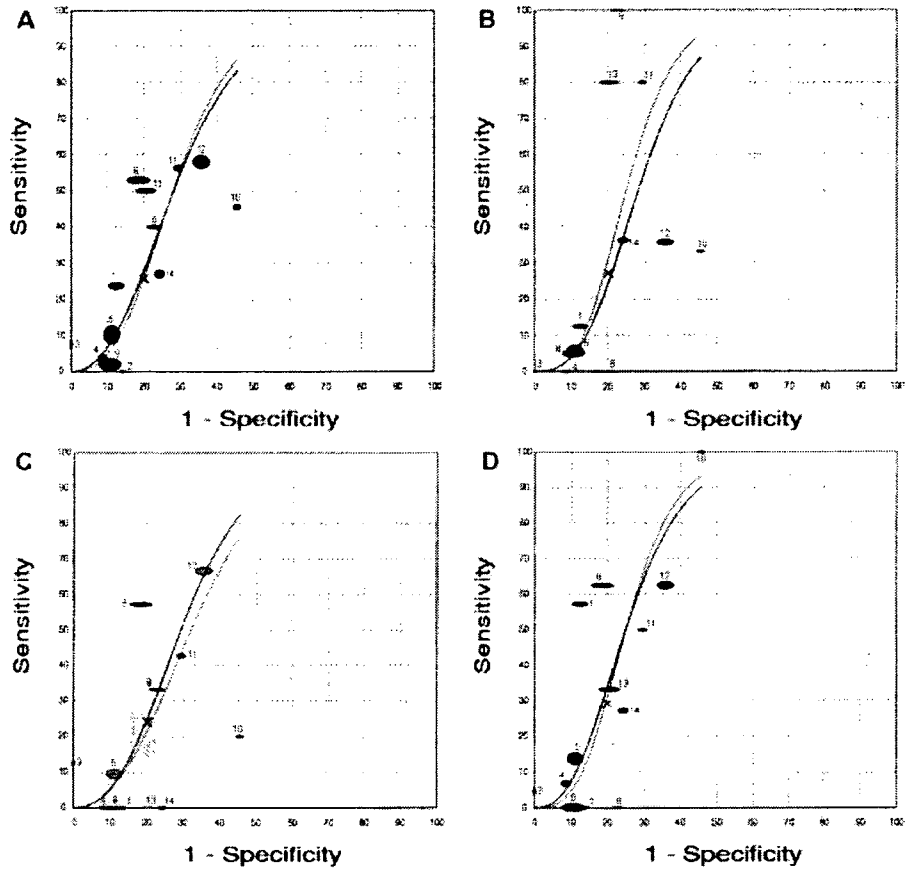


Figure 1. Summary receiver operating characteristic curves for the performance of antibodies to ribosomal P proteins in the diagnosis of various forms of neuropsychiatric systemic lupus erythematosus (NPSLE). Results are from the main analysis. Each ellipse corresponds to a study estimate of sensitivity and specificity; the area of each ellipse is proportional to the study size. Numbers beside the ellipses are study identification numbers and correspond to those shown in Table 1. Thin lines indicate nonweighted analyses; thick lines indicate weighted analyses. Shaded rectangles mark the 95% confidence intervals of the pooled sensitivity and pooled specificity obtained by random-effects calculations. × indicates exact estimates. **A**, NPSLE overall versus non-NPSLE. **B**, Psychosis and/or mood disorder versus non-NPSLE. **C**, Other diffuse neuropsychiatric manifestations versus non-NPSLE. **D**, Focal neurologic events versus non-NPSLE.

chiatric syndromes, and 2 provided insufficient data for calculating the sensitivity and specificity in any comparison considered.

Twenty-four additional publications (6,8–13,15–20,22,23,25–29,31–34) were retrieved from the database search, representing a total of 38 studies involving 3,713 lupus patients. Nevertheless, data for the comparison of NPSLE versus non-NPSLE groups were available in only 18 of the 24 additional studies; data for other comparisons were available in even fewer reports (Table 3). The results were consistent with those derived from the collaborative meta-analysis (Table 3 and Figure 3), but between-study heterogeneity was always considerable (Table 3). The overall weighted sensitivity and specificity estimates for identifying patients with NPSLE were 28% (95% CI 22–35%) and 80% (95% CI 75–85%), respectively. The SROC curve for this comparison was located very close to the diagonal, indicating poor diagnostic performance (Figure 3A). The overall sensitivity for psychosis, mood disorder, or both was slightly

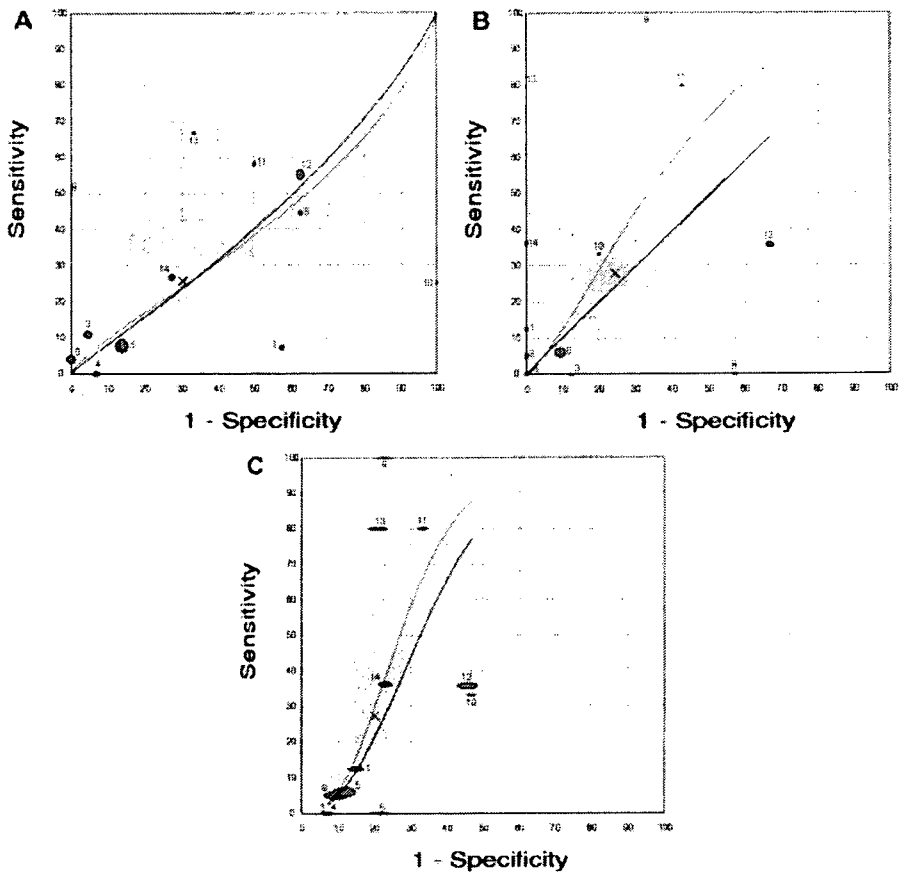


Figure 2. Summary receiver operating characteristic curves for the performance of antibodies to ribosomal P proteins in the diagnosis of various forms of neuropsychiatric systemic lupus erythematosus. Each ellipse corresponds to a study estimate of sensitivity and specificity; the area of each ellipse is proportional to the study size. Numbers beside the ellipses are study identification numbers and correspond to those shown in Table 1. Thin lines indicate nonweighted analyses; thick lines indicate weighted analyses. Shaded rectangles mark the 95% confidence intervals of the pooled sensitivity and pooled specificity obtained by random-effects calculations. × indicates exact estimates. **A,** All diffuse neuropsychiatric manifestations versus focal neurologic events. **B,** Psychosis and/or mood disorder versus other diffuse neuropsychiatric manifestations. **C,** Patients with psychosis and/or mood disorder versus all other lupus patients.

improved, but it was still suboptimal (42%), and the specificity remained essentially the same (81%). There was still significant asymmetry in the SROC curves for the diagnosis of psychiatric disorders (Figures 3B and C). Anti-P antibody testing was not more accurate when used to discriminate active NPSLE from non-NPSLE (Table 3 and Figure 3D). Weighted and nonweighted SROC curves were almost coincident in all these contrasts (Figure 3).

Findings of other sensitivity analyses. Analyses limited to studies that used the ACR criteria for NPSLE yielded similar results. The weighted sensitivity for NPSLE overall was 29% (95% CI 17–45%) and the weighted specificity was 79% (95% CI 73–84%). Analyses excluding studies that did not specify blinding yielded a sensitivity of 25% (95% CI 13–43%) for the diagnosis of NPSLE and a specificity of 79% (95% CI 70–86%). Likewise, the diagnostic performance of anti-

Table 3. Summary results of additional analyses that included published studies from database searches*

Comparison	No. of studies	No. of subjects	Weighted sensitivity (95% CI)	Weighted specificity (95% CI)
NPSLE versus non-NPSLE	32	2,861	0.28 (0.22–0.35)	0.80 (0.75–0.85)
Psychosis and/or mood disorder versus non-NPSLE	25	1,909	0.42 (0.30–0.53)	0.81 (0.76–0.85)
Patients with psychosis and/or mood disorder versus all other lupus patients	31	3,309	0.41 (0.31–0.52)	0.81 (0.77–0.85)
Active NPSLE versus non-NPSLE	10	1,025	0.34 (0.27–0.43)	0.82 (0.74–0.87)

* Data from the studies shown in Table 1 as well as from additional studies retrieved from a search of the Medline, EMBase, and Cochrane databases are included. Weighted sensitivity and specificity were determined according to the random-effects model. Between-study heterogeneity was statistically significant for all comparisons ($P < 0.01$). 95% CI = 95% confidence interval; NPSLE = neuropsychiatric systemic lupus erythematosus.

