Mixed Connective Tissue Disease with Severe Pulmonary Hypertension and Extensive Subcutaneous Calcification

Osamu Itoh, Tomoe Nishimaki, Masayuki Itoh, Hiromasa Ohira, Atsushi Irisawa, Syunji Kaise and Reiji Kasukawa

The results of the autopsy of a 38-year-old female with mixed connective tissue disease who had suffered from painful subcutaneous calcification in her buttocks and extremities for 14 years and died from rapidly progressive pulmonary hypertension are reported. On autopsy, her heart and lungs revealed changes of severe pulmonary hypertension with intimal thickening and plexiform lesions in the small pulmonary arteries which had resulted in the collapse of both lungs and caused marked dilatation and hypertrophy of the right ventricle of the heart. Microscopic examinations of the subcutaneous calcified tissues indicated that the calcification may have been caused by repeated panniculitis.

Key words: mixed connective tissue disease (MCTD), pulmonary hypertension (PH), calcinosis, pericarditis

Introduction

Mixed connective tissue disease (MCTD) is a disease with features which overlap those of systemic lupus erythematosus (SLE), scleroderma and polymyositis and is associated with the presence of a high serum titer of anti-U1 RNP antibodies. It has been classified as a benign disease entity since it was first described by Sharp et al (1). Recent reports however, have suggested that MCTD may be closely associated with pulmonary hypertension (2, 3). In this report, we describe the autopsy findings of a subject with MCTD complicated by severe pulmonary hypertension, who had suffered from extensive subcutaneous calcification in the buttocks and lower extremities. This type of calcification has rarely been reported in MCTD.

For editorial comment, see also p 347.

Case Report

A 38-year-old woman was healthy until the age of 24, when she developed a low grade fever, polyarthritis, swollen fingers, Raynaud’s phenomenon and muscle weakness. From her first admission to our department in June 1980 until her fifth and last admission in May 1994, her major clinical features of MCTD were Raynaud’s phenomenon, swollen fingers, polyarthritis of the knee, wrist, elbow and hand joints, muscle weakness of the extremities, digital pitting ulcers, pleuritis and pericarditis. Major serological abnormalities observed throughout the 14-year clinical course were seropositivity for anti-nuclear antibodies, anti-U1RNP antibodies, anti-dsDNA antibodies and Rheumatoid factor. The abnormal laboratory findings observed at her first admission were, a low level of complement plasma level of complement (CH50) (6.4/ml) and elevated levels of myogenic enzymes such as creatine kinase (2,355 U/ml) and lactate dehydrogenase (LDH) (2,155 Wr. U); these values returned to normal within 3 months, after treatment with corticosteroids and immunosuppressants. Renal dysfunction, leucocytopenia, or thrombocytopenia were not observed at any point in her clinical course.

Throughout the clinical course, the subject had been treated with betamethasone at 1-2 mg/day and azathioprine at 50-100 mg/day which stabilized her condition. When her illness flared up, most often manifested by pericarditis, pleuritis and polyarthritis with fever, she was admitted and administered methylprednisolone pulse therapy. Other than the corticosteroids and immunosuppressants, digoxin, furosemide, nifedipine and prostaglandin E1 were used for the treatment of her cardiovascular symptoms.

The symptom of subcutaneous induration, 2-4 cm in diam-

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Figure 1. A plain X-ray of the pelvis taken in February 1994 revealed diffuse subcutaneous calcification in the patient.

eter, was first observed in October 1980 near her left knee joint. Thereafter, the subcutaneous indurations occurred repeatedly on the back of both legs and buttocks, and small calcifications near the left femoral head and the right buttock were detected by a pelvic X-ray taken in March 1983. The subcutaneous calcifications were distributed diffusely on her buttocks and legs, as shown in Fig. 1.

