An Adult Case of Mixed Connective Tissue Disease Associated with Perimyocarditis and Massive Pericardial Effusion

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SUMMARY

We report the case of a 55-year-old woman with mixed connective tissue disease (MCTD), who developed perimyocarditis associated with massive pericardial effusion. The diagnosis of MCTD was based on clinical and serological findings. We confirmed myocarditis by right ventricular endomyocardial biopsy. The pericardial effusion gradually disappeared after the administration of prednisolone. Although there have been several reports of cardiac disease in adult MCTD, few cases of adult MCTD having perimyocarditis associated with massive pericardial effusion have been reported.

Additional Indexing Words:
Mixed connective tissue disease (MCTD)

MIXED connective tissue disease (MCTD), described by Sharp et al in 1972,1) is a rheumatic syndrome characterized by overlapping features of systemic lupus erythematosus, progressive systemic sclerosis and polymyositis and by high titers of antibody to ribonuclease-sensitive ribonucleoprotein (RNP). It has been distinguished from other connective tissue diseases by a relative lack of renal involvement, its steroid responsiveness and benign prognosis.1) Pericarditis and congestive heart failure occur as the cardiovascular manifestations of MCTD in childhood.2) However, reports of cardiac disease in adult MCTD comprise only a few cases.3),4) In this communication, we describe a 55-year-old woman with MCTD
who developed perimyocarditis associated with a massive pericardial effusion.

**Case Report**

A 55-year-old woman was admitted to the Fukui Cardiovascular Center on October 8, 1982 with the chief complaint of dyspnea. Episodes of Raynaud’s phenomenon, polyarthritis involving the elbow, knee and wrist joints and polymyalgia involving the proximal muscles had occurred for a few months prior to admission. On August 15 and September 12, 1982, episodes of a low grade fever (37–38°C) of unknown origin had occurred. For 2 weeks prior to admission, she had complained of progressively increasing dyspnea and orthopnea.

Pertinent physical findings at admission included a temperature of 35.8°C, blood pressure of 200/80 mmHg, pulse rate of 80/min, anemic palpebral conjunctiva, dilatation of the jugular vein and enlarged cardiac dullness. The liver and spleen were not palpable. Although Raynaud’s phenomenon and myalgia of the proximal groups existed, no scleroderma, pigmentation of the skin, poikiloderma, deformities of the joints or muscle weakness was found.

A complete blood count showed a hemoglobin of 9.8 g/dl, a red blood cell count of 344×10⁴/cmm, a hematocrit of 31%, a white blood cell count of 3400/cmm and a platelet count of 8.1×10⁴/cmm. The bone marrow was hypocellular. Fibrinogen was 360 mg/dl. Serum creatinine, blood urea nitrogen and uric acid were within normal limits. The total protein concentration was 7.4 g/dl with albumin, 47.4%; α₁-globulin, 3.7%; α₂-globulin, 8.2%; β-globulin, 6.8%; γ-globulin, 33.9%. Serum glutamic-oxaloacetic transaminase was 16 Karmen units (normal, 11 to 27 Karmen units), serum glutamic-pyruvic transaminase 6 Karmen units (normal, 6 to 19 Karmen units), creatine phosphokinase 24 U/L (normal, 16 to 68 U/L), aldolase 4 u (normal, 3 to 8 u) and creatine 1.2 mg/dl (normal, 0.2 to 0.9 mg/dl). Renal function tests including the phenolsulfonphthalein test, renal scan and renogram were normal. The daily urinary excretion of creatine was 150 mg. The erythrocyte sedimentation rate was 50 mm/hour. C-reactive protein and rheumatoid factor tests were both positive. However, serologic test for syphilis, LE test, LE cell, and direct and indirect Coombs’ test were negative. The fluorescent antinuclear antibody test was positive with a speckled pattern at a titer of 1:10240, and anti-DNA antibody was weakly positive at 1:11. There were also antibodies to RNP at a titer of 1:81920, but none to ribonuclease-resistant Sm antigen. Antibodies to the myocardium were also positive, and both the thyroid and microsome tests were positive with titers of 1:1600. The IgG was 3210 mg/dl, IgA 320 mg/dl, IgM 178 mg/dl, CH₅₀
Fig. 1. A: Chest roentgenogram on admission (October 8, 1982) showing marked cardiomegaly with a CTR of 75% and normal lung fields. B: Chest roentgenogram obtained during the administration of prednisolone (May 13, 1983). CTR is decreased to 59%.

Fig. 2. Electrocardiogram on admission showing a delta wave and depressed ST segment in I, aV L, V 4, V 5, V 6.

26.7 u/ml, C 3 76 mg/dl and C 4 32 mg/dl. Pulmonary function tests including a spirogram and pulmonary perfusion scan were normal. Arterial blood gases obtained while the patient was breathing room air showed a pH of 7.46, an arterial carbon dioxide tension (PaCO 2 ) of 37 mmHg and oxygen tension (PaO 2 ) of 75 mmHg.

A roentgenogram of the chest on admission showed marked cardiomegaly (CTR 75%), but there was no interstitial shadow in the lung fields (Fig. 1A). An electrocardiogram on admission showed a delta wave on the QRS complexes and a depressed ST segment in I, aV L, V 4, V 5, V 6 (Fig. 2). An echocardiogram performed immediately after admission showed a “swinging heart” by the massive pericardial echo-free space anterior to the right ven-
Fig. 3.  A:  Echocardiogram on admission (October 8, 1982), demonstrating "swinging heart" by the massive pericardial echo-free space anterior to the right ventricle and posterior to the left ventricle, fluttering of the anterior mitral leaflet at diastole and no aortic valve abnormalities.  B:  Echocardiogram obtained during the administration of prednisolone (May 13, 1983).  The massive pericardial echo-free space has disappeared.  AO=aorta; LA=left atrium; RV=right ventricle; MV=mitral valve; PE=pericardial effusion; LV=left ventricle.

