Primary Biliary Cirrhosis (PBC)-CREST (Calcinosis, Raynaud's Phenomenon, Esophageal Dysfunction, Sclerodactyly and Telangiectasia) Overlap Syndrome Complicated by Sjögren's Syndrome and Arthritis

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A 36-year-old woman with primary biliary cirrhosis (PBC)-CREST (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly and telangiectasia) overlap syndrome complicated by Sjögren's syndrome and arthritis is reported. She had suffered from Raynaud's phenomenon, sclerodactyly, morning stiffness, arthralgia and sicca symptoms since 34 years of age. She exhibited an increased level of alkaline phosphatase and hyperglobulinemia at 2.8 g/dl without any symptoms, and histological findings from the biopsy specimen of the liver were consistent with those of PBC. Her human leukocyte antigen (HLA) typing was DR8 homozygous. (Internal Medicine 34: 451-454, 1995)

Key words: human leukocyte antigen (HLA), CREST syndrome, arthritis, Sjögren's syndrome, CRESTAS syndrome, PBC-CRESTAS overlap syndrome

Introduction

Complications of autoimmune diseases such as Sjögren's syndrome in patients with PBC have been described. Recently, CREST syndrome, one of the varieties of progressive systemic sclerosis (PSS), has been noted to associate with PBC. Arthritis with bone destruction is one of the findings in PSS, but not in CREST syndrome. HLA DR9 is frequently found in Japanese patients with PBC-CREST overlap syndrome (1). We describe here a Japanese woman with PBC-CREST overlap syndrome complicated further by Sjögren's syndrome and arthritis, whose HLA type was homozygous haplotype of DR8.

Case Report

A 36-year-old Japanese woman had suffered from Raynaud's phenomenon, sclerodactyly, morning stiffness, arthralgia and dry mouth for 2 years. At the age of 35, an increased serum level of alkaline phosphatase of 450 IU/l was noted from tests conducted at Takebayashi Hospital in Iwaki district. No history of blood transfusion, alcohol or drug abuse was noted. She was admitted to our hospital for further investigation of

liver dysfunction in April 1993 at 36 years of age.

On admission, severe telangiectasia of both hands and swelling of the left wrist and the right index finger were noted. No hepato-splenomegaly or jaundice was observed.

Laboratory data showed an increased erythrocyte sedimentation rate of 42 mm/hour. Hypochronic anemia with hemoglobin at 10.7 g/dl, white blood cell count at 5,200/mm³ and eosinophils at 12% were noted. Results of liver function tests were as follows: alanine transaminase level of 19 IU/l (normal 6-29 IU/l), serum aspartate transaminase level of 22 IU/l (normal 10-30 IU/l), alkaline phosphatase level of 687 IU/l (normal 125-335 IU/l), gamma glutamyl transpeptidase level of 94 IU/l (normal 6-30 IU/l), leucine aminopeptidase level of 146 IU/l (normal 40-75 IU/l), cholinesterase level of 269 IU/l (normal 200-460 IU/l), serum bilirubin level of 0.5 mg/dl, serum hyaluronic acid level of 102 ng/ml (normal <50 ng/ml), serum albumin level of 3.5 g/dl and cholesterol level of 117 mg/dl. Serum immunoglobulin G, A and M levels were increased to 2140, 538 and 362 mg/dl, respectively. Results of serological tests were as follows: positive for rheumatoid factor at a titer of 40 U/ml, antimitochondrial antibody at a titer of 1:80, anti-M2 antibody at a titer of 850 U/ml, antinuclear antibody at a titer of 1:640

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Fig. 1. Roentgenogram of the right hand showing destruction of the second and the third metacarpal bones at their distal end and radial side as indicated by arrows.

Fig. 2. A) Histological findings of the liver. Widened portal areas were noted with increased numbers of inflammatory cells. The number of the interlobular bile ducts was decreased and some of them were damaged and surrounded by inflammatory cells (HE stain, $\times 200$). B) Histological findings of the salivary glands. Infiltration of numerous lymphocytes was noted around the intralobular duct. The ductal epithelium showed degeneration with interepithelial infiltration of a few lymphocytes (HE stain, $\times 165$).

with speckled and discrete speckled pattern, anticentromere antibody at a titer of 22.3 cutoff index; and negative for antibodies to Scl-70, SS-A, SS-B, DNA and smooth muscle. Viral markers for hepatitis B or hepatitis C were all negative. X-ray findings of the right hand showed destruction of the second and the third metacarpal bones (Fig. 1).

