INTERNAL MEDICINE

□ CASE REPORT □

Sarcoidosis Accompanied by Systemic Lupus Erythematosus and Autoimmune Hepatitis

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Abstract

A 52-year-old woman was admitted to our hospital for further examination of blurred vision, abnormal lung shadows and an elevated level of angiotensin-converting enzyme. Sarcoidosis was suspected, however, careful history taking revealed the existence of photosensitivity and polyarthralgia. Laboratory tests showed lymphocytopenia, liver dysfunction, hypergammaglobulinemia, and positive anti-nuclear, anti-double stranded DNA and anti-smooth muscle antibodies. Liver biopsy examination showed chronic active hepatitis. She was diagnosed with the triplex of sarcoidosis, systemic lupus erythematosus and autoimmune hepatitis. Marked improvement was noted after corticosteroid therapy.

Key words: sarcoidosis, systemic lupus erythematosus, autoimmune hepatitis

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Introduction

Sarcoidosis is a systemic granulomatous disease of unknown cause and the most commonly affected organs are the lung, lymph nodes, eyes, and skin. Similarly, systemic lupus erythematosus (SLE) is an autoimmune disorder affecting multiple organs. Although sarcoidosis and SLE are both considered to result from abnormal regulation of the immune system, their coexistence in the same patient is quite rare (1-17).

Autoimmune hepatitis (AIH), a chronic hepatitis of unknown etiology, exhibits prominent extrahepatic features of autoimmunity. Diseases that may commonly be seen in patients with AIH include autoimmune thrombocytopenia, type 1 diabetes, thyroiditis, and ulcerative colitis (18, 19). However, sarcoidosis and SLE have been reported infrequently in association with AIH (20-23). Here, we describe a rare case of a patient with these three disorders. Our case emphasizes the importance of considering the co-existence of other autoimmune diseases in patients with sarcoidosis.

Case Report

In September 2004, an asymptomatic 52-year-old Japanese woman was incidentally found to have enlargement of the upper mediastinal lymph nodes on a routine chest X-ray film taken at an annual medical check-up (Fig. 1A). A follow-up chest computed tomography showed mediastinal and left hilar lymphadenopathy accompanied by small nodules and consolidations in both lung fields (Fig. 1B). Blood tests showed elevated levels of serum angiotensin-converting enzyme (ACE) and lysozyme titers, raising the suspicion of sarcoidosis. She was referred to our hospital for further management.

In 1992, at the age of 40, the patient was found to be hypertensive with liver dysfunction of unknown cause on the annual medical check-up. In 2000, at the age of 48, she visited a hospital for arthralgia in both hands and knee joints. Since no clear cause was identified, she was not treated although arthralgia persisted until the current admission. In 2002, at the age of 50, she complained of blurred vision and ocular floater. While she consulted her physician, no oph-

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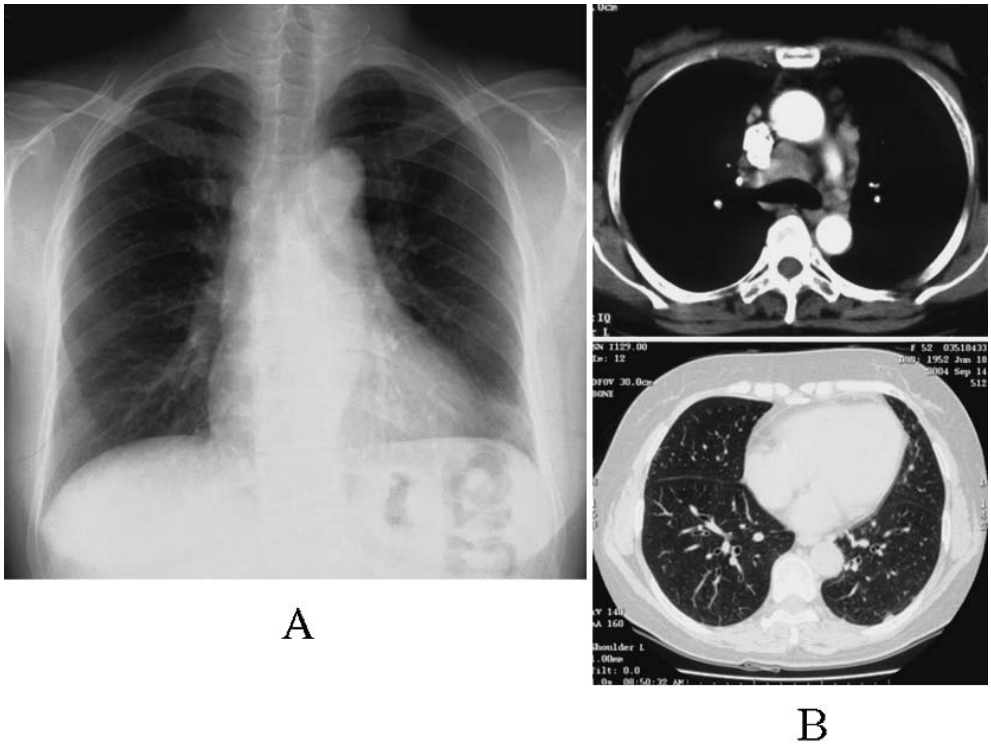