From these results, pericarditis with a massive pericardial effusion was suspected, and pericardial paracentesis was performed.  Three hundred ml of straw-yellow colored fluid was obtained.  The fluid contained 4800 mg/dl protein, 107 mg/dl sugar and no bacteria (including mycobacterium tuberculosis).  Cytological examination of the fluid revealed that it was Papanicolaou’s class 1.  An echocardiogram after pericardial paracentesis still demonstrated a massive pericardial echo-free space, but the "swinging heart" signs had disappeared.
An aortogram made on the 60th hospital day showed aortic regurgitation of Sellers' grade II. However, abnormal levogram findings were not detected. The histopathological findings of a myocardial sample, obtained by right ventricular endomyocardial biopsy at catheterization, revealed disorganization and fragmentation of myocytes, a scarcity of myofibrils and myocytolysis. Fatty degeneration and perivascular and diffuse interstitial fibrosis were also found. These findings were suggestive of myocarditis (Fig. 4).

Daily administration of 30 mg prednisolone was promptly started, and the polyarthralgia and polymyalgia improved several days later. The massive pericardial echo-free space on the echocardiogram gradually disappeared (Fig. 3B), and cardiomegaly on chest roentgenogram was decreased (Fig. 1B). The pericardial effusion has not appeared since the administration of prednisolone and the dose of prednisolone has been tapered gradually to 5 mg every other day.

Fig. 4. Photomicrographs of the myocardium obtained by right ventricular endomyocardial biopsy. A: Disorganization of myocytes and perivascular fibrosis are shown. B: Fragmentation of myocytes and diffuse interstitial fibrosis are shown. C: Fatty degeneration is shown. Scarcity of myofibrils and myocytolysis are also seen in A, B and C. The bar at the bottom represents 30 µ (Hematoxylin and eosin stain; original magnification ×100).
In 1972, Sharp et al. described MCTD as a clinical syndrome with overlapping features of systemic lupus erythematosus, progressive systemic sclerosis and polymyositis. Patients with MCTD commonly develop the clinical features of all three connective tissue diseases. However, since this initial report of MCTD as a specific clinical entity, cardiac abnormalities in adult MCTD have been noted sporadically. Emlen et al. reported the case of a 31-year-old man with MCTD who developed progressive cardiac conduction system disease during his illness, leading to complete heart block which required permanent pacing. This case was lacking in histologic confirmation. However, the author argued that the progressive involvement of all fascicles and a slow ventricular response during periods of complete heart block strongly suggested conduction system fibrosis, as has been described in progressive systemic sclerosis and polymyositis. Whitlow et al. reported the case of an 18-year-old woman with MCTD associated with congestive heart failure due to myocarditis. Despite treatment with steroids and cyclophosphamide, progressive myocarditis resulted in death 20 months after cardiomegaly first developed. Autopsy findings included infiltration of the myocardium with lymphocytes around degenerating muscle fibers and patches of fibrosis.

Our case had MCTD associated with perimyocarditis and a massive pericardial effusion. The diagnosis of MCTD in our patient was based on the typical clinical findings and serological examinations, including a high titer of antinuclear antibody with a speckled pattern, a high titer of antibody to ribonuclease-sensitive RNP, no antibody to ribonuclease-resistant Sm antigen, and hyper γ-globulinemia. In our case, cardiac abnormalities became the predominant clinical feature, and a massive pericardial effusion was demonstrated by echocardiography. According to Alpert et al., acute perimyocarditis and/or effusion associated with MCTD was seen in 29% of the patients, but there was only one patient manifesting massive pericardial effusion. The histopathological findings of right ventricular endomyocardial biopsy included the disorganization and fragmentation of myocytes, a scarcity of myofibrils, myocytolysis, fatty degeneration, and perivascular and diffuse interstitial fibrosis. These findings are indicative of myocarditis. The degree of myocarditis in this case was not as severe as the autopsy case reported by Whitlow et al. However, myocarditis which was diagnosed by endomyocardial biopsy as in our case has not been reported previously in patients with MCTD.

There have been a few reports mentioning the relationship between
the titer of antibody to ribonuclease-sensitive RNP and myocarditis due to connective tissue disease. Antibody to ribonuclease-sensitive RNP was detected in a high titer in all systemic lupus erythematosus patients with myocarditis described by Borenstein et al.\(^8\) and in all pediatric patients with MCTD and myocarditis reported by Singsen et al.\(^2\) Our case extends the association of high titers of antibody to ribonuclease-sensitive RNP and myocarditis to an adult with MCTD. Further studies on patients with connective tissue disease and myocarditis are needed to define the correlation between high titers of anti-ribonuclease-sensitive RNP and disease states.

The aortogram of our case also revealed aortic regurgitation. Singsen et al.\(^2\) reported that only one pediatric patient out of 14 children with MCTD had aortic regurgitation, but there has been no adult case of MCTD having aortic regurgitation. A deformity, a thickening or a bicuspid aortic valve was not found in the echocardiogram and/or aortogram. Thus, the etiology of the aortic regurgitation is unknown in our case.

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**References**