***Case report***

# A case of mixed connective tissue disease complicated with hypertrophic obstructive cardiomyopathy

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***Running title***: **HOCM in MCTD**

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**Abstract**

A 54-year-old female was diagnosed as mixed connective tissue disease (MCTD) complicated with secondary Sjögren's syndrome. Although she had no dyspnea on exertion, the chest X-ray showed cardiomegaly with interstitial pneumonia. The echocardiogram demonstrated asymmetric hypertrophy of the interventricular septum. Diagnosis of hypertrophic obstructive cardiomyopathy (HOCM) was confirmed by left ventriculography and myocardial biopsy. She was treated with prednisolone, resulting in improvement of swollen hand, elevated muscle enzymes and interstitial pneumonia. A rare complication of HOCM with MCTD was described.

***Key words:*** mixed connective tissue disease, hypertrophic obstructive cardiomyopathy, HLA-DR4

## Introduction

Mixed connective tissue disease (MCTD) is characterized by the presence of Raynaud's phenomenon, sclerodactyly, partial manifestations of systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and polymyositis (PM) with anti-ribonucleoprotein (RNP) antibody **(1)**. With regards to cardiovascular involvement, pulmonary hypertension is crucial because it regulates the prognosis **(2)**. The presence of hypertrophic cardiomyopathy (HCM) was mainly reported in SSc **(3)**. We describe the first report of MCTD complicated with hypertrophic obstructive cardiomyopathy (HOCM).

## Case report

A 54-year-old female was admitted to our hospital with general fatigue, arthralgia and muscle weakness on her thigh in walking without dyspnea on exertion. Her grandfather and uncle had both died suddenly without known cause. On admission, blood pressure was 100/60 mmHg and her heart sound manifested a grade II-III systolic murmur at the left parasternal border and fourth sound. Fine crackle was heard on her dorsal lung field. Swollen hands and sclerosis were present on her forearm.

Laboratory findings showed a hemoglobin level of 11.8 g/dl, total leukocyte count of 6,500/$mm^3$, and platelet count of 29.2 x $10^4$/$mm^3$. Elevation of aspartate aminotransferase (45 IU/l), lactic dehydrogenase (427 IU/l), creatinine kinase (438 IU/l) and aldolase (10.4 IU/l) was observed along with positive C-reactive protein (CRP) (1.59 mg/dl) and elevation of serum IgG to 4540 mg/dl. The level of serum

creatinine was normal (0.6 mg/ml, normal range; 0.4-1.1) without proteinuria. Anti-nuclear antibody was positive as 2560x with a speckled pattern and anti-double-stranded deoxyribonucleic acid (dsDNA) antibody (72.7 U/ml), anti-Sm antibody (127.5 U/ml), anti-RNP antibody (247.4 U/ml), anti-SS-A antibody (140.1 U/ml) and anti-SS-B antibody (103.4 U/ml) were detected without anti-Scl-70 antibody, anti-centromere antibody, anti-Jo-1 antibody and cardiolipin antibody. As for the human leukocyte antigens (HLA) typing, she possessed HLA-A2, A31, B51, B60, DR4 and DR8.

Computed tomography confirmed the presence of interstitial pneumonia on the lower bilateral lung fields, while no serositis such as pleuritis or pericarditis was observed. Electrocardiogram revealed left ventricular hypertrophy with T wave repolarization abnormalities. The respiratory function test showed reduction of percent diffusing power of carbon monoxide (CO) as % DLCO to 46.4 % showing normal vital capacity and percent of forced expiratory volume in first second as FEV1.0%. Magnetic resonance imaging (MRI) showed elevated intensity in her gluteus maximus by the short inversion time (TI) inversion recovery method. An electromyogram of her vastus medialis muscle demonstrated the polyphasic potential, suggesting the existence of myogenic conversion. The skin biopsy of her forearm confirmed the presence of sclerosis of the skin presenting atrophy of epidermides and growth of collagenous fibers. Sjögren's syndrome (SS) was diagnosed by the criteria proposed by American-European Consensus Group **(4),** but the diagnosis of SLE was not confirmed despite the positive anti-Sm antibody and anti-ds DNA antibody.