P antibodies was largely unaffected in all other comparisons (data not shown).

DISCUSSION

This meta-analysis demonstrated with large-scale evidence that the value of anti-P antibody testing for the diagnosis of NPSLE overall or for particular disease phenotypes is negligible. No large differences in diagnostic performance with ELISA measurements or with Western blotting were discerned. Serum anti-P antibodies are detected by ELISA in less than one-third of patients with NPSLE, while 15–25% of lupus patients without neuropsychiatric involvement have this autoantibody specificity. Testing for anti-P antibody is not useful in excluding disease-mediated psychosis or mood disorder with enough certainty, since more than 60% of cases are false negative. Also, a false-positive rate of ~20% militates against the dependence on this laboratory test for diagnosing psychiatric disorders in lupus patients.

Whereas nearly all studies suggested poor diagnostic performance, the exact test performance varied substantially. Variability beyond chance could be attributed to ethnic differences in the study patients, the clinical setting, the type of assay used, differences in test thresholds, and differences in therapy at the time of testing. Anti-P antibodies were more prevalent in Asian patients with lupus than among those of other racial ancestries. This finding is consistent with the observation that their production is influenced by certain class II major histocompatibility complex alleles (8). Despite the use of uniform criteria for defining neuropsychiatric disease, the prevalence of NPSLE differed across centers. This difference probably reflects varying referral patterns at the research sites, as well as varying practice patterns for performing anti-P antibody testing in lupus patients with possible NPSLE syndromes.

The immunoassays used for anti-P antibody determination often differed in terms of the antigenic source, the conditions of protein extraction and denaturation, the nature of the coating antigen, and the carrier proteins and coupling agents used for binding antigen to the plate. The selected cutoff value designating a positive result in enzyme immunoassays could also affect the sensitivity and specificity. Nevertheless, a standardization of anti-P antibody testing is essential to avoiding technical or analytical differences among centers. Treatment with immunosuppressive drugs at the time of testing might influence the antibody response and, therefore, could also account for the discrepancies in test performance. Heterogeneity stemming from all these sources is probably unavoidable, and it reflects actual clinical practice.

Our analysis addressed heterogeneity by using a random-effects model that incorporated the uncertainty arising from between-study differences. SROC curves, which correct for variation due to differences in test thresholds across studies, were also consistent with the independently weighted estimates, and accordingly, the results of the meta-analysis should be generalizable to diverse settings.

Specific design flaws of primary studies of diagnostic tests including lack of blinding, use of different reference tests according to the results of the experimental test, and insufficient description of the population under study can lead to biased, usually optimistic estimates of diagnostic accuracy (48). Our study had the methodologic advantage of using data from adequately described lupus cohorts in which a consistent application of standardized definitions of NPSLE syndromes, and

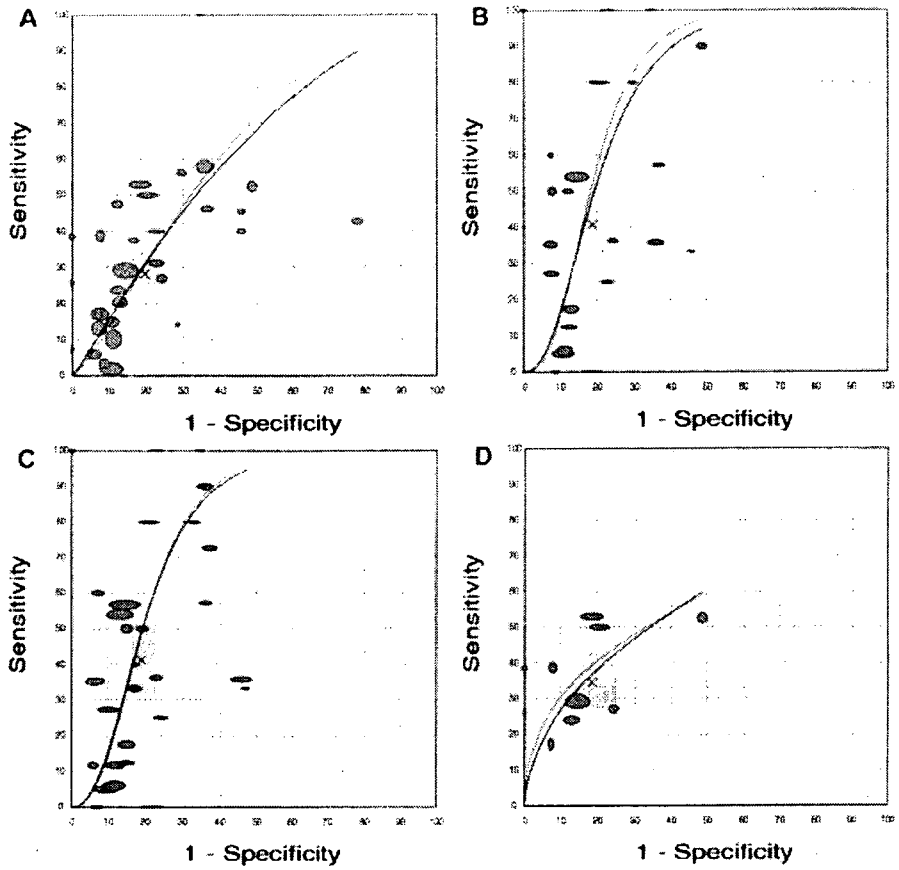


Figure 3. Summary receiver operating characteristic curves for the performance of antibodies to ribosomal P proteins in the diagnosis of various forms of neuropsychiatric systemic lupus erythematosus (NPSLE). Results are from sensitivity analyses that included additional published data. Each ellipse corresponds to a study estimate of sensitivity and specificity; the area of each ellipse is proportional to the study size. Thin lines indicate nonweighted analyses; thick lines indicate weighted analyses. Shaded rectangles mark the 95% confidence intervals of the pooled sensitivity and pooled specificity obtained by random-effects calculations. × indicates exact estimates. **A,** NPSLE overall versus non-NPSLE. **B,** Psychosis and/or mood disorder versus non-NPSLE. **C,** Patients with psychosis and/or mood disorder versus all other lupus patients. **D,** Active NPSLE versus non-NPSLE.

blinded interpretation of both the test results and the reference standard was ensured in most cases. In addition, the overall estimates did not materially change after we excluded the few studies that did not specify blinding or did not use the ACR case definitions for NPSLE.

We should acknowledge that the ACR criteria may not be a perfect reference standard for assessing the presence or absence of NPSLE syndromes in lupus patients. In fact, this classification system has been criticized for some lack of specificity: disorders such as headache, anxiety, mild cognitive dysfunction, mild depression, and polyneuropathy without electrophysiologic confirmation may not truly be NPSLE syndromes (1,49). Nevertheless, until revised criteria (49,50) are accepted and validated, the ACR case definitions constitute the best available tool with which to categorize neuropsychiatric events in SLE (4,51).

Another limitation of the study is that patients having both diffuse and focal NPSLE events were clas-

sified according to the predominant disorder. Such complex presentations might reflect a multifactorial pathogenic etiology with overlapping mechanisms (2,3,6), and therefore, we cannot completely exclude the possibility that some of these patients may have been misclassified. Nevertheless, this limitation is unlikely to have significantly affected the estimated performance, since anti-P antibodies had poor discriminating ability for all disease subtypes. Another possibility is that some patients who tested positive for anti-P antibodies could have been misclassified as non-NPSLE patients, because the disease phenotype may not have had adequate time to express itself. This seems implausible, since nervous system involvement occurs within the first 2 years of disease onset in most patients and rarely presents late (52). The median disease duration in the study population was 7.3 years. A further explanation for anti-P positivity in patients without neuropsychiatric involvement could be the presence of other manifestations that have been linked with these antibodies, such as liver or renal disease, but here, the evidence is far sparser than for NPSLE (53–56). Titers may also fluctuate with the course of the disease (53,55), making the appraisal of a positive or negative result even more difficult. Finally, the diagnostic ability of anti-P antibody in the cerebrospinal fluid needs further study, although it seems to be even more limited than the ability of serum autoantibodies to detect NPSLE (6,16,26,27).

The overall sensitivity of anti-P antibodies for identifying lupus patients with disease-associated psychosis, mood disorder, or both was slightly improved when further published studies were included in the analyses. However, these estimates have widely overlapping confidence intervals with those obtained from the collaborative meta-analysis. Yet, methodologic weaknesses frequently encountered in the relevant reports, such as the use of less strict definitions of psychiatric disorders and the lack of blinding during test or reference standard interpretation, might well have led to inflated sensitivity estimates.

Although the extent of publication bias in diagnostic studies is unknown, we should be aware that studies that failed to show a diagnostic value for anti-P antibodies may have remained unpublished. If this is so, the true diagnostic performance of anti-P antibodies may be even worse than what was demonstrated in this analysis.

There is increasing interest in synthesizing diagnostic information on tests used in autoimmune diseases (57–59). Based on the categorization standards adopted in meta-analyses conducted by the ACR Ad Hoc Committee on Immunologic Testing, the diagnostic performance of anti-P antibodies would be rated as "not useful" for most of the comparisons that we examined, since the observed sensitivity and specificity estimates would correspond to a positive likelihood of ratio <2 and a negative likelihood ratio of >0.5. Previous meta-analyses (57–59) have been based on published data, whereas in our meta-analysis, we made an effort to include the primary investigators and to obtain additional unpublished and prospectively accrued data. It is important to encourage such collaborations in an attempt to obtain large-scale unbiased evidence in the field.