Figure 1. **A: Chest X-ray showing enlargement of the upper mediastinum. B: Chest CT showing mediastinal lymphadenopathy accompanied by small nodules and consolidations of both lung fields.**

thalmologic evaluation was conducted. The blurred vision improved spontaneously, but ocular floater persisted until admission to our hospital. She also had a history of severe photosensitivity. The patient was a current smoker (Brinkman index 375) and had history of alcohol drinking (half a bottle of whiskey per day, until two years before the current admission). There was no history of recent infection or new drug therapy.

Physical examination showed body temperature of 36.2℃, blood pressure of 108/72 mmHg and pulse rate of 70/min with regular rhythm. No superficial lymphadenopathy was found. Lung and heart auscultation was normal. Abdominal examination revealed mild hepatomegaly. Neurological and skin examinations were also negative. Laboratory tests on admission (Table 1) showed mild lymphocytopenia (1,104/μl), mild liver dysfunction and elevated serum levels of γ-globulin (2.3 g/dl), IgG, ACE (reference range: 7-25.0 U/l) and lysozyme (reference range: 5.0-10.2 μg/ml). Serum was positive for anti-nuclear antibody (ANA), anti-double stranded (ds) DNA antibody and anti-smooth muscle antibody (SMA), the elevation of these antibodies persisted in the clinical course, but negative for liver/kidney microsomal type 1 antibodies (LKM-1) and anti-mitochondrial antibody (AMA). Human leukocyte antigen (HLA) typing analysis was positive for HLA-DR4. Examination of bronchoalveolar lavage fluid showed increased total cell count (3.53×10^5/ml) with a high CD4/CD8 ratio (8.43), but normal proportion of lymphocytes (11.5%). Transbronchial lung biopsy specimens showed no abnormalities such as alveolitis or granuloma. The tuberculin skin reaction was negative. ^{67}Gallium scintigraphy demonstrated abnormal isotope uptake in the mediastinum and the right hilum of the lung. A slight uptake was also seen in the hand joints and legs. Ophthalmologic evaluation showed evidence of previous uveitis.

A clinical diagnosis of sarcoidosis was made based on the above findings although we could not find non-caseating epithelioid granulomas. She was also found to have first-degree atrioventricular block on the electrocardiogram, but echocardiography was normal finding. Abdominal ultrasonography showed mild fatty liver. In addition, the patient fulfilled the American Rheumatism Association criteria for SLE (24) with a history of severe photosensitivity, polyarthritis, lymphocytopenia and positivity of both ANA and anti- dsDNA antibody. Histological examination of liver biopsy specimens revealed extensive necrosis of hepatocytes with severe infiltration of lymphocytes and plasma cells in the portal areas, and bridging fibrosis linking these portal tracts to others (Fig. 2). These findings were compatible with AIH. The score for AIH based on the criteria of the International Autoimmune Hepatitis (25) was 18, which was relatively high, and accordingly was considered to require steroid therapy.

Treatment was initiated by administration of prednisolone 30 mg daily with subsequent reduction to 5 mg. Within the first week of treatment, the arthralgia disappeared and serum transaminase levels returned to normal levels. At one year after commencement of steroid therapy, liver function was normal and pulmonary lesions showed marked improvement.

