CASE REPORT

Mixed Connective Tissue Disease Associated with von Recklinghausen’s Neurofibromatosis


Abstract

We report a 42-year-old Japanese woman with Recklinghausen’s neurofibromatosis 1 (NF1) who developed mixed connective tissue disease (MCTD). Previously experiencing good health without an increase in subcutaneous nodules, she presented with Raynaud’s phenomenon, swollen hands and polyarthralgia. Clinical examination revealed a high titer of anti-RNP antibody, and she was thus diagnosed as having MCTD. She was treated with oral prednisolone (10 mg/day) and her symptoms improved rapidly. Since the association of MCTD and NF1 has not been reported previously, we concluded that this association is rare. We also discussed the association of NF1 and autoimmune diseases including MCTD.

Key words: anti-UlRNP antibody, HLA-DR2, autoimmune disease

Case Report

A 42-year-old woman was referred to our department on March 13, 1997, for Raynaud’s phenomenon. Since her twenties, she had noticed small skin nodules with pigmented lesions over her body. The skin nodules on her back had increased to the size of 0.5–1 cm by the time she was 40. Six months prior to her visit to our department, she had experienced generalized arthralgia, hair loss, swollen hands and Raynaud’s phenomenon.

On physical examination, her height was measured at 154 cm and body weight was 44 kg. She was afebril and her BP was 120/70 mmHg. Her oral mucous membrane was not dry. There were no abnormal findings in her chest and abdomen. Her extremities were cyanotic and cold. She had sclerodactyly as well as swollen hands. Her metacarpophalangeal (MP) joints of both fingers were swollen. Skin examination revealed cafe au lait spots and subcutaneous nodules (Fig. 1, 0.5–1 cm in diameter) on her trunk. She was thus diagnosed as having von Recklinghausen’s neurofibromatosis (NF1).

The laboratory findings were as follows. There was no abnormality in urinalysis. Complete blood cell count demonstrated mild anemia (Hg 10.4 g/dl), but neither leukocytopenia nor thrombocytopenia was noted. Blood chemistry analysis showed her liver, kidney functions, and muscle enzymes to be normal. Serological tests revealed some autoantibodies. Rheumatoid factor was negative. Anti-nuclear antibody (ANA) was positive at a titer of 1:2,560 with speckled pattern. Although the anti-DNA Ab (RIA) was at borderline levels (12.4 IU/ml; <7.0), her serum level of complement (CH50) was normal (53 U/ml). Antibody to extractable nuclear antigen for U1-RNP was positive with a titer >256X, but those for Sm and Scl-70 were negative. Serum immune complex was not detected. Serologic HLA Class I (A, B and C) and Class II (DR) typing was HLA-A2 A31; B35 B62; Cw 3; DR 2 DR8.

X-ray analysis of hands showed no abnormalities of the joints.

The diagnosis of MCTD was made according to the diagno-
sis criteria by Japan Ministry of Health and Welfare (3). She was administered prednisolone (10 mg/day) plus beraprost sodium (40 μg/day) orally, after which her symptoms were improved.

Discussion

Mixed connective tissue disease (MCTD) was originally described as a syndrome that consists of a combination of features found in systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and polymyositis/dermatomyositis (PM/DM) with a high-titer of anti-U1nRNP antibody (1, 4). Controversy has continued regarding whether MCTD is a distinct entity (undifferentiated) or an overlap syndrome differentiated into either SLE, SSc, or RA (5, 6). In this patient, clinical manifestations compatible with SLE, SSc, and PM/DM were not seen and she met none of the ACR criteria for individual disease. On the other hand, NF1 is the most common form and presents mainly peripheral involvement: cafe-au-lait spots, skeletal involvement, and cutaneous neurofibromas (2). As described in our patient's history, signs of neurofibromatosis are more evident after puberty. The pathogenesis by which MCTD is associated with NF1 is unknown. Gerosa et al (7) investigated the immunological parameters such as complement, anti-DNA antibodies, and immune complex (IC) in patients with NF1. Interestingly, the data showed borderline levels of anti-DNA Ab and IC in some patients. The association of autoimmune diseases such as membranous glomerulonephritis and RA has been demonstrated in NF1 (8–10). Also, the association of NF1 in SLE was reported in 3 cases (11, 12). However, the association of MCTD has not been demonstrated in NF1 up to the present time. Associations between certain HLA types and MCTD have been reported by several investigators (3). Gendi et al (13) demonstrated that non-differentiated MCTD is associated with HLA-DR2 or DR4. This genetic factor (HLA-DR2) may contribute to the occurrence of MCTD in the present patient. Alternatively, MCTD manifesting in the presence of NF1 may be coincidental. The details of the relationship between these two diseases are unknown.

In conclusion, this is the first case report demonstrating an association between MCTD and von Recklinghausen's neurofibromatosis, also raising the question as to why this association has not been seen more often.

References

4) Smolen JS, Steiner G. Mixed connective tissue disease: to be or not to be? Arthritis Rheum 41: 768–777, 1998 (see comments).