Mod Rheumatol (2001) 11:168–171

CASE REPORT

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Systemic sclerosis in two second cousins: a case report

Received: September 20, 2000 / Accepted: January 9, 2001

Abstract We describe two second cousins who developed systemic sclerosis. These patients had major histocompatibility complex (MHC) class I alleles in common, including A2, A26(10), B60(40), and Cw7 as well as class II allele DR2. This DR2 was thought to be associated with the onset of the disease. Our patients both experienced a limited type of systemic sclerosis, but the expression of autoantibodies was different.

Key words HLA · Relatives · Systemic sclerosis

Introduction

Systemic sclerosis is a connective-tissue disease with a wide range of clinical manifestations, including varying degrees of skin and internal organ involvement. The cause remains unknown, although immunogenetic evidence suggests that some persons are inherently predisposed to develop the disorder. There are a few reports of familial occurrence.[1] Certain chemicals and metabolic or hormonal factors are thought to trigger systemic sclerosis in genetically susceptible people. There is evidence for the influence of a diverse range of environmental agents from silica to cocaine.[2] On the other hand, there is also thought to be an association with human leukocyte antigen (HLA) class I and II alleles, specifically DP, DQ, and DR, and the major histocompatibility complex (MHC). Molecular genetic research has found susceptibility alleles and discriminated between DP, DQ, and DR. As yet, there is no clear pattern of association between specific MHC antigens or alleles and systemic sclerosis.[3] However, there is agreement that class II rather than class I alleles are involved.[1] To clarify the association between HLA and systemic sclerosis, case reports may be important. In this paper, we describe two systemic sclerosis patients who are second cousins, i.e., their fathers were first cousins.

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Case report

Case 1

A 55-year-old Japanese woman was admitted to Niigata Prefectural Senami Hospital with polyneuropathy in July 1995. Her family history showed no marriage of consanguinity. She had developed Raynaud phenomenon and swollen hands in September 1989. She was well until August 1989. Her progrees was followed by the hospital, and skin sclerosis was noticed in April 1990. Follow-up tests showed that she was ANA-positive (1:320 speckled pattern), anti-SS-A antibody positive, anti-RNP antibody positive, and anti-Scl-70 antibody negative. In 1995, a finger-tip ulcer and a cough were noted on admission to the hospital. Physical examination showed blood pressure of 104/68 mmHg, a regular heart beat of 84/min, and a temperature of 35.8°C. The skin felt hard on both hands and forearms. On lung and cardiac examinations, fine crackles were noticed from both lower lungs. An abdominal examination was normal. Her skin was taut and indurated, and there were limitations to both fist closure and finger extension. The skin thickening was not present on the trunk, and she was considered to have a limited type of systemic sclerosis. Laboratory studies revealed a leukocyte count of 8900/mm^3, hemoglobin of 10.8 g/dl, platelet count of 43.3×10^4 mm^3, and erythrocyte sedimentation rate (ESR) of 35 mm/h (Westergren method). Urinalysis detected microscopic hematuria without proteinuria and with a creatinine clearance rate (Ccr) of 75.7 ml/min. Electrolytes were normal. Other laboratory values were CRP $<$ 0.1 mg/ml, IgG 2720 mg/dl, IgA

991 mg/dl, IgM 114 mg/dl, C_3 100.0 mg/dl, C_4 16.6 mg/dl, and CH50 51.7 U/ml. Hypergammaglobulinemia was recognized. The rheumatoid factor (RF) was under 5 IU/ml (negative). She was positive for Anti-SS-A antibody, anti-SS-B antibody, and anti-RNP antibody, and negative for anticentromere antibody, anti-dsDNA antibody, anti-Sm antibody, and anti-Scl-70 antibodies. The titer of anti-RNP antibodies was low (18.3 index, normal range 0–15 index). Her ANA was 1:80. Her creatinine kinase was normal and there was no muscle weakness. In addition, she had no symptoms and no laboratory findings of systemic lupus erythematosus, and therefore she did not fulfill the diagnostic criteria of the MCTD Research Committee of the Japanese Health and Welfare Ministry (Kasukawa's criteria).[4] The tissue type of the patient is shown in Table 1. An abdominal ultrasonogram showed one small gall bladder stone. An electrocardiogram and a chest X-ray were normal. Chest computed tomography (CT) revealed pulmonary fibrosis in the bilateral lower lungs. To treat the polyneuropathy, high-dose prednisolone (60 mg daily) and prostagrandine were started in June 1995. The prednisolone was tapered to 7.5 mg/day and she was discharged in June 1997 in good general health. The polyneuropathy had improved but had not disappeared.