The initial clinical evidence of pulmonary hypertension, shortness of breath on exertion and an accentuated second pulmonic sound, was first observed in September 1993. Echocardiography performed in February 1994 revealed right ventricular hypertrophy and enlargement, leading to the diagnosis of pulmonary hypertension (PH). In May 1994, the subject was admitted to our department due to aggravated dyspnea, marked cardiomegaly as detected on a chest X-ray and massive pericardial effusion as detected by echocardiography, indicating pericarditis due to exacerbation of the MCTD and a rapid progression of PH. Puncture of the pericardium with aspiration of 500 ml of bloody pericardial fluid under echocardiography monitoring, followed by methylprednisolone pulse therapy resulted in a reduction in the severity of her pericarditis (cardiothoracic ratio (CTR) 78% → 55%) and hypoxia (partial pressure of oxygen (PaO₂) 48.7 mmHg → 67.2 mmHg). Data obtained on biochemical and immunological analysis of the pericardial fluid are compared with the data from the serum analysis of the subject obtained on the same day (Table 1). A higher titer of anti-U1RNP antibody and a markedly lower titer of complement CH50 in the pericardial fluid compared with those in the serum were noted. Right cardiac catheterization, performed on July 5, 1994, revealed an increased mean pulmonary artery pressure of 86 mmHg and a decreased cardiac output of 2.34 l/min, confirming the presence of severe PH in the subject. Treatments including inhalation of O₂ and administration of calcium antagonists, diuretics and digitalis were not effective and the patient died on November 2, 1994.

Histopathological examination of the autopsied lungs, heart and the subcutaneous calcifications revealed the following; 1) severe damage of the pulmonary arteries; intimal thickening (Fig. 2) and plexiform lesions (Fig. 3) in the small arteries, from 45 μm to 175 μm in diameter, and collapse of the lungs, 2) severe fibrous pericarditis and marked dilatation and hypertrophy of the right ventricle of the heart, 3) severe panniculitis (Fig. 4) in her buttocks and the lower extremities with focal calcifications and ossifications (Fig. 5).

Table 1. Biochemical and Immunological Analysis of the Serum and Pericardial Fluid

<table>
<thead>
<tr>
<th></th>
<th>Serum</th>
<th>Pericardial fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein (g/dl)</td>
<td>7.3</td>
<td>6.2</td>
</tr>
<tr>
<td>Albumin (%)</td>
<td>47.1</td>
<td>52.3</td>
</tr>
<tr>
<td>γ-Globulin (%)</td>
<td>26.4</td>
<td>24.3</td>
</tr>
<tr>
<td>Antibodies to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dsDNA antigen (U)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>U1RNP antigen (U)</td>
<td>146.6</td>
<td>218.4</td>
</tr>
<tr>
<td>β2GPI-cardiolipin</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>CH50 (U/ml)</td>
<td>51.3</td>
<td>&lt;10</td>
</tr>
<tr>
<td>C3 (mg/dl)</td>
<td>62</td>
<td>36</td>
</tr>
<tr>
<td>C4 (mg/dl)</td>
<td>26</td>
<td>13</td>
</tr>
<tr>
<td>Immune complex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clq (μg/ml, N &lt;2.9)</td>
<td>8.1</td>
<td>13.6</td>
</tr>
<tr>
<td>anti-C3d (μg/ml, N &lt;9)</td>
<td>&lt;9</td>
<td>&lt;9</td>
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Discussion

Since its first description by Sharp et al in 1972 (1), MCTD has been recognized worldwide as one rheumatic disease entity among the various inflammatory connective tissue diseases. The characteristic features, initially described for the disease (4), were the presence of a high titer of anti-nRNP antibodies in the patients’ sera and a milder clinical course than that of SLE or scleroderma and responsiveness to small doses of corticosteroids. In Japanese patients, diagnoses of MCTD have been made according to the internationally accepted diagnostic criteria proposed by The Research Committee of MCTD of the Japanese Ministry of Health and Welfare (5), and one of the recent discoveries in the clinicopathology of MCTD is a strong association of the disease with a high frequency of development of PH. The prognosis of MCTD patients with PH is extremely poor, and the mean period from the diagnosis of PH to death has been noted to be less than 5 years (3).