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Table 1. **Results of Laboratory Tests on Admission. RF: Rheumatoid Factor, ANA: Antinuclear Antibody, Anti-dsDNA Ab: Anti-Double Strand DNA Antibody, Anti-RNP Ab: Anti-Ribonucleoprotein Antibody, Anti-Scl-70 Ab: Anti-scleroderma-70 Antibody, Anti-SMA-Ab: Anti-smooth Muscle Antibody, Anti-LKM-1 Ab: Anti-liver/kidney Microsome Type 1 Antibody, MPO-ANCA: Myeloperoxidase-anti-Neutrophil Cytoplasmic Autoantibody, PR3-ANCA: Proteinase 3 Anti-neutrophil Cytoplasmic Autoantibody**

Blood Cell Count

WBC	4800	/ μl
Neu	61 %	
Lym	23 % (1104 / μl)	
Eos	5 %	
Bas	1 %	
Mon	10 %	
RBC	442	× 10⁴/μl
Hb	13.5	g/dl
Ht	44.3	%
Plt	19.7	× 10⁴/μl
ESR	41.8	mm/H

Blood Chemistry

TP	7.1	g/dl
γ-globulin	2.3	g/dl
T.Bil	0.9	mg/dl
AST	49	IU/L
ALT	58	IU/L
LDH	192	IU/L
ALP	269	IU/L
ChE	122	IU/L
γ-GTP	59	IU/L
ZTT	29.1	U
Amylase	67	IU/L
T.Cho	178	mg/dl
TG	104	mg/dl
Glucose	80	mg/dl
BUN	12	mg/dl
Cr	0.7	mg/dl

Serology

IgG	2688	mg/dl
IgA	211	mg/dl
IgM	240	mg/dl
CRP	0.62	mg/dl
sIL-2R	960	U/ml
ACE	32.5	U/L
Lysozyme	15.3	μg/ml

Viral Markers

HBsAg	0.1	IU/ml
HCV-Ab	0.2	
Anti-HTLV-1 Ab	0.1	×

Urinalysis

Protein	-
Glucose	-
Blood	-
Ketone	-

Immunological tests

RF		11.5	IU/ml
ANA	homogeneous	40	×
	nucleolar	320	×
C3		109.0	mg/dl
C4		16.9	mg/dl
CH50		38.7	U/ml
anti-dsDNA Ab		>400.0	IU/ml
anti-Sm Ab		1.3	index
anti-RNP Ab		18.5	index
anti-SS-A Ab		6.5	index
anti-SS-B Ab		4.0	index
anti-Scl-70 Ab		3.7	U/ml
anti-cardiolipin Ab		2.1	U/ml
anti-SMA Ab		160	
anti-LKM-1 Ab		11	
anti-mitochondrial Ab		<20	×
MPO-ANCA		<10	EU
PR3-ANCA		<10	EU

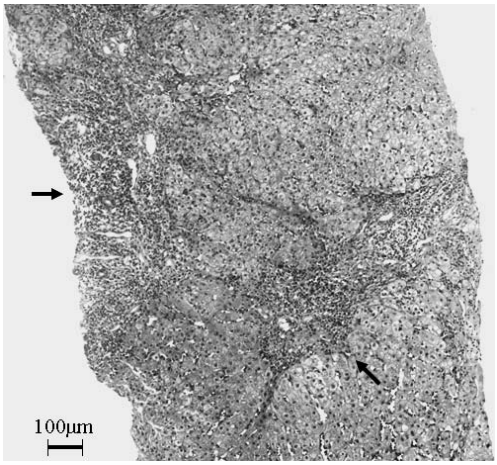

Figure 2. **Histological examination of liver biopsy specimens revealed extensive necrosis of hepatocytes with severe infiltration of lymphocytes and plasma cells in the portal areas and bridging fibrosis linking these portal tracts to others (Arrow, Hematoxylin and Eosin staining×40).**

Discussion

Here, we described a rare case of simultaneous occurrence of sarcoidosis, SLE and AIH conditions in one patient. These three conditions are considered to result, at least in part, from abnormal regulation of the immune system. Despite the theoretical association, to our knowledge, this is the first case of triple conditions reported in the English literature.