In conclusion, anti-P antibody testing has negligible diagnostic utility for NPSLE overall or for particular neuropsychiatric presentations of SLE. A consortium approach with synthesis of standardized data through a comprehensive meta-analysis may offer a powerful method by which to rigorously evaluate diagnostic tests in SLE. Such an approach could limit health care costs by preventing unnecessary testing.

ACKNOWLEDGMENTS

We acknowledge the contributions of the other investigators of the collaborating study teams involved in this project, as follows: Borut Bozic, PhD, and Blaz Rozman, MD, University Medical Centre, Ljubljana, Slovenia; Nuray Gurel Polat, PhD, and Bahar Artim Esen, MD, Istanbul Medical Faculty, Istanbul University, Turkey; Eric Chan, MD, Queen Mary Hospital, Hong Kong, SAR, China; Takashi Sawada, MD, Teikyo University School of Medicine, Tokyo, Japan; and Veronica Bellomio, MD, Eleonora Lucero, MD, Alberto Berman, MD, and Silvia Presti, MD, School of Medicine, Universidad Nacional de Tucumán, Tucumán, Argentina.

REFERENCES

1. Hanly JG, McCurdy G, Fougere L, Douglas JA, Thompson K. Neuropsychiatric events in systemic lupus erythematosus: attribution and clinical significance. J Rheumatol 2004;31:2156–62.
2. Hermosillo-Romo D, Brey RL. Diagnosis and management of patients with neuropsychiatric systemic lupus erythematosus (NPSLE). Best Pract Res Clin Rheumatol 2002;16:229–44.
3. West SG. Neuropsychiatric lupus. Rheum Dis Clin North Am 1994;20:129–58.
4. Karassa FB, Ioannidis JP, Boki KA, Touloumi G, Argyropoulou MI, Strigaris KA, et al. Predictors of clinical outcome and radiologic progression in patients with neuropsychiatric manifestations of systemic lupus erythematosus. Am J Med 2000;109:628–34.
5. Rood MJ, Breedveld FC, Huizinga TW. The accuracy of diagnosing neuropsychiatric systemic lupus erythematosus in a series of 49 hospitalized patients. Clin Exp Rheumatol 1999;17:55–61.
6. West SG, Emlen W, Wener MH, Kotzin BL. Neuropsychiatric

lupus erythematosus: a 10-year prospective study on the value of diagnostic tests. Am J Med 1995;99:153–63.
7. ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999;42:599–608.
8. Arnett FC, Reveille JD, Moutsopoulos HM, Georgescu L, Elkon KB. Ribosomal P autoantibodies in systemic lupus erythematosus: frequencies in different ethnic groups and clinical and immunogenetic associations. Arthritis Rheum 1996;39:1833–9.
9. Bonfa E, Golombek SJ, Kaufman LD, Skelly S, Weissbach H, Brot N, et al. Association between lupus psychosis and anti-ribosomal P protein antibodies. N Engl J Med 1987;317:265–71.
10. Chan EY, Ko OK, Lawton JW, Lau CS. The use of anti-ribosomal P antibodies in the diagnosis of cerebral lupus: superiority of western blotting over enzyme-linked immunosorbent assay. Hong Kong Med J 1998;4:145–50.
11. Conti F, Alessandri C, Bompane D, Bombardieri M, Spinelli FR, Rusconi AC, et al. Autoantibody profile in systemic lupus erythematosus with psychiatric manifestations: a role for anti-endothelial-cell antibodies. Arthritis Res Ther 2004;6:R366–72.
12. Corres Gonzalez JM, Rodriguez Hernandez C, Zea Mendoza AC, Sequi Navarro J, Sanchidrian Fernandez I. Anti-ribosomal antibodies in systemic lupus erythematosus. Rev Clin Esp 1995;195:16–21.
13. Gerli R, Caponi L, Tincani A, Scorza R, Sabbadini MG, Danieli MG, et al. Clinical and serological associations of ribosomal P autoantibodies in systemic lupus erythematosus: prospective evaluation in a large cohort of Italian patients. Rheumatology (Oxford) 2002;41:1357–66.
14. Hoffman IE, Peene I, Meheus L, Huizinga TW, Cebecauer L, Isenberg D, et al. Specific antinuclear antibodies are associated with clinical features in systemic lupus erythematosus. Ann Rheum Dis 2004;63:1155–8.
15. Isenberg DA, Garton M, Reichlin MW, Reichlin M. Long-term follow-up of autoantibody profiles in black female lupus patients and clinical comparison with Caucasian and Asian patients. Br J Rheumatol 1997;36:229–33.
16. Isshi K, Hirohata S. Association of anti–ribosomal P protein antibodies with neuropsychiatric systemic lupus erythematosus. Arthritis Rheum 1996;39:1483–90.
17. Johanet C, Andre C, Sibilia J, Baquey A, Oksman F, San Marco M, et al, and the Study Group on Autoimmunity (GEAI). Clinical significance of antiribosomal antibodies. Rev Med Interne 2000;21:510–6.
18. Jonsen A, Bengtsson AA, Nived O, Ryberg B, Truedsson L, Ronnblom L, et al. The heterogeneity of neuropsychiatric systemic lupus erythematosus is reflected in lack of association with cerebrospinal fluid cytokine profiles. Lupus 2003;12:846–50.
19. Kao CH, Ho YJ, Lan JL, Changlai SP, Liao KK, Chieng PU. Discrepancy between regional cerebral blood flow and glucose metabolism of the brain in systemic lupus erythematosus patients with normal brain magnetic resonance imaging findings. Arthritis Rheum 1999;42:61–8.
20. Mahler M, Kessenbrock K, Raats J, Williams R, Fritzler MJ, Bluthner M. Characterization of the human autoimmune response to the major C-terminal epitope of the ribosomal P proteins. J Mol Med 2003;81:194–204.
21. Massardo L, Burgos P, Martinez ME, Perez R, Calvo M, Barros J, et al. Antiribosomal P protein antibodies in Chilean SLE patients: no association with renal disease. Lupus 2002;11:379–83.
22. Nojima Y, Minota S, Yamada A, Takaku F, Aotsuka S, Yokohari R. Correlation of antibodies to ribosomal P protein with psychosis in patients with systemic lupus erythematosus. Ann Rheum Dis 1992;51:1053–5.
23. Press J, Palayew K, Laxer RM, Elkon K, Eddy A, Rakoff D, et al. Antiribosomal P antibodies in pediatric patients with systemic lupus erythematosus and psychosis. Arthritis Rheum 1996;39:671–6.
24. Sanna G, Piga M, Terryberry JW, Peltz MT, Giagheddu S, Satta L, et al. Central nervous system involvement in systemic lupus erythematosus: cerebral imaging and serological profile in patients with and without overt neuropsychiatric manifestations. Lupus 2000;9:573–83.
25. Sato T, Uchiumi T, Ozawa T, Kikuchi M, Nakano M, Kominami R, et al. Autoantibodies against ribosomal proteins found with high frequency in patients with systemic lupus erythematosus with active disease. J Rheumatol 1991;18:1681–4.
26. Schneebaum AB, Singleton JD, West SG, Blodgett JK, Allen LG, Cheronis JC, et al. Association of psychiatric manifestations with antibodies to ribosomal P proteins in systemic lupus erythematosus. Am J Med 1991;90:54–62.
27. Teh LS, Bedwell AE, Isenberg DA, Gordon C, Emery P, Charles PJ, et al. Antibodies to protein P in systemic lupus erythematosus. Ann Rheum Dis 1992;51:489–94.
28. Teh LS, Hay EM, Amos N, Black D, Huddy A, Creed F, et al. Anti-P antibodies are associated with psychiatric and focal cerebral disorders in patients with systemic lupus erythematosus. Br J Rheumatol 1993;32:287–90.
29. Teh LS, Lee MK, Wang F, Manivasagar M, Charles PJ, Nicholson GD, et al. Antiribosomal P protein antibodies in different populations of patients with systemic lupus erythematosus. Br J Rheumatol 1993;32:663–5.
30. Tzioufas AG, Tzortzakis NG, Panou-Pomonis E, Boki KA, Sakarellos-Daitsiotis M, Sakarellos C, et al. The clinical relevance of antibodies to ribosomal-P common epitope in two targeted systemic lupus erythematosus populations: a large cohort of consecutive patients and patients with active central nervous system disease. Ann Rheum Dis 2000;59:99–104.
31. Van Dam A, Nossent H, de Jong J, Meilof J, ter Borg EJ, Swaak T, et al. Diagnostic value of antibodies against ribosomal phosphoproteins: a cross sectional and longitudinal study. J Rheumatol 1991;18:1026–34.
32. Weiner SM, Otte A, Schumacher M, Klein R, Gutfleisch J, Brink I, et al. Diagnosis and monitoring of central nervous system involvement in systemic lupus erythematosus: value of F-18 fluorodeoxyglucose PET. Ann Rheum Dis 2000;59:377–85.
33. Williams RC Jr, Sugiura K, Tan EM. Antibodies to microtubule-associated protein 2 in patients with neuropsychiatric systemic lupus erythematosus. Arthritis Rheum 2004;50:1239–47.
34. Yalaoui S, Gorgi Y, Hajri R, Goucha R, Chaabouni L, Kooli C, et al. Autoantibodies to ribosomal P proteins in systemic lupus erythematosus. Joint Bone Spine 2002;69:173–6.
35. Yoshio T, Masuyama J, Ikeda M, Tamai K, Hachiya T, Emori T, et al. Quantification of antiribosomal P0 protein antibodies by ELISA with recombinant P0 fusion protein and their association with central nervous system disease in systemic lupus erythematosus. J Rheumatol 1995;22:1681–7.
36. Elkon K, Skelly S, Parnassa A, Moller W, Danho W, Weissbach H, et al. Identification and chemical synthesis of a ribosomal protein antigenic determinant in systemic lupus erythematosus. Proc Natl Acad Sci U S A 1986;83:7419–23.
37. Ghirardello A, Caponi L, Franceschini F, Zampieri S, Quinzanini M, Bendo R, et al. Diagnostic tests for antiribosomal P protein antibodies: a comparative evaluation of immunoblotting and ELISA assays. J Autoimmun 2002;19:71–7.
38. Mahler M, Kessenbrock K, Raats J, Fritzler MJ. Technical and clinical evaluation of anti-ribosomal P protein immunoassays. J Clin Lab Anal 2004;18:215–23.
39. Rayno K, Reichlin M. Evaluation of assays for the detection of autoantibodies to the ribosomal P proteins. Clin Immunol 2000;95:99–103.

40. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
41. Owens DK, Holodniy M, Garber AM, Scott J, Sonnad S, Moses L, et al. Polymerase chain reaction for the diagnosis of HIV infection in adults: a meta-analysis with recommendations for clinical practice and study design. Ann Intern Med 1996;124:803–15.
42. Ioannidis JP. The value of meta-analysis in rheumatology research. Autoimmun Rev 2004;3 Suppl 1:S57–9.
43. Fleiss JL. The statistical basis of meta-analysis. Stat Methods Med Res 1993;2:121–45.
44. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22: 719–48.
45. Littenberg B, Moses LE. Estimating diagnostic accuracy from multiple conflicting reports: a new meta-analytic method. Med Decis Making 1993;13:313–21.
46. Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. Stat Med 1993;12:1293–316.
47. Irwig L, Macaskill P, Glasziou P, Fahey M. Meta-analytic methods for diagnostic test accuracy. J Clin Epidemiol 1995;48:119–30.
48. Lijmer JG, Mol BW, Heisterkamp S, Bonsel GJ, Prins MH, van der Meulen JH, et al. Empirical evidence of design-related bias in studies of diagnostic tests. JAMA 1999;282:1061–6.
49. Ainiala H, Hietaharju A, Loukkola J, Peltola J, Korpela M, Metsanoja R, et al. Validity of the new American College of Rheumatology criteria for neuropsychiatric lupus syndromes: a population-based evaluation. Arthritis Rheum 2001;45:419–23.
50. Hanly JG. ACR classification criteria for systemic lupus erythematosus: limitations and revisions to neuropsychiatric variables. Lupus 2004;13:861–4.
51. Afeltra A, Garzia P, Mitterhofer AP, Vadacca M, Galluzzo S, del Porto F, et al. Neuropsychiatric lupus syndromes: relationship with antiphospholipid antibodies. Neurology 2003;61:108–10.
52. Kovacs JA, Urowitz MB, Gladman DD. Dilemmas in neuropsychiatric lupus. Rheum Dis Clin North Am 1993;19:795–814.
53. Chindalore V, Neas B, Reichlin M. The association between anti-ribosomal P antibodies and active nephritis in systemic lupus erythematosus. Clin Immunol Immunopathol 1998;87:292–6.
54. Hulsey M, Goldstein R, Scully L, Surbeck W, Reichlin M. Anti-ribosomal P antibodies in systemic lupus erythematosus: a case-control study correlating hepatic and renal disease. Clin Immunol Immunopathol 1995;74:252–6.
55. Reichlin M, Broyles TF, Hubscher O, James J, Lehman TA, Palermo R, et al. Prevalence of autoantibodies to ribosomal P proteins in juvenile-onset systemic lupus erythematosus compared with the adult disease. Arthritis Rheum 1999;42:69–75.
56. Arnett FC, Reichlin M. Lupus hepatitis: an under-recognized disease feature associated with autoantibodies to ribosomal P. Am J Med 1995;99:465–72.
57. Kavanaugh AF, Solomon DH, and the American College of Rheumatology Ad Hoc Committee on Immunologic Testing Guidelines. Guidelines for immunologic laboratory testing in the rheumatic diseases: anti-DNA antibody tests. Arthritis Rheum 2002;47:546–55.
58. Solomon DH, Kavanaugh AJ, Schur PH, and the American College of Rheumatology Ad Hoc Committee on Immunologic Testing Guidelines. Evidence-based guidelines for the use of immunologic tests: antinuclear antibody testing. Arthritis Rheum 2002;47:434–44.
59. Benito-Garcia E, Schur PH, Lahita R, and the American College of Rheumatology Ad Hoc Committee on Immunologic Testing Guidelines. Guidelines for immunologic laboratory testing in the rheumatic diseases: anti-Sm and anti-RNP antibody tests. Arthritis Rheum 2004;51:1030–44.

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

Hideto Kameda* and Tsutomu Takeuchi

Division of Rheumatology/Clinical Immunology, Department of Internal Medicine, Saitama Medical Center, Saitama Medical University, 1981 Tsujido-machi, Kamoda, Kawagoe, Saitama 350-8550, Japan

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

*Address correspondence to this author at the Division of Rheumatology/Clinical Immunology, Department of Internal Medicine, Saitama Medical Center, Saitama Medical University, 1981 Tsujido-machi, Kamoda, Kawagoe, Saitama 350-8550, Japan; Tel./Fax: +81-49-228-3574; E-mail: kamehide@saitama-med.ac.jp

1871-5303/06 $50.00+.00

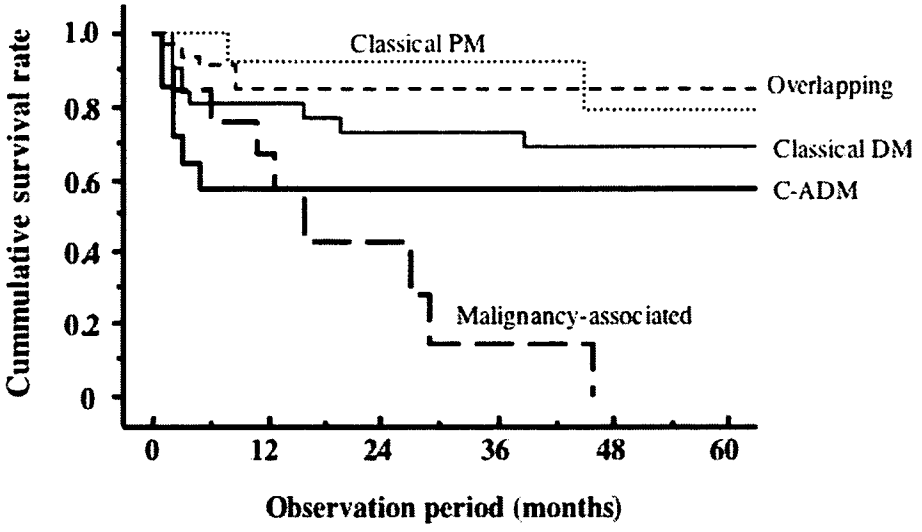


Fig. (1). Cumulative survival rate after diagnosis of PM/DM.

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 according to the criteria proposed by Sontheimer (a thick solid line) (3). Patients diagnosed as having mixed connective tissue disease were not included in the study because most of these patients only had modest myopathy, while the manifestations of systemic lupus erythematosus or scleroderma were more prevalent. Classical PM (n=18) and classical DM (n=32) are represented as a fine dotted line and a thin solid line, 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

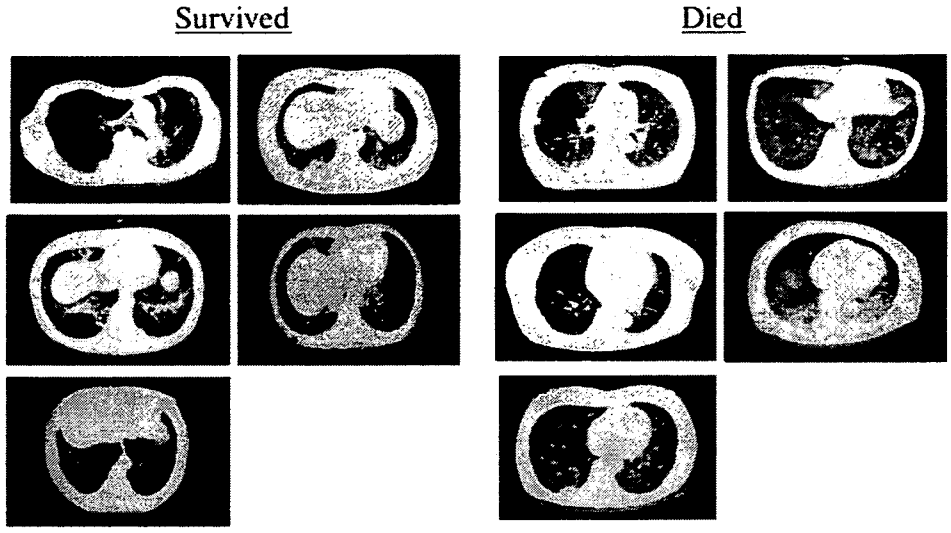


Fig. (2). Representative chest CT images of patients with A/SIP at the commencement of a combination treatment regimen comprised of high-dose corticosteroids, CsA and IV-CYC.

