop ILD [11-13]. Furthermore, a disproportionately large number of cases of fatal A/SIP have been reported among Japanese patients with C-ADM [3,8,14]. This devastating and fulminant condition is currently an issue of great concern in this country [15,16], although only successfully treated cases tend to be reported.

Japanese patients with diseases other than PM/DM also seem to be at a greater risk of developing ILD, often resulting in a fatal outcome. For instance, gefitinib-induced AIP occurs at a markedly higher rate in Japan than in Western countries [17]. Leflunomide-induced ILD rarely develops in Western countries (~ 0.02%), but as many as approximately 1.1% of Japanese patients who receive leflunomide develop ILD, often resulting in a fatal outcome [18,19]. Genetic studies, including the analysis of single nucleotide polymorphisms, are needed to explain these racial differences in susceptibility.

PATHOGENESIS AND SUBTYPES OF ILD IN PM/DM

Although the pathogenesis of ILD in PM/DM is largely unknown, autoimmune processes are likely to be involved. The prevalence of ILD is associated with the presence of autoantibodies against Jo-1 (histidyl) and other aminoacyl transfer RNA synthetase (tRNAS) in the serum of patients [10,20]. In addition to the fact that certain HLA genes, such as the HLA-DRB1*0301 alleles in Caucasian patients [21] and the DRB1*0803 allele in Japanese patients [22], are associated with PM/DM, the HLA-DRB1*03-DQA1*05-DQB1*02 haplotype is strongly associated with ILD, irrespective of the myositis subtype or the presence of anti-tRNAS antibodies in Caucasian patients with PM/DM living in the UK [23].

Cytotoxic T cells are thought to invade muscle fibers expressing major histocompatibility complex (MHC) class I antigens in PM, leading to the necrosis of muscle fibers via the perforin pathway [21,24]. In contrast, microangiopathic endomysial ischemia resulting from the activation of the complement system is predominant in patients with DM [21,24]; thus, DM is associated with manifestations that suggest vasculitis, including palmar or finger lesions, intestinal perforations and, possibly, pneumomediastinum [25,26].

The clinical courses of patients with ILD associated with PM/DM can be categorized into 4 groups: 1) A/SIP with rapid deterioration within a month (acute) or within 2-3 months (subacute); 2) chronic progression of pulmonary fibrosis causing non-productive coughing, breath-shortening upon exertion, and occasionally leading to respiratory failure after more than 6 months; 3) acute or subacute exacerbation of chronic ILD that is recurrent in some cases; and 4) asymp-

tomatic ILD detected in a milder form by radiographic examinations or pulmonary function tests in the absence of clinically apparent signs and symptoms throughout the observation period.

The American Thoracic Society/European Respiratory Society (ATS/ERS) international multidisciplinary consensus classification is usually used for the classification of idiopathic interstitial pneumonias (IIP) [27]. However, whether PM/DM-ILD resembles IIP remains debatable. In general, biopsies are performed using video-assisted thoracic surgery (VATS), and NSIP is the most prominent histological diagnosis, followed by organizing pneumonia (OP) and DAD [10,21,28,29]. Usual interstitial pneumonia (UIP) is rare, especially when the diagnosis is made according to the ATS/ERS consensus. A diagnosis of DAD is usually confirmed at the time of autopsy. Histological examinations are limited due to the following reasons: 1) timely biopsy specimens (obtained upon acute exacerbation, for example) are not easily available; 2) the histological findings may change spontaneously or in response to treatment, and repeating biopsies is difficult; and 3) the histological findings may consist of the overlapping features of two or more patterns (typically NSIP and OP, or NSIP and UIP).

Recently, a new histologic pattern of acute/subacute lung injury, acute fibrinous and organizing pneumonia (AFOP), has been proposed [30]. The histopathologic features of AFOP include dominant findings of organizing intra-alveolar fibrin, organizing pneumonia and a patchy distribution. The mortality rate of AFOP is reported to be 50%, similar to that of DAD. Since one patient with PM was included among 17 reported cases of AFOP, this histologic pattern should be taken into consideration when diagnosing PM/DM-ILD.

BAL specimens can be obtained from most patients with PM/DM-ILD. However, relationship between BAL findings and a diagnosis of PM/DM or the histological patterns of surgical lung biopsy specimens has not been well defined. Nevertheless, it has been reported that neutrophilia [13] and an elevated CD4+CD25+ T cells count [31] in BAL fluid may predict a poor response to corticosteroid treatment. No significant differences in the CD4/CD8 T cell ratios obtained from BAL fluids were observed between patients with PM and those with DM [32].