Histopathology of the liver specimen obtained by needle biopsy indicated an inflammation of the portal tract and damaged interlobular bile duct as shown in Fig. 2A. The number of bile ducts was also decreased. Histological findings did not show typical chronic non-suppurative destructive cholangitis; rather, findings were compatible with those of PBC.

Decreased excretion of tears at 4 mm wetting in Schirmer's test, decreased excretion of saliva at 10 ml in 30 min in the gum test, and massive infiltration of lymphocytes in biopsy specimen of salivary glands in lip as shown in Fig. 2B indicated complication by Sjögren's syndrome.

From these findings, the patient was diagnosed as having several diseases including asymptomatic PBC, incomplete CREST syndrome (Raynaud's phenomenon, sclerodactyly and telangiectasia), Sjögren's syndrome and arthritis.

The results of HLA typing of our patient and her parents are shown in Table 1. Her parents were consanguineous, and therefore, she had homozygous haplotypes of DR8 as well as HLA A11.1, B54, Cw1 and DQ1.

Discussion

We describe a patient with PBC-CREST overlap syndrome (Raynaud's phenomenon, sclerodactyly and telangiectasia) complicated by Sjögren's syndrome and arthritis. PBC is one of the autoimmune liver diseases characterized by progressive destruction of the intrahepatic bile ducts, and it has been known to be complicated by various types of autoimmune diseases such as Sjögren's syndrome, rheumatoid arthritis, Hashimoto's disease and progressive systemic sclerosis (2-4). Sjögren's syndrome is the most frequent complication in PBC; it occurs in 66 out of 113 (58%) patients with PBC (2). PSS, mainly the CREST type, does not occur as frequently as Sjögren's syndrome [10 out of 113 (9%) patients with PBC (2)]. We have diagnosed 7 patients with PBC-CREST overlap syndrome out of 47 (14.8%) patients with PBC observed in our clinic (15-18, 21, 22). Only 26 patients with PBC-CREST overlap syndrome have been reported in Japan (Table 2) and 16 of these (61.5%) showed complication with Sjögren's syndrome (Table 2). The

Table 1. HLA Typing of the Patient and Her Parents

	Father	Mother	Patient
HLA -A	24, 11.1	2, 11.1	11.1, 11.1
-B	52, 54	(54), 54	54, 54
-C	-, W1	(W1), W1	W1, W1
-DR	2, 8	9, 8	8, 8
-DQ	1, 1	3, 1	1, 1

PBC-CREST Overlap Syndrome

Table 2. Japanese Patients with PBC-CREST Overlap Syndrome

Author	Year	Age	Sex	PBC	PSS/ CREST	SjS	Arthritis	AMA	ACA	Others	HLA-DR
Miyasaka (5)	1977	54	f	s-PBC	RS	+	—	+		aSM	
Tanaka (6)	1981	54	f	s-PBC	PSS	+	—	—		aMic	
Daiguji (7)	1982	60	f	a-PBC	REST	+	—			aMic	2, W9
Moriyama (8)	1985	63	f	a-PBC	CRST	—	—	+			1, W9
Mita (9)	1986	64	f	a-PBC	RST	+	—	+	+	RF, aSS-A	2, 3
Kaneko (10)	1987	61	f	a-PBC	CREST	+	—	+	+	RF	3, W8
Sanada (11)	1988	42	f	a-PBC	PSS	+	—	+	+	RF	2, 4
Hirakata (12)	1988	65	f	a-PBC	CREST			+	+		
		47	f	s-PBC	CRST			+	+	aSM	
Koyama (13)	1989	60	f	a-PBC	CRST	—	—	+	+	aSS-A	W8, 9
		64	f	a-PBC	CREST	—	—	+	+		W8, 9
Ando (14)	1990	50	f	a-PBC	CREST			+	—	RF	
		59	f	a-PBC	PSS	+	—	+	+	aSS-A	
		48	f	a-PBC	PSS	+	—	+	—	RF	
		57	f	a-PBC	PSS	+	—	+	—	RF	
Onami (15, 16)	1990	73	f	a-PBC	CRST	+	—	+	+	RF, aDNA	4, 9
	1991	66	f	a-PBC	CREST	—	—	+	+		2, W8
Kojima (17)	1991	53	f	a-PBC	CREST	+	—	+	+	RF	1, 9
		64	f	a-PBC	RET	—	—	+	+	RF	4, 9
Onami (18)	1992	50	f	a-PBC	RT	+	—	+	+		1, 9
Mikami (19)	1992	52	f	a-PBC	CRST	+	—	+	—		W6, 9
Onami (20)	1994	57	f	a-PBC	CREST	+	—	+	+	RF	4, W8
	1994	60	f	a-PBC	R	+	—	—	+		4, W8
Takeda (21)	1994	51	f	a-PBC	RES	—	—	+	+		2, W8
		67	f	a-PBC	REST	—	—	+	+	RF	1, W6
Present case	1995	36	f	a-PBC	RST	+	+	+	+	RF	W8, W8