Initial chest CT images from patients who survived (left) and died (right) are shown. Subpleural consolidation and linear/reticular opacity were predominant findings, even in most of the patients who eventually died of respiratory failure. It appears that initial chest CT images are 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-

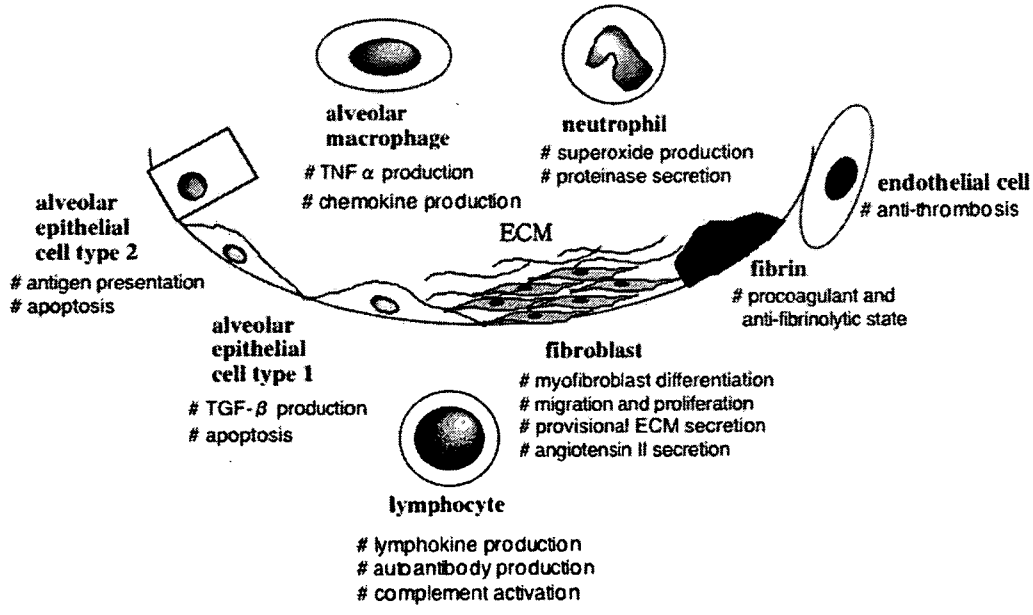


Fig. (3). Predicted molecular mechanisms and possible therapeutic targets of PM/DM-ILD.

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.

REFERENCES

[1] Bohan, A. and Peter, J.B. (1975) *N. Eng. J. Med.*, **292**, 344-7.
[2] Bohan, A. and Peter, J.B. (1975) *N. Eng. J. Med.*, **292**, 403-7.
[3] Sontheimer, R.D. (2002) *Dermatol. Clin.*, **20**, 387-408.
[4] Marie, I.; Hachulla, E.; Hatron, P-Y.; Hellot, M-F.; Levesque, H.; Devulder, B. and Courtois, H. *J. Rheumatol.*, **28**, 2230-7.
[5] Fujisawa, T.; Suda, T.; Nakamura, Y.; Enomoto, N.; Ide, K.; Toyoshima, M.; Uchiyama, H.; Tamura, R.; Ida, M.; Yagi, T.; Yasuda, K.; Genma, H.; Hayakawa, H.; Chida, K. and Nakamura, H. *J. Rheumatol.*, **32**, 58-64.
[6] Dankó, K.; Ponyi, A.; Constantin, T.; Borgulya, G. and Szegedi, G.. (2004) *Medicine*, **83**, 35-42.
[7] Euwer, R. and Sontheimer, R. (1991) *J. Am. Acad. Dermatol.*, **24**, 959-66.
[8] Gerami, P.; Schope, J.M.; McDonald, L.; Walling, H.W. and Sontheimer, R.D. (2006) *J. Am. Acad. Dermatol.*, **54**, 597-613.
[9] Trautmann, C.; Abdel-Naser, M.; Soehnchen, R.; Detmar, M. and Orfanos, C. *Hautarzt*, **46**, 47-52.
[10] Hirakata, M. and Nagai, S. (2000) *Curr. Opin. Rheumatol.*, **12**, 501-8.
[11] Douglas, W.W.; Tazelaar, H.D.; Hartman, T.E.; Hartman, R.P.; Decker, P.A.; Schroeder, D.R. and Ryu, J.H. (2001) *Am. J. Respir. Crit. Care Med.*, **164**, 1182-5.
[12] Marie, I.; Hachulla, E.; Chérin, P.; Dominique, S.; Hatron, P-Y.; Hellot, M-F.; Devulder, B.; Herson, S.; Levesque, H. and Courtois, H. (2002) *Arthritis Rheum.*, **47**, 614-22.
[13] Schnabel, A.; Reuter, M. and Biederer, J. (2003) *Semin. Arthritis Rheum.*, **32**, 273-84.
[14] Sontheimer, R.D. and Miyagawa, S. (2003) *J. Am. Acad. Dermatol.*, **48**, 797-8.
[15] Kuroda, H.; Morinaga, H.; Satoh, C.; Miyata, A. and Sunami, K. (2003) *Mod. Rheumatol.*, **13**, 313-8.
[16] Kameda, H.; Nagasawa, H.; Ogawa, H.; Sekiguchi, N.; Takei, H.; Tokuhira, M.; Amano, K. and Takeuchi, T. (2005) *J. Rheumatol.*, **32**, 1719-26.
[17] Inoue, A.; Saijo, Y.; Maemondo, M.; Gomi, K.; Tokue, Y.; Kimura, Y.; Ebina, M.; Kikuchi, T.; Moriya, T. and Nukiwa, T. (2003) *Lancet*, **361**, 137-9.
[18] Kamata, Y.; Nara, H.; Kamimura, T.; Haneda, K.; Iwamoto, M.; Masuyama, J.; Okazaki, H. and Minota, S. (2004) *Intern. Med.*, **43**, 1201-4.
[19] Sakai, F.; Noma, S.; Kurihara, Y.; Yamada, H.; Azuma, A.; Kudoh, S. and Ichikawa, Y. (2005) *Mod. Rheumatol.*, **15**, 173-9.
[20] Yoshida, S.; Akizuki, M.; Mimori, T.; Yamagata, H.; Inada, S. and Homma, M. (1983) *Arthritis Rheum.*, **26**, 604-11.
[21] Dalakas, M.C. and Hohlfeld, R. (2003) *Lancet*, **362**, 971-82.
[22] Furuya, T.; Hakoda, M.; Tsuchiya, N.; Kotake, S.; Ichikawa, N.; Nanke, Y.; Nakajima, A.; Takeuchi, M.; Nishinarita, M.; Kondo, H.; Kawasaki, A.; Kobayashi, S.; Mimori, T.; Tokunaga, K. and Kamatani, N. (2004) *J. Rheumatol.*, **31**, 1768-74.
[23] Chinoy, H.; Salway, F.; Fertig, N.; Shephard, N.; Tait, B.D.; Thomson, W.; Isenberg, D.A.; Oddis, C.V.; Silman, A.J.; Ollier, W.E.R.; Cooper, R.G. and the UK Adult Onset Myositis Immunogenetic Collaboration (AOMIC). (2006) *Arthritis Res. Ther.*, **8**, R13.
[24] Mantegazza, R.; Bernasconi, P.; Confalonieri, P. and Cornelio, F. (1997) *J. Neurol.*, **244**, 277-87.
[25] Kono, H.; Inokuma, S.; Nakayama, H. and Suzuki, M. (2000) *Ann. Rheum. Dis.*, **59**, 372-6.
[26] Cicuttini, F.M. and Fraser, K.J. (1989) *J. Rheumatol.*, **16**, 384-386.
[27] American Thoracic Society; European Respiratory Society. A (2002) *J. Respir. Crit. Care Med.*, **165**, 277-304.
[28] Arakawa, H.; Yamada, H.; Kurihara, Y.; Nakajima, Y.; Takeda, A.; Fukushima, Y. and Fujioka, M. (2003) *Chest*, **123**, 1096-103.
[29] Tansey, D.; Wells, A.U.; Colby, T.V.; Ip, S.; Nikolakoupolou, A.; du Bois, R.M.; Hansell, D.M. and Nicholson, A.G. (20040 *Histopathology*, **44**, 585-96.
[30] Beasley, M.B.; Franks, T.J., Galvin, J.R.; Gochuico, B. and Travis, W.D. (2002) *Arch. Pathol. Lab Med.*, **126**, 1064-70.
[31] Kurasawa, K.; Nawata, Y.; Takabayashi, K.; Kumano, K.; Kita, Y.; Takiguchi, Y.; Kuriyama, T.; Sueishi, M.; Sito, Y. and Iwamoto, I. (2002) *Clin. Exp. Immunol.*, **129**, 541-48.
[32] Yamadori, I.; Fujita, J.; Kajitani, H.; Bandoh, S.; Tokuda, M.; Ohtsuki, Y.; Yoshinouchi, T.; Okahara, M.; Yamaji, Y.; Tanimoto, Y.; Sato, Y. and Ishida, T. (2001) *Rheumatol. Int.*, **21**, 89-93.
[33] Schnabel, A.; Hellmich, B. and Gross, W.L. (2005) *Curr. Rheumatol. Rep.*, **7**, 99-105.
[34] Mastaglia, F.L. and Zilko, P.J. (2003) *J. Clin. Neurosci.*, **10**, 99-01.
[35] Villalba, L.; Hicks, J.E.; Adams, E.M.; Sherman, J.B.; Gourley, M.F.; Leff, R.L.; Thornton, B.C.; Burgess, S.H.; Plotz, P.H. and Miller, F.W. (1998) *Arthritis Rheum.*, **41**, 392-9.
[36] Ohosone, Y.; Okano, Y.; Kameda, H.; Fujii, T.; Hama, N.; Hirakata, M.; Mimori, T.; Akizuki, M. and Ikeda, Y. (1997) *J. Rheumatol.*, **24**, 2299-303.
[37] Kremer, J.M.; Alarcon, G.S.; Weinblatt, M.E.; Kaymakcian, M.V.; Macaluso, M.; Cannon, G.W.; Palmer, W.R.; Sundy, J.S.; St. Clair, E.W.; Alexander, R.W.; Smith, G.J. and Axiotis, C.A. (1997) *Arthritis Rheum.*, **40**, 1829-37.
[38] Gruhn, W.B. and Diaz-Buxo, J.A. (1987) *J. Rheumatol.*, **14**, 1045-7.
[39] Harigai, M.; Hara, M.; Kamatani, N. and Kashiwazaki, S. (1999) *Ryumachi*, **39**, 819-28.