THERAPEUTIC AGENTS FOR PM/DM-ILD

In view of its rapid and relatively valid efficacy, high-dose corticosteroid therapy (1 mg/kg/day of prednisolone equivalent) is a mainstay of treatment for PM/DM-ILD. However, primary or secondary failure is not uncommon in patients receiving corticosteroid monotherapy, and immunosuppressive agents or alternatives should be added to the therapeutic regimens of these patients [33]. Although azathioprine (AZ) and methotrexate (MTX) are typically used for the treatment of corticosteroid-resistant myositis [21,34,35], the efficacy of such regimens for PM/DM-ILD has not yet been established; indeed, the use of MTX for ILD is very limited because of potential lung toxicity, as demonstrated in patients with rheumatoid arthritis [36,37].

The efficacy of cyclosporine A (CsA) in patients with PM/DM-ILD was first reported by Gruhn *et al.* in 1987 [38]. A nationwide survey conducted in Japan concerning the use of CsA for the treatment of ILD associated with collagen diseases revealed that 7 out of 13 DM patients with A/SIP responded favorably to CsA treatment [39]. In another 4 patients with steroid-resistant ILD associated with DM, including 3 C-ADM patients, CsA treatment with a serum trough level of 160-200 ng/ml was effective [40]. Several subsequent reports have indicated that CsA should be used early during the course of ILD to obtain a favorable response [41-44]. Recently, another calcineurin inhibitor, tacrolimus (FK506), has been reported to be an effective and tolerable treatment for patients with PM/DM-ILD, especially those positive for anti-tRNAS antibodies [45,46].

Cyclophosphamide, especially when used as intravenous pulse therapy (IV-CYC), is the drug of choice for the treatment of various lung diseases, including PM/DM-ILD [13,33,47-49]. In one study, a total of 10 patients with progressive PM/DM-ILD were treated with IV-CYC, and experienced some functional improvement [13]. However, most of the patients were positive for anti-Jo-1, similar to the 5 out of 7 patients reported by Meyer *et al.* [48], suggesting that treatment with tacrolimus might also have been effective [46]. Very recently, Yamasaki *et al.* reported 17 patients with PM/DM-ILD who had been treated with IV-CYC (300-800 mg/m^2) [49]. The pulmonary function and HRCT findings improved in more than half of these patients.

Some patients with PM/DM (almost exclusively DM) develop fulminant A/SIP, which is rapidly progressive and fatal despite intensive treatment with corticosteroids, CsA, and IV-CYC [15,50,51]. The histologic patterns of lung biopsy specimens obtained from these patients typically revealed DAD, although fibrotic NSIP was also occasionally seen. Therefore, we conducted a pilot trial of combined immunosuppressive therapy using high-dose corticosteroids, 10-30 mg/kg of IV-CYC every 3-4 weeks, and 2-4 mg/kg/day of CsA to improve the survival rate of such patients, rather than determining which single immunosuppressive agent might be more effective [16]. The rationale for the combined use of CsA and IV-CYC is based on the fact that CsA is a selective T-cell inhibitor whereas IV-CYC mainly suppresses B-cell functions [52]. As a result of this combination therapy regimen, the survival rate of patients with A/SIP associated with DM improved from 25% by conventional therapy (sequential use of immunosuppressive drugs) to 50%. The survived patients have been doing well without respiratory symptoms thereafter. However, other patients died from respiratory failure within a few months, despite aggressive combination therapy initiated at a very early stage of the disease in most of the cases, as demonstrated by chest high-resolution computed tomography (HRCT) images obtained at the commencement of the combination regimen (Fig. **2**).

TREATMENT AND MANAGEMENT OF INDIVIDUAL PATIENT WITH PM/DM-ILD

The decision to treat a patient with PM/DM-ILD should be based on the extent and the speed of progression of the disease. Treatment may be postponed if the ILD is localized and non-progressive, typically an asymptomatic condition. In patients with chronic ILD, in whom the histological pattern