a: asymptomatic, s: symptomatic, PBC: primary biliary cirrhosis, PSS: progressive systemic sclerosis, C: calcinosis, R: Raynaud's phenomenon, E: esophageal dysfunction, S: sclerodactyly, T: telangiectasia, RS: R+S, REST: R+E+S+T, CRST: C+R+S+T, RST: R+S+T, CREST: C+R+E+S+T, RET: R+E+T, CRT: C+R+T, RT: R+T, RES: R+E+S, AMA: antimitochondrial antibody, ACA: anticentromere antibody, SjS: Sjögren's syndrome, aSM: anti-smooth muscle antibody, aMic: anti-microsome antibody, RF: rheumatoid factor, aSS-A: anti-SS-A antibody, aDNA: anti-DNA antibody.

present patient showed complication of not only Sjögren's syndrome but also arthritis with bone destruction. Acrolysis was found in 3 of 14 (21%) patients with PBC-CREST overlap syndrome and destructive arthropathy was found in 4 of 83 (4.8%) patients with PBC (23). Bone destruction, resembling rheumatoid arthritis, is seen in a few PSS patients with diffuse cutaneous scleroderma (24). Arthritis and Sjögren's syndrome as well as CREST syndrome were occasionally seen in patients with anticentromere antibodies (25). Based on these observations, Nishikai proposed a new syndrome, i.e., CRESTAS (CREST+Arthritis+Sjögren's syndrome), in 1986 (26). Following his proposal, the present patient could be diagnosed as having asymptomatic PBC-CRESTAS (RSTAS) overlap syndrome, which to our knowledge has been never reported.

HLA A1 and B8 were found in 5 of 10 (50%) non-Japanese patients with PBC-CREST overlap syndrome (23), but there is no literature on the HLA DR locus in PBC-CREST overlap syndrome in non-Japanese patient. HLA DR9 was found in 9 of 18 (50%) Japanese patients with PBC-CREST overlap syndrome and DR8 was also found in 8 of 18 (44.4%) Japanese patients with this syndrome (Table 2), suggesting that HLA DR9 and DR8 are associated with occurrence of PBC-CREST overlap syndrome. To date, there is no literature on the pre-

dominant HLA type in PBC-CRESTAS overlap syndrome. Further studies on patients with PBC-CRESTAS overlap syndrome are necessary to verify the association of HLA DR8 with this overlap syndrome. The present patient's HLA DR8 homozygosity was due to the consanguinity of her parents and might have increased the relative risk for occurrence of this PBC-CRESTAS overlap syndrome.

References

- 1) Kasukawa R. Primary biliary cirrhosis-CREST overlap syndrome. *Jpn J Clin Immun* **14**: 359, 1991 (in Japanese).
- 2) Culp KS, Fleming RC, Duffy J, Baldus WP, Dickson ER. Autoimmune associations in primary biliary cirrhosis. *Mayo Clin Proc* **57**: 365, 1982.
- 3) Murray-Lyon IM, Thompson RPH, Ansell ID, Williams R. Scleroderma and primary biliary cirrhosis. *Brit Med J* **8**: 258, 1970.
- 4) Reynolds TB, Denison EK, Frankl HD, Lieberman FL, Peters RL. Primary biliary cirrhosis with scleroderma, Raynaud's phenomenon and telangiectasia. *Am J Med* **50**: 302, 1971.
- 5) Miyasaka N, Otsuka M, Ito M, et al. A case of primary biliary cirrhosis with Sjögren's syndrome and sclerodactylia. *Jpn J Gastroenterol* **74**: 1392, 1977 (abstract in English).
- 6) Tanaka E, Imai K, Nosawa K, et al. A case report of primary biliary cirrhosis complicated with progressive systemic sclerosis, Sjögren's syndrome and Hashimoto's thyroiditis. *Kanzou (Liver)* **22**: 1473, 1981 (abstract in English).