[40] Nawata, Y.; Kurasawa, K.; Takabayashi, K.; Miike, S.; Watanabe, N.; Hiraguri, M.; Kita, Y.; Kawai, M.; Saito, Y. and Iwamoto, I. (1999) *J. Rheumatol.*, **26**, 1527-33.
[41] Maeda, K.; Kimura, R.; Komuta, K. and Igarashi, T. (1997) *Scand. J. Rheumatol.*, **26**, 24-9.
[42] Miyake, S.; Ohtani, Y.; Sawada, M.; Inase, N.; Miyazaki, Y. and Takano, S. (2002) *Sarcoidosis Vasc. Diffuse Lung Dis.*, **19**, 128-33.
[43] Kuroda, T.; Morioka, H.; Satou, T.; Tanabe, Y.; Murakami, S.; Ito, S.; Nakan, M. and Gejo, F. (2003) *Clin. Rheumatol.*, **22**, 45-8.
[44] Nagasaka, K.; Harigai, M.; Tateishi, M.; Hara, M.; Yoshizawa, Y.; Koike, T. and Miyasaka, N. (2003) *Mod. Rheumatol.*, **13**, 231-8.
[45] Ochi, S.; Nanki, T.; Takada, K.; Suzuki, F.; Komano, Y.; Kubota, T. and Miyasaka, N. (2005) *Clin. Exp. Rheumatol.*, **23**, 707-10.
[46] Wilkes, M.R.; Sereika, S.M.; Fertig, N.; Lucas, M.R. and Oddis, C.V. (2005) *Arthritis Rheum.*, **52**, 2439-46.
[47] Takizawa, H. and Ito, K. (1997) *Intern. Med.*, **36**, 448-9.
[48] Meyer, O.; Hayem, G.; Palazzo, E.; Crestani, B.; Debray, M.P. and Ballard, M. (2005) *Clin. Exp. Rheumatol.*, **23**, 724.
[49] Yamasaki, Y.; Yamada, H.; Yamasaki, M.; Ohkubo, M.; Azuma, K.; Matsuoka, S.; Kurihara, Y.; Osada, H.; Satoh, M. and Ozaki, S. (2006) *Rheumatology (Oxford)*, (Epub ahead of print).
[50] Lee, C-S.; Chen, T-L.; Tzen, C-Y.; Lin, F-J.; Peng, C-L.W. and Chen, P-J. (2002) *Clin. Rheumatol.*, **21**, 391-6.
[51] Selva-O'Callaghan, A.; Labrador-Horrillo, M.; Munoz-Gall, X.; Martinez-Gomez, X.; Majo-Masferrer, J.; Solans-Laque, R.; Simeon-Aznar, C.P.; Morell-Brotard, F. and Vilardell-Tarres, M. (2005) *Lupus*, **14**, 534-42.
[52] Tanaka, F.; Origuchi, T.; Migita, K.; Tominaga, M.; Kawakami, A.; Kawabe, Y. and Eguchi, K. (2000) *Intern. Med.*, **39**, 428-30.
[53] American Thoracic Society. (2000) *Am. J. Respir. Crit. Care Med.*, **161**, 646-64.
[54] Sato, S.; Hirakata, M.; Kuwana, M.; Suwa, A.; Inada, S.; Mimori, T.; Nishikawa, T.; Oddis, C.V. and Ikeda, Y. (2005) *Arthritis Rheum.*, **52**, 1571-6.
[55] Tashkin, D.P.; Elashoff, R.; Clements, P.J.; Goldin, J.; Roth, M.D.; Furst, D.E.; Arriola, E.; Silver, R.; Strange, C.; Bolster, M.; Seibold, J.R.; Riley, D.J.; Hsu, V.M.; Varga, J.; Schraufnagal, D.E.; Theodore, A.; Simms, R.; Wise, R.; Wigley, F.; White, B.; Steen, V.; Read, C.; Mayes, M.; Parsley, E.; Mubarak, K.; Connolly, M.K.; Golden, J.; Olman, M.; Fessler, B.; Rothfield, N. and Metersky, M for the Scleroderma Lung Study Research Group. (2006) *N. Engl. J. Med.*, **354**, 2655-66.
[56] Oryoji, K.; Himeji, D.; Nagafuji, K.; Horiuchi, T.; Tsukamoto, H.; Gondo, H. and Harada, M. (2005) *Clin. Rheumatol.*, **24**, 637-40.
[57] van Laar, J.M. and Farge, D. and Tyndall, A. (2005) *Ann. Rheum. Dis.*, **64**, 1515.
[58] Mino, M.; Noma, S.; Taguchi, Y.; Tomii, K.; Kohri, Y.; Oida, K. (1997) *AJR*, **169**, 83-7.
[59] Akira, M.; Hara, H. and Sakatani, M. (1999) *Radiology*, **210**, 333-8
[60] Bonnefoy, O.; Ferretti, G.; Calaque, O.; Coulomb, M.; Begueret, H.; Beylot-Barry, M. and Laurent, F. (2004) *Eur. J. Radiol.*, **49**, 235-44.
[61] Marie, I.; Hachulla, E.; Chérin, P.; Hellot, M-F.; Herson, S.; Levesque, H. and Hatron, P-Y. (2005) *Arthritis Rheum.*, **53**, 155-65.
[62] Lutz, H.U.; Stammler, P.; Bianchi, V.; Trüeb, R.M.; Hunziker, T.; Burger, R.; Jelezarova, E. and Späth, P.J. (2004) *Blood*, **103**, 465-72.
[63] Giradi, G.; Berman, J.; Redecha, P.; Spruce, L.; Thurman, J.M.; Kraus, D.; Holman, T.J.; Casali, P.; Caroll, M.C.; Wetsel, R.A.; Lambris, J.D.; Holers, V.M. and Salmon, J.E. (2003) *J. Clin. Invest.*, **112**, 1644-54.
[64] Raghu, G.; Brown, K.K.; Bradford, W.Z.; Starko, K.; Noble, P.W.; Schwartz, D.A. and King, Jr. TE for the Idiopathic Pulmonary Fibrosis Study Group. (2004) *N. Eng. J. Med.*, **350**, 125-33.
[65] Efthimiou, P.; Schwartzman, S. and Kagen, L. (2006) *Ann. Rheum. Dis.*, (Epub ahead of print).
[66] Crystal, R.G.; Bitterman, P.B.; Mossman, B.; Schwarz, M.I.; Sheppard, D.; Almasy, L.; Chapman, H.A.; Friedman, S.L.; King, Jr. TE.; Leinwand, L.A.; Liotta, L.; Martin, G.R.; Schwartz, D.A.; Schultz, G.S.; Wagner, C.R.; Musson, R.A. (2002) *Am. J. Respir. Crit. Care Med.*, **166**, 236-46.
[67] Kameda, H.; Ishigami, H.; Suzuki, M.; Abe, T. and Takeuchi, T. (2006) *Clin. Exp. Immunol.*, **144**, 335-41.
[68] Raghu, G.; Johnson, W.C.; Lockhart, D. and Mageto, Y. (1999) *Am. J. Repir. Crit. Care Med.*, **159**, 1061-9.
[69] Funauchi, M.; Shimadsu, H.; Tamaki, C.; Yamagata, T.; Nozaki, Y.; Sugiyama, M.; Ikoma, S. and Kinoshita, K. (2006) *J. Rheumatol.*, **33**, 903-6.
[70] Levine, T.D. (2005) *Arthritis Rheum.*, **52**, 601-7.