Case 2

A 41-year-old Japanese woman was admitted to Niigata University Hospital because of Raynaud phenomenon and swollen hands in October 1996. This woman's father was the first cousin of the previous patient's father, making the women second cousins. She lived about 30 km away from case 1, but both of them were housewives and their environmental factors were similar. This patient was well until March 1995, when her hands swelled. A finger-tip ulcer and a dry cough occurred in February 1996. Physical examination showed a blood pressure of 104/60 mmHg, a regular heart beat of 68/min, and a temperature of 35.3°C. Her face was mask-like and the skin of the hands, forearms, and feet was hard. On lung and cardiac examinations, fine crackles were noticed from both lower lungs. An abdominal examination was normal. The skin thickening was not present on the trunk, and she was considered to have a limited type of systemic sclerosis. Laboratory studies on admission revealed a leukocyte count of 5300/mm^3, hemoglobin of 11.7 g/dl, platelet count of 17.2 $\times$ 10^4 mm^3, and ESR of 12 mm/h. Urinalysis, electrolytes, and renal function were normal, with a Ccr of 134.2 ml/min. Other laboratory values were CRP $<$ 0.1 mg/ml, IgG 1640 mg/dl, IgA 292 mg/dl, IgM 144 mg/dl, C_3 62.6 mg/dl, C_4 15.8 mg/dl, and CH50 33 U/ml. The RF level was 10.2 IU/ml (positive). Anti-SS-A antibody, anti-SS-B antibody, anti-Sm antibody, anti-dsDNA antibody, anti-RNP antibody, and anti-centromere antibody were all negative. Anti-Scl-70 antibody was positive, and ANA was 1:2560 (speckled pattern). The tissue type of the patient is shown in Table 1. An electrocardiogram and a chest X-ray were normal. In a Barium enema study of the esophagus, no delay was observed. However, chest CT showed pulmonary fibrosis in both lower lungs. Low-dose prednisolone (20 mg daily) and D-penicillamine at 100 mg daily was started in November 1996. The prednisolone was tapered to 7.5 mg daily, and the patient was discharged in December 1996. Her general condition was good, but the Raynaud phenomenon and skin sclerosis remained.

Table 1. HLA typing of two patients

HLA typing	Patient 1	Patient 2
A locus	A2, A26(10)	A2, A26(10)
B locus	B48, B60(40)	B35, B60(40)
C locus	CW7	CW3, CW7
DR locus	DR2	DR2, DR8

Discussion

Systemic sclerosis is uncommon and its etiology is unknown. However, the association of several different antibodies with clinical subsets of scleroderma patients suggests an immunological pathogenesis. Scleroderma has been associated with exposure to vinyl chloride, silica, contaminated rape seed oil, L-triptophan, uranium, quartz, and some other agents.[2] Both of our patients were housewives, but because the places they lived in were quite different, it was difficult to determine the influences of environmental factors. Immunogenetic associations were studied first in families, and later by an analysis of the prevalence of MHC alleles associated with systemic sclerosis. The reports of familial occurrence are shown in Table 2. Systemic sclerosis has different manifestations, which may or may not have familial links.[5] In our cases, a relative had autoimmune disease. Many studies have investigated systemic sclerosis and MHC antigens, but the pattern of association is still not clear. The main focus of interest has been on MHC class II alleles and some of the class I alleles.[1] In the United States, early reports found a weak positive association with HLA Bw35 and DR1.[6] In Canada, early reports showed that systemic sclerosis had a strong association with DR5.[7] Early reports from Europe found a link with haplotype HLA A1-B8-DR3.[8] In the United Kingdom, weak associations were found with HLA A1-B8-DR3, Bw35, and DR1, but there was a strong association with DR5.[9] In Australia, two