- 7) Daiguji Y, Izumi N, Hattori K, Kawada K, Hasumura Y, Takeuchi J. A case of primary biliary cirrhosis associated with Sjögren's syndrome, incomplete CREST and cutaneous granuloma. *Kanzou (Liver)* **23**: 72, 1982 (abstract in English).
- 8) Moriyama M, Ikeda Y, Yasuda M, et al. A case of primary biliary cirrhosis complicated with CRST syndrome. *Jpn J Gastroenterol* **82**: 1398, 1985 (in Japanese).
- 9) Mita T, Yasue A. A case of CREST syndrome associated with Sjögren's syndrome. *Jpn J Clin Dermatol* **40**: 45, 1986 (in Japanese).
- 10) Kaneko K, Tsukimoto A, Oryu F, Hiden A, Shibata K, Obata H. CREST syndrome associated with Sjögren's syndrome and primary biliary cirrhosis. *Jpn J Clin Dermatol* **41**: 321, 1987 (in Japanese).
- 11) Sanada H, Ueno T, Takeda R, Nakanuma Y. A case of primary biliary cirrhosis complicated with progressive systemic sclerosis. *Jpn J Soc Inter Med* **77**: 1721, 1988 (in Japanese).
- 12) Hirakata M, Akizuki M, Miyachi K, et al. Coexistence of CREST syndrome and primary biliary cirrhosis. Serological studies of two cases. *J Rheumatol* **15**: 1166, 1988.
- 13) Koyama T, Kaneoka H, Yanase K, et al. Two cases of CREST syndrome complicated with primary biliary cirrhosis and their correlation with HLA-DR. *J Jpn Soc Inter Med* **78**: 61, 1989 (in Japanese).
- 14) Ando S, Takasaki Y, Hashimoto H, Namiyama T, Hirose S. Eight cases of primary biliary cirrhosis associated with rheumatic diseases. *Jpn J Clin Immun* **14**: 55, 1991 (Abstract in English).
- 15) Onami K, Kikuta Y, Nakagawa Y, et al. A case of primary biliary cirrhosis associated with Sjögren's syndrome, CRST syndrome and early gastric cancer. *Jpn J Clin Immun* **13**: 391, 1990 (abstract in English).
- 16) Onami K, Kikuta Y, Nishimaki T, Kasukawa R. Two sisters of progressive systemic sclerosis and CREST syndrome. *Jpn J Clin Immun* **14**: 439, 1991 (abstract in English).
- 17) Kojima T, Ohira Y, Ishibashi K, et al. Two patients of CREST-primary biliary cirrhosis overlap syndrome with common HLA types. *Jpn J Gastroenterol* **88**: 1479, 1991 (in Japanese).
- 18) Onami K, Umetsu Y, Nishimaki T, Kasukawa R, Moteki S, Yoshida H. Clinical studies on patients with anticentromere antibody. *Jpn J Clin Immun* **15**: 142, 1992 (abstract in English).
- 19) Mikami R, Kusunoki J, Kokuto M, Ishikawa A, Tsuchihashi K, Shibuya A. A case of primary biliary cirrhosis complicated with CREST syndrome and Sjögren's syndrome. *Kitasato Igaku (Kitasato Med)* **22**: 359, 1992 (in Japanese).
- 20) Onami K, Fukui A, Takahashi M, et al. Two patient with positive anticentromere antibody showing different clinical features of CREST syndrome or primary biliary cirrhosis. *Jpn J Gastroenterol* **91**: 2004, 1994 (in Japanese).
- 21) Takeda I, Igarashi S, Oyanagi H, et al. Two cases of asymptomatic primary biliary cirrhosis accompanied with CREST syndrome. *The Ryumachi* **34**: 767, 1994 (abstract in English).
- 22) Nishimaki T, Takagi T, Saitho K, Kasukawa R, Moritho T, Onami K. Primary biliary cirrhosis-CREST overlap syndrome is a genetically associated new disease? Clinicogenetical analysis of reported cases in Japan. *Igaku No Ayumi* **159**: 139, 1991 (in Japanese).
- 23) Clarke AK, Galbraith RM, Hamilton EBD, Williams R. Rheumatic disorders in primary biliary cirrhosis. *Ann Rheum Dis* **37**: 42, 1978.
- 24) Medsger TA. Systemic sclerosis and localized scleroderma. in: *Primer on the Rheumatic diseases*, Ninth edition. Schumacher HR, Ed. Arthritis Foundation, Atlanta GA, 113, 1988.
- 25) Steen VD, Ziegler GL, Rodnan GP, Medsger TA. Clinical and laboratory associations of anticentromere antibody in patients with progressive systemic sclerosis. *Arthritis Rheum* **27**: 125, 1984.
- 26) Nishikai. Diseases and HLA of anticentromere antibody positive patients. *Ketsugososhiki* **18**: 264, 1986 (in Japanese).