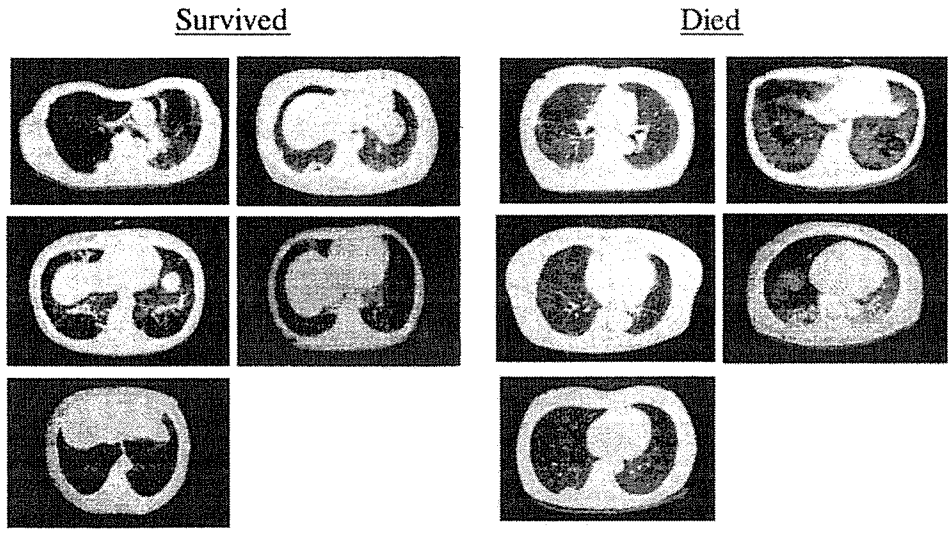

Fig. (2). Representative chest CT images of patients with A/SIP at the commencement of a combination treatment regimen prised of high-dose corticosteroids, CsA and IV-CYC.

Initial chest CT images from patients who survived (left) and died (right) are shown. Subpleural consolidation and linear/reticular o were predominant findings, even in most of the patients who eventually died of respiratory failure. It appears that initial chest CT image not particularly helpful in predicting prognosis.

is likely to be UIP, the administration of 0.5 mg/kg/day of prednisolone or equivalent, and either 1-3 mg/kg/day of AZ or 1-2 mg/kg/day of CYC, is recommended according to the international consensus statement for the treatment of IIP [53]. The administration of CsA or tacrolimus may also be tried.

For patients with A/SIP, including the acute exacerbation of chronic ILD, high-dose corticosteroids treatment should be included in the therapeutic regimen. If OP is confirmed by surgical biopsy or strongly suggested based on the results of HRCT, an additional immunosuppressant therapy is not essential. If DAD is apparent or very likely, the combination regimen should include the administration of high-dose corticosteroids, CsA (or tacrolimus), and (IV-) CYC.

Most patients with PM/DM-ILD are likely to have NSIP. The treatment strategy in these patients depends on the dermatological features, the predominance of fibrosis (cellular *vs.* fibrotic NSIP), and the rate of progression. We identified some characteristic clinical features of DM patients who developed A/SIP [16]: 1) milder myositis, in terms of either the absence of muscle weakness or a serum CK level less than twice the value of the normal upper limit; 2) the presence of heliotrope rash and Gottron's papules/signs; 3) the presence of palmar papules; 4) the presence of fever; and 5) negative test results for serum antinuclear antibodies and anti-Jo-1. Since 14 out of 22 DM patients with A/SIP died in that study [16], these factors, as well as the presence of pneumomediastinum, may indicate not only the presence or development of A/SIP, but also a fatal outcome. Recently, Selva-O'Callaghan *et al.* reported that 5 out of 81 patients with PM/DM had devastating AIP with histology of DAD complicated by pneumomediastinum and an unfavorable outcome [51]. Tests for anti-tRNAS antibodies were negative in these patients. In this context, the recent identification of autoantibodies against a 140-kD polypeptide, CADM-140, in Japanese patients with C-ADM is very interesting [54]. Rapidly progressive ILD developed in 4 (50%) of 8 patients with C-ADM who were positive for anti-CADM-140.

We prefer the use of a combination regimen comprised of high-dose corticosteroids and a T-cell-inhibitor (CsA or tacrolimus) as the initial therapy for patients with (or ILD suggestive of) NSIP who do not have the risk factors related to a fatal outcome mentioned above, especially PM patients with (or seem to have) cellular NSIP complications. For patients with (or with ILD suggestive of) fibrotic NSIP complications, we prefer IV-CYC over CsA/tacrolimus; this preference is partially based on our experience with scleroderma lung disease, which typically has histology of fibrotic NSIP. Substantial evidence suggests that CYC is better at preserving lung function and promoting survival than other immunosuppressants in this condition [33,55]. However, another immunosuppressant is immediately added to the treatment regimen if the A/SIP is refractory to the initial therapy. After the initiation of a combination regimen including CsA/tacrolimus and (IV-) CYC, the dosage of corticosteroids should be tapered as soon as possible to avoid serious infections.