The case presented herein is that of a typical MCTD patient whose symptoms fulfilled the diagnostic criteria of the Research Committee of MCTD. Thirteen years after the diagnosis of MCTD was made, the patient developed PH, and she died 14 months after the diagnosis of PH. The histopathological analysis of her autopsied lung specimens revealed severe PH with intimal thickening and plexiform lesions in the small pulmonary arteries. Foci of inflammatory cell infiltration and interstitial pneumonitis in the lesions were sparse as shown in Fig. 2. The presence of plexiform lesions has been considered to be one of the characteristic histopathological findings of PH in MCTD patients (2), and has been thought to be the result of a rapid increase in the pulmonary artery pressure (6). Collapse of both lungs and marked dilatation and hypertrophy of the right
ventricle of the heart as clearly observed in the autopsied specimens, confirmed the rapid progression of PH in the present patient.

Autoimmune mechanisms such as evidenced by the presence of antibodies to U1RNP, endothelial cells or cardiolipins have been assumed to play a role in inducing PH in association with connective tissue diseases by damaging pulmonary endothelial cells (7). However, other possibilities such as the overproduction of endothelin-1 from pulmonary arterial endothelial cells by unknown mechanisms, which could induce hyperplasia of the endothelial cells and the myointimal cells of pulmonary arteries, as observed in patients with primary PH (8), have also been proposed (9). The serum of the present patient was negative for anti-endothelial cells or anti-cardiolipin antibodies, and serum endothelin-1 measured at the time of diagnosis of PH progression was also within the normal range, in contrast to the presence of high titters of anti-U1RNP antibodies in the serum and also in the pericardial fluid. Concerning the relationship between PH and pericarditis, a statistically higher frequency of pericarditis in MCTD patients with PH than in those without PH has been reported (10). In fact, in the present case, the rapid progression of PH diagnosed in May 1994 was thought to be associated with the exacerbation of pericarditis. These observations indicate that the presence of high titters of anti-U1RNP antibodies might be associated with the development of PH, but elucidation of the precise mechanisms requires further investigation.

An uncommon symptom found in this patient was subcutaneous calcification, which was distributed diffusely in her buttocks and lower extremities. The serum levels of calcium, phosphate and parathyroid hormones in the patient were within the normal range at each examination, indicating that the components of the disease spectrum. No treatment was administered for calcification in our patient with MCTD based on its association with the patient's left knee joint, and found the calcific tissues which were excreted with connective tissue diseases (11). We used polarizing microscopy to analyze the calcific tissues which were excised from the skin of the patient’s left knee joint, and found the calcific tissue to be composed of hydroxyapatite. A dystrophic type of calcification in connective tissue diseases is frequently seen in scleroderma (12), CREST syndrome (13), dermatomyositis (14) and to a lesser extent in SLE (15), and is usually limited to the fingers in scleroderma or CREST syndrome, to the shoulder or hips in dermatomyositis and to the cutaneous lupus lesions in SLE. In contrast to patients with limited forms of calcification, patients exhibiting diffuse subcutaneous calcification in association with connective tissue diseases have been infrequently reported (16–18), and only one such case in association with MCTD, to the best of our knowledge, has been reported by Baurle and Hornstein (19). The precise mechanisms underlying diffuse subcutaneous calcification in association with connective tissue diseases are obscure, but there are several hypotheses such as damaged tissue proteins, serving as a nidus (20), or increasing alkalinity (21) might enhance the level of ectopic calcium deposition, or local ischemia induced by pressure exerted by hypertrophied fat cells resulting from steroid administration for a long period might result in diffuse ectopic calcinosis (22). For the present patient, the subcutaneous calcification, clinically observed in association with panniculitis, was also confirmed histopathologically in the autopsied specimens. Panniculitis in association with ectopic dystrophic calcification has been observed in various connective tissue diseases (23, 24), and repeated episodes of panniculitis appear to have caused the diffuse ectopic subcutaneous calcification in our patient.

The efficacy of orally administered aluminium hydroxide (25) or bisphosphonate (26) has been reported for the dystrophic type of calcification; however, the treatment of the dystrophic type of calcification in connective tissue diseases often varies depending on the innocuous aspects of the serious components of the disease spectrum. No treatment was administered for calcification in our patient with MCTD based on its being an innocuous aspect of a life-threatening disease. Spontaneous dissolution has been documented in a case of SLE (17).
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