Table 2. Autoantibodies of two patients

Autoantibodies	Patient 1	Patient 2
ANA	$\times$80	$\times$2560 (speckled)
RF	(−)	(+)
Anti-SS-A	(+)	(−)
Anti-SS-B	(+)	(−)
Anti-Sm	(−)	(−)
Anti-dsDNA	(−)	(−)
Anti-RNP	(+)	(−)
Anti-centromere	(−)	(−)
Anti-Scl-70	(−)	(+)

reports showed a strong association with DR5. For white people of European descent, there was a strong association with DR1, DR5, and DR5. In Finland, one report showed that HLA B8, DR3, and DR52 were higher in patients with systemic sclerosis.[10] On the other hand, studies of Japanese patients showed that the disease was associated with HLA-DR2 and DR4.[11] This diversity of findings is recognized as ethnic and genetic variability. Recently, a molecular genetic investigation of systemic sclerosis discriminated between MHC class I and II alleles. Certain HLA-DRB1 and/or DQB1 alleles correlated more strongly with the specific antibody profile of systemic sclerosis. In the Japanese population, the frequency of the DR15 antigen was higher among patients with systemic sclerosis. It was proposed that the primary association would be to an amino acid sequence shared by DR11, DR15, and DR8 at position 67–70 in the first domain of the DRB1 coded β-chain.[12] Another study of Japanese patients found an increased frequency of the haplotype DRB1*1502-DRB5*0.02 in some patients with diffuse disease.[13]

Another study of Japanese patients showed an increased association with HLA-DR2, which confirmed previous studies.[14] This report also showed that HLA DR2 was associated with diffuse systemic sclerosis and DR1 with limited systemic sclerosis. Our two patients had diffuse disease, and both had DR2. The study showed that the frequency of DR2 was significantly higher in patients with anti-Scl-70 antibodies, and that anticentromere antibodies were not detected in patients with DR2, but only in those with DR1. In a Choctaw Native Americans study, a case-control study of 12 Choctaw systemic sclerosis cases and 48 matched controls revealed no significant differences in environmental exposures, but all the matched systemic sclerosis cases possessed HLA-DRB1*1602;DQA1*0501;DQB1*0301, which was significantly associated with systemic sclerosis. In contrast, among a population of 5000 full-blooded Choctaws living in the southeastern United States where the Oklahoma Choctaw originated, no cases of systemic sclerosis were found despite similar frequencies of the same HLA haplotype.[15] Stimultaneous genealogical studies unequivocally traced 20 of 25 known contemporary Choctaw systemic sclerosis cases to five founding families in the late 1700s, suggesting that common founders may have introduced the disease gene into the Choctaw population about ten generations ago. Because of the high disease prevalence and the evidence of a founder effect among the Oklahoma Choctaw, this population was well suited for a study to identify systemic sclerosis susceptibility genes. Researchers analyzed microsatellite markers in the three candidate regions and identified a shared haplotype on chromosome 15q containing the fibrillin 1 (FBN1) gene that is significantly overexpressed in Choctaw systemic sclerosis cases. FBN1 mutations in humans are known to cause Marfan's syndrome. The relationship between the gene polymorphism of FBN1 and systemic sclerosis has not been fully investigated, and further analysis is needed in this study.[16] Another recent report showed that DRB1*0101, *0405, and *1302 alleles were associated with high anticentromere antibody titers in the Japanese population.[17] Neither of our patients had detectable anticentromere antibodies. Anti-Scl-70 antibodies were detected in patient 2, but not in patient 1. Both had HLA-DR2, and their MHC class I was very similar. However, this MHC class I portion (A2, A26(10), B60(40), and Cw7), has not been found to be associated with systemic sclerosis. The Collection of additional well-documented familial cases of scleroderma is necessary. Although the MHC of our two cases was similar, the clinical manifestations and antibodies were different. The HLA differences may contribute to the differences in clinical and serological manifestations, and these differences may indicate that the cause of systemic sclerosis is multifactorial, and that other genetic and environmental factors may affect the clinical manifestations.

The fact that there are now several reports of familial scleroderma, including these two cases, may encourage further research into a possible genetic predisposition to the disease.

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