As for the co-existence of sarcoidosis and SLE, to our knowledge, it has been reported in less than 20 cases in the English literature to date (1-17). As shown in Table 2, SLE was first diagnosed in ten cases and sarcoidosis first in four cases. In other cases, SLE and sarcoidosis were diagnosed simultaneously as in the present case. In nine of those cases, the secondary disease appeared after the reduction of steroid therapy for the first disease. Interestingly, although almost all patients were woman, there is no common pattern among these reports with regard to which disease presented first or the course of each condition. Because both diseases may present with similar non-specific clinical features, including fever, arthralgia, lymphadenopathy, sicca symptoms and rash, it is possible that the true incidence of sarcoidosis in patients with SLE is underestimated. Enzenauer and West (9) reviewed 569 patients with a variety of autoimmune conditions including rheumatoid arthritis, primary systemic sclerosis and SLE, and found the incidence of sarcoidosis in these patients to be 1%. This is considerably greater than the incidence of sarcoidosis in the general population (ranging from less than 1 to 40 per 100,000) (26-28). In this context, SLE and sarcoidosis have similar genetic associations. Both conditions share a high incidence in the Afro-Caribbean and African-American populations. Risk HLA al-

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Table 2. **Clinical Features of 19 Cases of Co-existence of Sarcoidosis and Systemic Lupus Erythematosus Reported in the English Literature. M: Male, F: Female, SLE: Systemic Lupus Erythematosus, N.D.: Not Described**

Authors	Year	Age/Sex/Race	Order of diagnosis	Reduction of steroid before the secondary diagnosis	Coexisting illness
Harrison, et al. [1]	1979	54/F/N.D.	SLE→sarcoidosis	−	
Wiesenhutter, et al. [2]	1979	20/F/Black	SLE→sarcoidosis	+	Hemolytic anemia, thrombocytopenia, thyroid disease
Hunter, et al. [3]	1980	62/F/Caucasian	simultaneously		Hypothyroidism
Needleman, et al. [4]	1982	49/F/Caucasian	SLE→sarcoidosis	+	
Aronson, et al. [5]	1985	82/M/Caucasian	simultaneously		
Askari, et al.[6]	1988	52/F/Caucasian	SLE→sarcoidosis	−	
Soto-Aguilar, et al. [7]	1988	43/F/Black	SLE→sarcoidosis	+	
Fivenson, et al. [8]	1989	50/F/Black	SLE→sarcoidosis	+	
Enzenauer, et al. [9]	1992	57/F/Caucasian	SLE→sarcoidosis	−	Hypertension, atrial fibrilation
Magasic, et al. [10]	1993	43/F/N.D.	sarcoidosis→ SLE	+	
Collins, et al. [11]	1996	54/F/India	SLE→sarcoidosis	+	
Schnabel, et al. [12]	1996	23/F/N.D.	simultaneously		
Umeki,et al. [13]	2000	60/F/Japanese	SLE→sarcoidosis	+	
Begum, et al. [14]	2002	40/F/Mixed	SLE→sarcoidosis	+	
		23/F/Caucasian	sarcoidosis→ SLE	N.D.	Autoimmune thyroiditis
		28/F/Caucasian	sarcoidosis→ SLE	−	
Papaioannides, et al. [15]	2004	49/F/N.D.	sarcoidosis→ SLE	+	
Migita, et al. [16]	2005	42/F/Japanese	simultaneously		
Our case	2007	52/F/Japanese	simultaneously		Hypertension, autoimmune hepatitis

leles for lupus include HLA-B8 (29), the HLA-A1-B8-DR3 haplotype as a whole, as well as HLA-DR2 (30). In contrast to these data there are few studies addressing the genetics of sarcoidosis. HLA-B8-DR3 has been reported to be a risk haplotype, in particular for acute-onset sarcoidosis, including sarcoid arthritis (31, 32). This haplotype also confers an increased risk of a set of other autoimmune diseases such as thyrotoxicosis, type 1 diabetes, and myasthenia gravis (33, 34). It is possible that some of the genes that confer a high risk of SLE are also involved in the pathogenesis of sarcoidosis. More genetic markers are needed to enhance our understanding of the mechanisms that influence the association of sarcoidosis and autoimmune disorders.