Received: 05 June, 2006 **Accepted: 21 July, 2006**

膠原病に合併するニューモシスチス肺炎の早期診断，早期治療

齋藤和義*　田中良哉*

ニューモシスチス肺炎は，*Pneumocystis jirovecii* により引き起こされる日和見感染症である．診断が遅れると致死的になることより早期診断がきわめて重要であるが，培養困難で診断は必ずしも容易ではない．早期診断には，ネブライザーにて誘発した喀痰を検体としてPCR法によるニューモシスチスのDNA診断が，検出率，特異性，迅速性などにおいて有用である．発症リスクの検討により一次予防指標を策定した．①プレドニゾロン(PSL)換算≧1 mg/kg 使用，②PSL 換算≧0.5 mg/kg かつ免疫抑制薬併用，③リンパ球≦400/mm³，④IgG≦700 mg/dl のうち，①または②，かつ，③または④を満たす症例と定め，本基準に該当するリウマチ性疾患症例に対してST合剤による一次予防を施行したところ，関節リウマチ以外の膠原病でのニューモシスチス肺炎発症は防止し得た．

はじめに

ニューモシスチス肺炎は，*Pneumocystis jirovecii* により引き起こされる日和見感染症である．膠原病では，原病にもとづく免疫異常や免疫抑制薬使用に伴なう獲得免疫の低下が存在しており，時にニューモシスチス肺炎が併発する．最近，膠原病の生存率が改善される一方で，感染症による死亡率が相対的に高くなり，死因の30～50%を占めるに至り，このなかにはニューモシスチス肺炎による死亡も含まれる．ニューモシスチス肺炎による致死率は診断の時期に依存するとされ，いかに早期に治療を開始するかが重要であるが，そのためには早期診断が不可欠である．ニューモシスチスは培養できず確定診断は必ずしも容易ではない．

われわれは，ネブライザーにて2%食塩水を吸入して誘発した喀出痰を検体としてpolymerase chain reaction(PCR)法によるニューモシスチスのDNA診断を導入し，検出率，特異性，迅速性などにおいてその有用性を報告するとともに，本法を用いて膠原病に併発するニューモシスチス肺炎の早期診断・治療，さらには一次予防基準を策定し実践して成果をあげてきたので概説する．

Key Words
膠原病
ニューモシスチス肺炎
一次予防
PCR 診断
免疫抑制薬

*SAITO Kazuyoshi, TANAKA Yoshiya/産業医科大学医学部第一内科学講座

1．ニューモシスチス肺炎に関する概論

1）ニューモシスチスとは

ニューモシスチスは，Antonio Carinii によりモルモットの肺で確認されたが，当時は新種の原虫と考えられ *Pneumocystis carinii* と名づけられた．1988年になり16S

リボソームやミトコンドリアDNAの解析により真菌に分類されたが[1]，その後の研究でニューモシスチス感染には，かなり厳格に宿主特異性があり，ヒトに感染するニューモシスチスは*Pneumocystis jirovecii* 1種類であることが解明された．したがって現在では“カリニ肺炎”から“ニューモシスチス肺炎”へ改称された．細胞壁成分として他の真菌と同様にβ-D-グルカンを豊富に含有し，血清β-D-グルカンの上昇はニューモシスチス肺炎の活動期に高頻度でみられ，治療効果の評価にも有用である[2]．一方，他の真菌と異なり細胞増殖に関してエルゴステロール合成が関与しないために，エルゴステロール合成系を標的とするアムホテリシンBやアゾール系の抗真菌薬は無効である．

2～3歳以上のヒト血清には，ほとんどニューモシスチスに対する抗体が検出されることより，ヒトに対しては，幼少時に不顕性感染すると考えられている．感染経路に関しては，まだ不明な点が多いが，集団感染や家族内感染がみられることなどより，経気道感染であることが類推されている．膠原病の治療中に発症するニューモシスチス肺炎は，免疫力の低下に伴い潜在しているニューモシスチスが再活性化されるのではなく，新たな経気道感染にて生じるとの見方が強い．

2）ニューモシスチス肺炎の病態

ニューモシスチス表面に存在するglycoprotein Aは，I型肺胞上皮より産生されるムチンと高い親和性をもち，肺胞壁に強固に固着した状態で増殖する．ニューモシスチス肺炎の進行性低酸素血症は，著しい肺胞-毛細血管における酸素化障害によりもたらされるが，ニューモシスチスの増殖による単なる物理的な肺胞上皮の被覆による酸素化障害が起こるのではなく，肺胞上皮に固着したニューモシスチスに対して，宿主の免疫応答による局所での炎症が惹起されることによりガス交換の障害が生じるとされる．

3）ニューモシスチス肺炎の臨床症状

一般的には，極初期の症状は非特異的な全身倦怠感などの全身症状であり，その後呼吸器症状に移行する．乾性咳嗽(1～2週)，歩行時などの息切れ，胸骨後部のtightness(咳，吸気にて増強)などが呼吸器症状の初期症状として認められ，8～9割にて発熱がみられるが必発ではない．これらの臨床症状の聴取はきわめて早期診断に重要である．低酸素血症は，胸写上の変化に先んじて認められることが多く，胸部単純撮影にてとくに異常を認めない進行性低酸素血症，安静時には認めないが歩行後に出現する強い息切れなどがみられた場合には，ニューモシスチス肺炎を強く疑って鑑別診断すべきである．また，通常初期に呼吸音異常はないとされるが，後期には30～40%でラ音が聴取される．

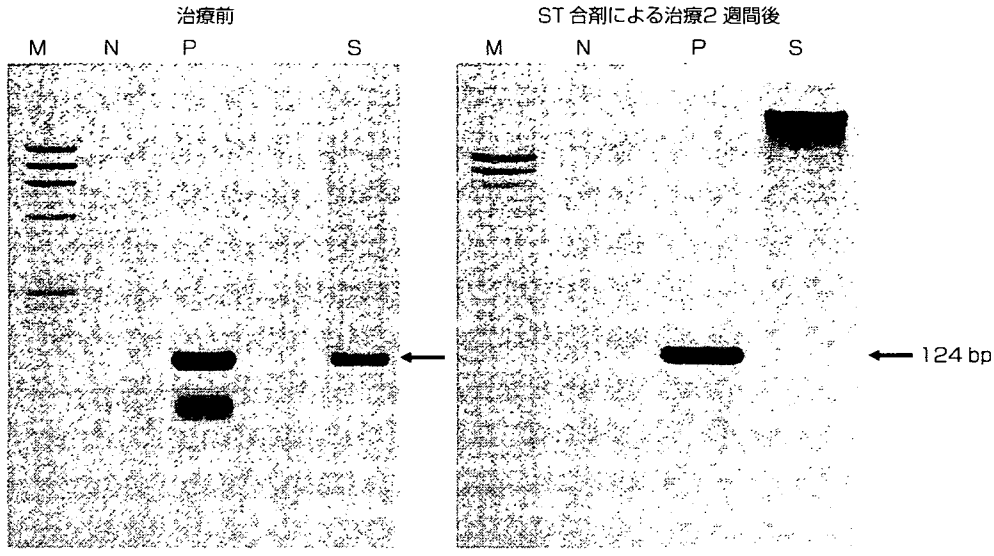
4）ニューモシスチス肺炎の臨床検査所見と画像所見

ニューモシスチス肺炎では乳酸脱水素酵素(LDH)，C反応性蛋白(CRP)，血清中シアル化糖鎖抗原(KL-6)などが上昇することが知られる．KL-6値は予後とも相関するとされ，治療の指標ともなるが，膠原病による間質性肺炎，サイトメガロウイルス肺炎やメトトレキサートによる間質性肺炎においても上昇することから特異性は低い．一方，低酸素血症や間質性肺炎とともにβ-D-グルカンの上昇がみられた場合，積極的にニューモシスチス肺炎を疑う根拠となる[2]．血清β-D-グルカン値は，ニューモシスチス肺炎の重症度・治療の効果を評価するのにきわめて有用である．ただし，ごく早期の場合，β-D-グルカン値はほぼ正常のこともあり，正常値をもって除外することなく，経過を慎重に追って再検する必要がある．

放射線学的には，胸部単純撮影におき典型的には肺門部より生じる間質影を呈する．通常，蝶型に下肺から上肺野に広がる病変を認めるが，胸膜直下や肺門部近傍あるいは肺尖部は保たれることが多いcomputed tomography(CT)においては，胸部単純撮影で異常が認められなくても，びまん性に肺胞のconsolidationや肺胞壁の肥厚像がみられるが，これらの所見の早期検出には高分解能CT(HRCT)が有用であり，ニューモシスチス肺炎が疑われる症例では必ず施行することが推奨される．

2. ニューモシスチス肺炎の早期診断のために

まず，ニューモシスチス肺炎を疑う根拠となるのは患



M：Marker 4（ϕX174 HaeIII digest），N：negative control，P：positive control，S：sample

図❶ *Pneumocystis* の PCR による DNA 診断

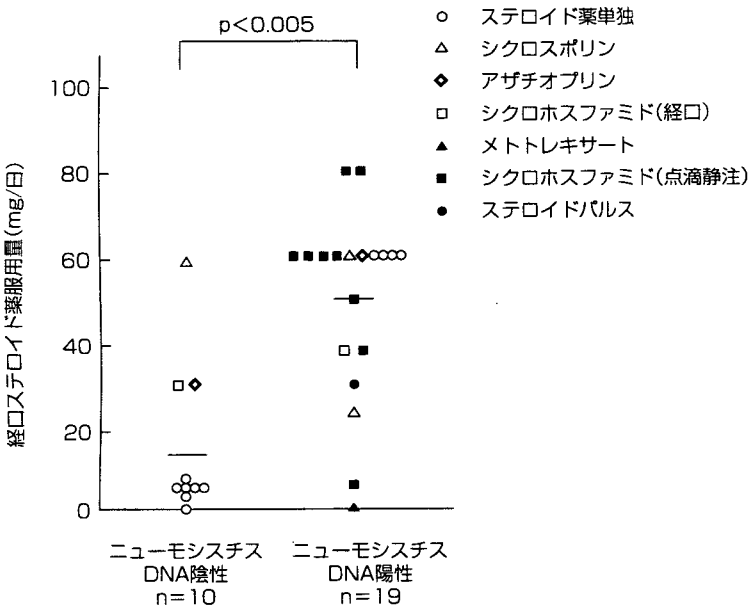
者の自覚症状であり，これを問診などにおいて大切にする必要がある．①乾性咳嗽，労作時息切れ，発熱，②進行性低酸素血症，③胸写・胸部 CT にて間質性肺炎を呈した症例は強くニューモシスチス肺炎が疑われる．現時点ではニューモシスチスを *in vitro* で培養することは不可能であり，診断は患者呼吸器由来検体を鏡検してニューモシスチスの存在を確認することによる．しかしながら，初発症状は乾性咳嗽であり，初期には良質の喀痰を採取できないことが多い．鏡検による診断では，2%食塩水を吸入後に採取する誘発喀痰をサンプルとした場合，50～90%の陽性率が得られるとされる．したがって，検体採取は，まず非侵襲的に誘発喀痰を用いて検査し，これで診断がつかない場合に気管支鏡を用いて肺胞洗浄液を採取するように提唱されている[3]．