Our preliminary analysis on the relationship between the peripheral total leukocyte counts after IV-CYC treatment and clinical response suggested that an intensified dose of IV-CYC to reduce the leukocyte count by 50% may be associated with a better response to the combination therapy. These findings may be consistent with a recent report on the successful treatment of rapidly progressive ILD in a DM patient who underwent an autologous peripheral blood stem cell transplantation. In this patient, 4 g/m^2 of IV-CYC was administered followed by the administration of granulocyte colony-stimulating factor to mobilize hematopoietic stem cells and progenitor cells into the peripheral blood [56]. High-dose IV-CYC (50 mg/kg/day × 4 days) was adminis-

tered as a pretransplant conditioning regimen before the infusion of autologous CD34+ cells. Therefore, we must determine an optimal dosage of IV-CYC, balancing its efficacy and safety. In that sense, the proceedings of the ASTIS (Autologous Stem Cell Transplantation International Scleroderma), which was launched in 2001, may be of great interest [57]. In the ASTIS trial, the efficacy and safety of autologous hematopoietic stem cell transplantation was compared with the administration of IV-CYC (750 mg/m^2).

We recommend, as much as possible, that serial HRCT of the chest be performed to 1) confirm the diagnosis, 2) clarify the mode of ILD progression [58-60], and 3) rule out the presence of opportunistic infections. Importantly, the chest CT findings obtained at the time of the commencement of the combined immunosuppressive therapy were typically not severe, even in patients who eventually died of respiratory failure within a few months (Fig. **2**). Therefore, the initial CT findings do not seem to predict patients' prognosis. It is noted that HRCT images do not always represent the actual extent and severity of A/SIP, as is frequently the case in sarcoidosis. Biopsy specimens obtained from regions that are apparently normal on HRCT images may reveal the existence of considerable interstitial pneumonia. Thus, the extent and severity of ILD should be evaluated using multiple modalities including arterial blood gas examinations, pulmonary function tests, and gallium scanning. Interestingly, A/SIP tends to develop at about the same time as the onset of DM and rarely relapses in surviving patients who are followed for several years [16].

Aspiration pneumonia and infections with opportunistic organisms, including Candida species, Aspergillus species, tuberculous or non-tuberculous Mycobacteria, Pneumocystis jirovecii (formerly Pneumocystis carinii), and cytomegalovirus, occur frequently during the course of PM/DM [61]. Thus, serum levels of β-D-glucan should be regularly monitored, sputum samples should be cultured regularly, and polymerase chain reaction (PCR) analyses for the detection of Pneumocystis jirovecii in sputum and to determine the copy number of cytomegalovirus in whole blood should be regularly performed. Trimethoprim-sulfamethoxazole for preventing Pneumocystis jirovecii pneumonia should be routinely given to tolerable patients receiving combined immunosuppressive therapies.

FUTURE DIRECTIONS

As discussed above, some cases of ILD associated with DM are resistant to treatment with corticosteroids and immunosuppressant, and the use of immunosuppressive agents is inevitably accompanied by an increased risk of serious and life-threatening infections. Therefore, further therapeutic strategies targeting other cells or molecules are desirable (Fig. **3**). Complements, inflammatory cytokines and chemokines are likely to be involved in the pathogenesis of PM/DM-ILD. Intravenous immunoglobulin G has been shown to attenuate complement amplification [62]. Antibodies against complement components, like C5a, may be effective, as suggested by encouraging results in patients with antiphospholipid syndrome [63]. Inflammatory cytokines should be inten-