A prospective study revealed that about one-third of patients with SLE had elevated serum levels of transaminases associated with SLE activity (35). Differentiation of SLE-associated hepatitis from AIH with extrahepatic manifestations is usually not easy. Among the three subtypes of AIH based on the pattern of autoantibodies detected (36), AIH type 1 (AIH-1) is characterized by the presence of SMA and/or ANA. Both autoantibodies are detected in almost half of Caucasian patients with AIH-1, while ANA alone is detected in 15% and SMA alone in 35% (37). Their determination is of great diagnostic value in AIH (38). On the other hand, analysis of HLA-DR with AIH demonstrated DR4 specificity (relative risk=14.8) in Japanese patients (39). In the present case, the diagnosis of AIH was based on the results of laboratory tests, the histological findings of the liver and the positive results for SMA and HLA-DR4.

In conclusion, we reported a woman patient with triplex disease of sarcoidosis, SLE and AIH. The patient had no severe symptoms related to nephropathy and/or encephalopathy, which are characteristic of aggressive SLE; she responded well to corticosteroid therapy and achieved improvement of both sarcoidosis and/or lupus symptoms, and liver dysfunction. The association of these three conditions, along with the presence of numerous positive autoantibodies, may not be fortuitous and could be linked to complex immunological mechanisms. The etiology of this ternary complex remains unknown, but studies using modern DNA technologies, combined with a comprehensive understanding of the whole human genome, are needed to clarify this mechanism.

References

1. Harrison GN, Lipham M, Elguindi AS, Loebl DH. Acute sarcoidosis occurring during the course of systemic lupus erythematosus. South Med J **72**: 1387-1388, 1979.
2. Wiesenhutter GW, Sharma OP. Is sarcoidosis an autoimmune disease? Report of four cases and review of the literature. Semin Arthritis Rheum **9**: 124-144, 1979.
3. Hunter T, Arnott JE, McCarthy DS. Features of systemic lupus erythematosus and sarcoidosis occurring together. Arthritis Rheum **23**: 364-366, 1980.
4. Needleman SW, Silber RA, Von Brecht JH, Goeeken JA. Systemic lupus erythematosus complicated by disseminated sarcoidosis. Report of a case associated with circulating immune complexes. Am J Clin Pathol **78**: 105-107, 1982.
5. Aronson PJ, Fretzin DF, Morgan NE. A unique case of sarcoidosis with coexistent collagen vascular disease. Possible result of a compatible disease-sustaining immunologic environment. J Am

Acad Dermatol **13**: 886-891, 1985.

6. Askari A, Thompson P, Barnes C. Sarcoidosis: atypical presentation associated with features of systemic lupus erythematosus. J Rheumatol **15**: 1578-1579, 1988.

7. Soto-Aguilar MC, Boulware DW. Sarcoidosis presenting as antinuclear antibody positive glomerulonephritis. Ann Rheum Dis **47**: 337-339, 1988.

8. Fivenson DP, Crump G, Scheele P, Breneman DL. Systemic lupus erythematosus developing in a patient with longstanding pulmonary sarcoidosis. J Rheumatol **16**: 1116-1119, 1989.

9. Enzenauer RJ, West SG. Sarcoidosis in autoimmune disease. Semin Arthritis Rheum **22**: 1-17, 1992.

10. Magasic MV, Venkataseshan VS, Vitting KE. Concurrent renal sarcoidosis and lupus nephritis. Nephron **64**: 496-497, 1993.

11. Collins DA, Bourke BE. Systemic lupus erythematosus: an occasional misdiagnosis. Ann Rheum Dis **55**: 421-422, 1996.

12. Schnabel A, Barth J, Schubert F, Gross WL. Pulmonary sarcoidosis coexisting with systemic lupus erythematosus. Scand J Rheumatol **25**: 109-111, 1996.

13. Umeki K, Sawamura D, Sugawara T. Sarcoidosis developing after stopping oral prednisolone for systemic lupus erythematosus. Acta Derm Venereol **81**: 74, 2001.

14. Begum S, Li C, Wedderburn LR, Blackwell V, Isenberg DA. Concurrence of sarcoidosis and systemic lupus erythematosus in three patients. Clin Exp Rheumatol **20**: 549-552, 2002.

15. Papaioannides D, Korantzopoulos P, Latsi P, Orphanidou D. Systemic lupus erythematosus developing in a patient with pulmonary sarcoidosis. Joint Bone Spine **71**: 442-444, 2004.