当科では，乾性咳嗽，急速進行性低酸素血症，胸写・CT におけるすりガラス陰影など呈したニューモシスチス肺炎の疑診例に対して，積極的に PCR 法を用いた DNA 診断を施行し，ニューモシスチス肺炎の確定診断に非常に役立てている．方法は，2%食塩水 10 m*l* を超音波ネブライザーにて吸入した後，誘発喀痰をより DNA を調整し PCR を施行後，124 bp の特異的バンドとして検出する[4)~8)]．図❶にニューモシスチス肺炎を生じた患者誘発喀痰を用いた DNA 診断の結果を示す．ST 合剤による治療により通常 2 週間でバンドは消失する．

3. 膠原病疾患におけるニューモシスチス肺炎の実際

われわれは 1998 年から約 5 年の間に，臨床的にニューモシスチス肺炎が強く疑われたリウマチ性疾患患者 59 人中 30 人においてニューモシスチス DNA 陽性と診断した．本法による検出率は 52%で，鏡検診断の陽性率（4.5%）にくらべて高い検出率を示した．ステロイド薬単独で加療中での発症は全例プレドニゾロン（PSL）換算 1 mg/kg/日以上のステロイド薬服用者であった．ステロイド薬内服量がそれ以下での発症例は，全例ステロイドに加えて免疫抑制療法中であった（図❷）．なお，PCR による微量の病原微生物の DNA 診断においては，存在する DNA を高度に増幅するために，偽陽性がしばしば問題となるが，正常人および慢性閉塞性肺疾患患者由来の誘発喀痰ではニューモシスチス DNA は検出されなかった．さらに，DNA 診断にて陽性と診断した症例は，ST 合剤による治療開始後，ニューモシスチス DNA は臨床的改善とともに 2 週間前後で消失することを確認しており，本検討に用いた PCR の感度では偽陽性はないと考えられる．

一方，関節リウマチ（rheumatoid arthritis：RA）に対して TNF 阻害療法施行中のニューモシスチス肺炎発



図❷ 膠原病患者におけるステロイド薬，免疫抑制薬服用とニューモシスチス肺炎発症との関連性
(Saito K *et al*, 2004[6]より引用)

症が散見され，その診断・治療法の確立が急務となっている．厚生労働省の指導のもと，抗 TNF-α 抗体；インフリキシマブ市販後 5,000 例の全例調査が施行され，最近その調査結果が報告された．ニューモシスチス肺炎の発症は 22 例 (0.4%) で，当初懸念された結核の発症 (14 例；0.3%) を上回った．TNF-α はニューモシスチスの肺胞内でのクリアランスに関与し，その抗体による抑制はクリアランスの低下を招き，ニューモシスチス肺炎発症に密接に関与することが動物実験で明らかにされている[9]．

4. ニューモシスチス肺炎の治療の実際

ニューモシスチス肺炎の標準的治療法を**表❶**に示す．基本的には 80～90%以上の例で sulfamethoxazole/trimethoprim (SMX/TMP：ST) 合剤が奏効する．ニューモシスチス肺炎の治療後には局所で過剰な炎症反応が生じるために，治療後 3～4 日はかえって低酸素血症が増悪することが知られる．この過剰反応を抑制する目的で，一般的に中等症以上のニューモシスチス肺炎の治療では，ST 合剤の投与と同時にステロイドを 2～4 週間併用する．一般に ST 合剤，ペンタミジンが無効であることは少なく，治療経過中の増悪に関しては，サイトメガロウイルスを含む他の感染症の併発や薬剤に対するアレルギーなどを考えるべきである．加えて，肺胞-毛細血管の膜透過性が亢進して肺浮腫や成人呼吸窮迫症候群の病態に進展することもあり，輸液量を慎重に管理する必要がある．とくに，ST 合剤を静脈注射する場合，溶解にかなりの容量の輸液が必要であり，輸液量過剰には注意を要する．治療に対する反応が明らかになるまでの平均期間は 4～6 日であり，治療反応性は発熱，呼吸回数，動脈血酸素分圧 (PaO_2)，CRP，β-D-グルカン値にて確認しつつ，非 AIDS 患者での発症では 2 週間，AIDS 患者での発症例では 3 週間服薬するのが標準的治療である．

5. ニューモシスチス肺炎の一次予防とその問題点

われわれは，DNA 診断の結果より発症リスクを抽出し，一次予防指標を策定した．①PSL 換算≧1 mg/kg 使用，②PSL 換算≧0.5 mg/kg かつ免疫抑制薬併用，③リンパ球≦400/mm^3，④IgG≦700 mg/dl のうち，①または②，かつ，③または④を満たす症例と定め，本基準に該当するリウマチ性疾患症例に対して ST 合剤 1 g 連日あるいは 2 g 隔日投与などの一次予防を施行したところ，以後のニューモシスチス肺炎の発症は 1 例のみであった (1 例はペンタミジン吸入での一次予防者)．一方，一次予防基準に該当しない症例からのニューモシスチス肺炎の発症が 5 例あったが，レフルノミドとタクロリムスが 1

表❶ ニューモシスチス肺炎の標準的治療法

sulfamethoxazole/trimethoprim（SMX/TMP：ST 合剤）
trimethoprim 成分で 15～20 mg/kg/日を 6～8 時間に分割して
14 日間経口投与（BW 50 kg であればバクタ® 9～12 錠/日）
経口投与できない場合，効果が期待できない場合静注
（BW 50 kg であればバクトラミン® 3～4 アンプル×3 回/日）
ペンタミジン
ST 合剤がアレルギーなどで使用できないとき
3～4 mg/kg/日を 1 回/日で 14 日間点滴静注
予防には 300 mg を注射用蒸留水に溶解して吸入
プレドニゾロン
発症早期に中等度以上の重症例に上記治療と併用
80 mg 5 日間→ 40 mg 5 日間→ 20 mg

例ずつ，3 例が TNF 阻害療法中でありすべて RA 患者での発症であった．RA では使用されるステロイド服用量は少量であり，また生物学的製剤に関する項目を設けていないため，本基準には多くの症例が該当しなかった．一方，実際に ST 合剤の予防投与を施行してみると，有害事象が 22 人(28%)/全患者数 78 人で認められ，ST 合剤の市販後調査における頻度 10%にくらべてリウマチ性疾患では約 3 倍と明らかに高かった．

おわりに

膠原病に併発するニューモシスチス肺炎に対して，一次予防が有効であることが明らかであり，実践が肝要である．一方，早期診断に欠かせないのが，自覚症状を見逃さないようにする患者教育であり，他覚所見を確実に鑑別する医師の注意深い問診・診察である．さらに，疑われたときに確定診断するには，今回呈示したような誘発喀痰を用いた PCR による DNA 診断が感度，特異度，迅速性にすぐれる．一方，従来から RA におけるニューモシスチス肺炎の併発は散見され報告はなされていたが，最近，抗 TNF-α 抗体であるインフリキシマブ投与後や，新規抗リウマチ薬であるレフルノミドやタクロリムス使用中のニューモシスチス肺炎発症の報告がなされている．これらの新規治療の導入とともに，ニューモシスチス肺炎などの日和見感染症に対する対策，さらに早期診断法の普及と一次予防基準の設定が重要な課題と考えられる．

文 献

1) Edman JC, Kovacs JA, Masur H *et al*：Ribosomal RNA sequence shows *Pneumocystis carinii* to be a member of the fungi. *Nature* **334**：519-522, 1988
2) Obayashi T, Yoshida M, Mori T *et al*：Plasma (1→3)-β-D-glucan measurement in diagnosis of invasive deep mycosis and fungal febrile episodes. *Lancet* **345**：17-20, 1995
3) Thomas CF Jr, Limper AH：Pneumocystis pneumonia. *N Engl J Med* **350**：2487-2498, 2004
4) Oka S, Kitada K, Kohjin T *et al*：Direct monitoring as well as sensitive diagnosis of *Pneumocystis carinii* pneumonia by the polymerase chain reaction on sputum samples. *Mol Cell Probes* **7**：419-424, 1993
5) 齋藤和義，田中良哉：膠原病疾患におけるカリニ肺炎—膠原病疾患に併発するカリニ感染症の臨床上の留意点，PCR 法による DNA 診断の臨床応用．日臨免疫会誌 **25**：310-318, 2002
6) Saito K, Nakayamada S, Nakano K *et al*：Detection of *Pneumocystis carinii* by DNA amplification in patients with connective tissue diseases：re-evaluation of clinical features of *P. carinii* pneumonia in rheumatic diseases. *Rheumatology* (*Oxford*) **43**：479-485, 2004
7) 齋藤和義，田中良哉：膠原病疾患に併発するカリニ肺炎の早期診断と 1 次予防．九州リウマチ **23**：134-138, 2004
8) 田中良哉，齋藤和義：膠原病に於ける日和見感染症とそ

の対策. 日内会誌 **93**：1654-1659, 2004
9) Chen W, Havell EA, Harmsen AG：Importance of endogeneous tumor necrosis factor alpha and gamma interferon in host resisitance against *Pneumocystis carinii* infection. *Infect Immun* **60**：1279-1284, 1992