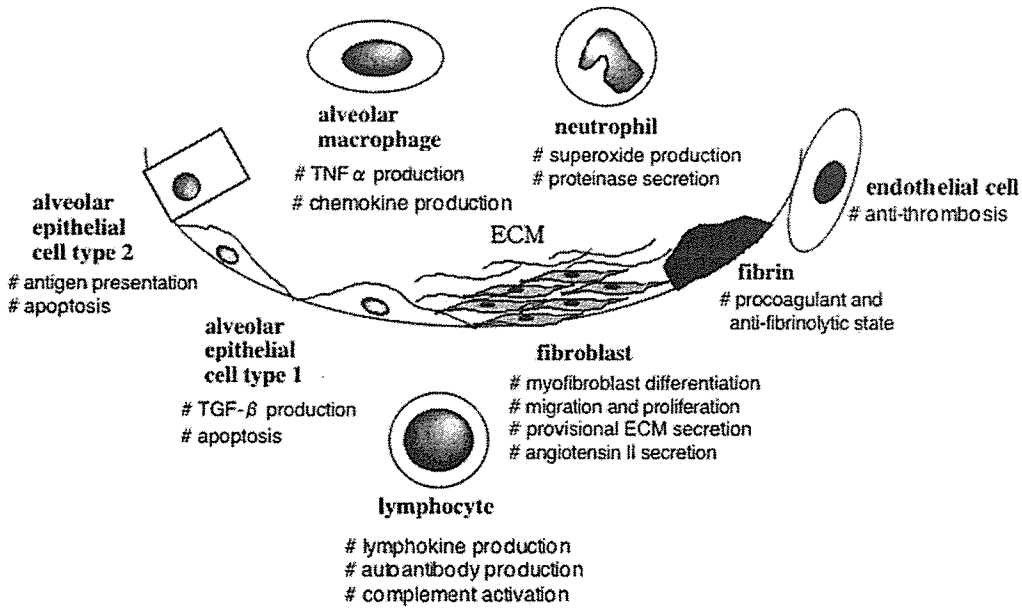

Fig. (3). Predicted molecular mechanisms and possible therapeutic targets of PM/DM-ILD.

Although the contribution of each aspect probably differs among the various histological types and phases of PM/DM-ILD, many of the cell types shown here are likely to be involved in the development and progression of PM/DM-ILD. Autoimmune responses and the subsequent interstitial infiltration of lymphocytes, mostly CD8+ T lymphocytes, are known to occur. Increased apoptosis of alveolar epithelial cells and delayed re-epithelialization may result in the formation of fibrin clots and a provisional matrix, initiating the proliferation of fibroblasts. The activation of endothelial cells and leukocytes perpetuates inflammation and consequently leads to further fibrotic progression. Any of these cells could serve as therapeutic targets in the treatment of PM/DM-ILD; more importantly, simultaneous control of many aspects seems to be essential for overwhelming the persistent inflammation. ECM: extracellular matrix.

sively studied as molecular targets to control ILD. Interferon gamma-1b did not show any beneficial effects in a well-defined placebo-controlled trial in patients with IIP [64]. Efthimou *et al.* reported the efficacy of tumor necrosis factor (TNF) inhibitors in the treatment of resistant PM/DM [65]. Five patients with PM were treated with etanercept, a recombinant soluble human TNF receptor fusion protein, and 3 patients with DM were treated with etanercept, infliximab (a chimeric anti-TNFα monoclonal antibody), or both etancercept and infliximab (one patient received each treatment). Four of 5 PM patients and 2 of 3 DM patients showed a favorable response, although the effects on the pulmonary involvement were not described.

Myofibroblasts may be another interesting target because they behave like kidney mesangial cells in terms of their migration and proliferation in response to growth factors, such as platelet-derived growth factor (PDGF) and transforming growth factor β (TGF-β) [66]. Thus, they play an important role in inflammation and subsequent fibrotic processes in ILD, just like mesangial cells do in glomerular inflammation. Furthermore, PDGF is likely to be a key molecule in the perpetuation of inflammation [66]. Very recently, we reported that imatinib mesylate inhibits the activation and proliferation of rheumatoid synovial fibroblast-like cells induced by PDGF stimulation [67]. Therefore, this kind of approach may also be promising for the treatment of PM/DM-ILD. In addition, another anti-fibrotic agent, pirfenidone, has been shown to effectively stabilize the lung function of IIP patients [68].

Endothelial damage might also be involved in the pathogenesis of PM/DM-ILD based on the increased blood levels of endothelin-1, thrombomodulin, and plasminogen activator inhibitor-1 in PM/DM patients with ILD, compared with those in patients without ILD; these measures were well correlated with TGF-β [69].

Thus, treatment strategies for other systemic autoimmune/rheumatic diseases, such as systemic sclerosis and systemic lupus erythematosus, may be applied to PM/DM-ILD. In this context, rituximab, an anti-CD20 chimeric antibody, was shown to improve myositis as well as lung function in patients with PM/DM [70]. Because rituximab is promising for the treatment of rheumatoid arthritis and systemic lupus erythematosus, this biologic agent might also be used as a first-line therapy for PM/DM-ILD in the near future.

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