16. Migita K, Udono M, Kinoshita A, et al. Lupus erythematosus and sarcoidosis. Clin Rheumatol **24**: 312-313, 2005.

17. Sharma OP. Sarcoidosis and other autoimmune disorders. Curr Opin Pulm Med **8**: 452-456, 2002.

18. Gregorio GV, Portmann B, Reid F, et al. Autoimmune hepatitis in childhood: a 20-year experience. Hepatology **25**: 541-547, 1997.

19. Choudhuri G, Somani SK, Baba CS, et al. Autoimmune hepatitis in India:profile of an uncommon disease. BMC Gastroenterol **5**: 27, 2005.

20. Tojo J, Ohira H, Abe K, et al. Autoimmune hepatitis accompanied by systemic lupus erythematosus. Intern Med **43**: 258-262, 2004.

21. Iwai M, Harada Y, Ishii M, et al. Autoimmune hepatitis in a patient with systemic lupus erythematosus. Clin Rheumatol **22**: 234-236, 2003.

22. West M, Jasin HE, Medhekar S. The development of connective tissue diseases in patients with autoimmune hepatitis: a case series. Semin Arthritis Rheum **35**: 344-348, 2006.

23. Suzuki K, Matsuki Y, Hidaka T, et al. Double filtration plasmapheresis in a patient with autoimmune hepatitis-systemic lupus erythematosus overlap. Intern Med **32**: 725-729, 1993.

24. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum **25**: 1271-1277, 1982.

25. Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol **31**: 929-938, 1999.

26. Henke CE, Henke G, Elveback LR, Beard CM, Ballard DJ, Kurland LT. The epidemiology of sarcoidosis in Rochester, Minnesota: a population-based study of incidence and survival. Am J Epidemiol **123**: 840-845, 1986.

27. Rybicki BA, Major M, Popovich J Jr, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol **145**: 234-241, 1997.

28. Bresnitz EA, Strom BL. Epidemiology of sarcoidosis. Epidemiol Rev **5**: 124-156, 1983.

29. Grumet FC, Coukell A, Bodmer JG, Bodmer WF, McDevitt HO. Histocompatibility (HL-A) antigens associated with systemic lupus erythematosus. A possible genetic predisposition to disease. N Engl J Med **285**: 193-196, 1971.

30. Harley JB, Moser KL, Gaffney PM, Behrens TW. The genetics of human systemic lupus erythematosus. Curr Opin Immunol **10**: 690-696, 1998.

31. Rutherford RM, Brutsche MH, Kearns M, Bourke M, Stevens F, Gilmartin JJ. HLA-DR2 predicts susceptibility and disease chronicity in Irish sarcoidosis patients. Sarcoidosis Vasc Diffuse Lung Dis **21**: 191-198, 2004.

32. Hedfors E, Lindstrom F. HLA-B8/DR3 in sarcoidosis. Correlation to acute onset disease with arthritis. Tissue Antigens **22**: 200-203, 1983.

33. Blecher M. Receptors, antibodies, and disease. Clin Chem **30**: 1137-1156, 1984.

34. Bhalla R, Swedler WI, Lazarevic MB, Ajmani HS, Skosey JL. Myasthenia gravis and scleroderma. J Rheumatol **20**: 1409-1410, 1993.

35. Miller MH, Urowitz MB, Gladman DD, Blendis LM. The liver in systemic lupus erythematosus. Q J Med **53**: 401-409, 1984.

36. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis:diagnosis, grading and staging. Hepatology **19**: 1513-1520, 1994.

37. Czaja AJ, Nishioka M, Morshed SA, Hachiya T. Patterns of nuclear immunofluorescence and reactivities to recombinant nuclear antigens in autoimmune hepatitis. Gastroenterology **107**: 200-207, 1994.

38. Dalekos GN, Zachou K, Liaskos C, Gatselis N. Autoantibodies and defined target autoantigens in autoimmune hepatitis: an overview. Eur J Intern Med **13**: 293-303, 2002.

39. Seki T, Kiyosawa K, Inoko H, Ota M. Association of autoimmune hepatitis with HLA-Bw54 and DR4 in Japanese patients. Hepatology **12**: 1300-1304, 1990.