Since she was diagnosed as MCTD according to the criteria defined by the

Health and Welfare Ministry of Japan, 30 mg of oral prednisolone was initiated, resulting in improvement of her myalgia, elevated muscle enzymes, CRP and interstitial pneumonia. Since she felt continuous palpitation showing sinus tachycardia in outpatient settings, metoprolol tartrate was initiated. When oral prednisolone was tapered to 12.5 mg a day, she was rehospitalized at our hospital. Echocardiography revealed asymmetrical hypertrophy, showing 26 mm of interventricular septum and 14 mm of posterior wall of the left ventricle. Although a treadmill stress test and Holter monitor showed no sustained ventricular tachycardia or atrial fibrillation, left ventriculography revealed mid-obstruction with 20 mmHg of pressure difference in the left ventricle **(Fig. 1)**. The cardiac catheter test showed slight pulmonary hypertension, although the echocardiography revealed no significant pulmonary hypertension. A myocardial biopsy was also performed **(Fig. 2)**, showing hypertrophy and disarray of the cardiomyocytes. These data demonstrated the existence of hypertrophic obstructive cardiomyopathy (HOCM). Informed consent for the invasive examinations was obtained from the patient.

## Discussion

The concept of MCTD is controversial because the clinical entity is obscure, but high mortality due to pulmonary hypertension ensures the clinical independence of MCTD from SLE or SSc **(2)**. In our case, sclerosis on her forearm along with interstitial pneumonia suggested the existence of SSc. In addition, arthralgia, muscle weakness, elevation of muscle enzymes and CRP implied existence of PM. Although overlap syndrome of SSc with PM could be also considered, MCTD was diagnosed by

both typical swollen hands and positive anti-RNP antibody. Although MCTD is characterized by parts of clinical manifestations from SSc, PM or SLE, clinically significant cardiovascular manifestations are rarely reported except for pulmonary hypertension.

Several reports described the relationship between MCTD and the HLA DR4 subtype, in which Gendi et al **(5)** reported that MCTD without differentiation into SLE or SSc was closely associated with HLA DR2 or DR4 in the UK. They emphasized that HLA subtyping can be a predictive factor for MCTD differentiation, implying that undifferentiated MCTD might be a dissimilar entity compared to differentiated MCTD into SLE or SSc. Kasukawa **(6)** also reviewed the clinical and genetic characteristics of MCTD, in which the preferential finding of HLA DR4 was found in some of the literature. In our case, the existence of HLA DR4 suggested that our case might belong to the undifferentiated MCTD, but the racial variation with respect to the HLA subtype should be considered. In some reports, both SLE and SSc as well as HOCM are considered to be HLA-DR3-associated disorders **(3, 7)**, suggesting this finding is a novel characteristic of such a condition.

In Southeast Asia, Shankarkumar et al. **(8)** reported that HLA-B51 and DR2 levels were significantly increased in HCM patients. Since our case showed SSc-like manifestation with HOCM showing both HLA B51 and DR4, these HLA phenotypes might explain the genetic preference for the case of HCM complicated with MCTD in Asia.

This is the first report to demonstrate the complication of HOCM in a patient with MCTD. For elucidation of the relationship between HOCM and MCTD,

molecular and genetic studies in association with an accumulation of cases are required.

**Abbreviations:**

ds DNA; double-stranded deoxyribonucleic acid, HCM; hypertrophic cardiomyopathy, HOCM; hypertrophic obstructive cardiomyopathy, MCTD; mixed connective tissue disease, MRI; magnetic resonance imaging, PM; polymyositis, RNP; ribonucleoprotein, SLE; systemic lupus erythematosus, SS; Sjögren's syndrome, SSc; systemic sclerosis

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**Figure legends**

**Figure 1 Pressure reduction in left ventricle**

Continuous pull-back pressure recording from the left ventricle apex up to the left ventricle outflow revealed 20 mmHg of pressure gradient, suggesting mid-ventricular obstruction.

**Figure 2 Results from myocardial biopsy**

Endocardial biopsy was performed, showing hypertrophy and disarray of alignment of myofibers, which is compatible with hypertrophic cardiomyopathy. Bar; 50μM

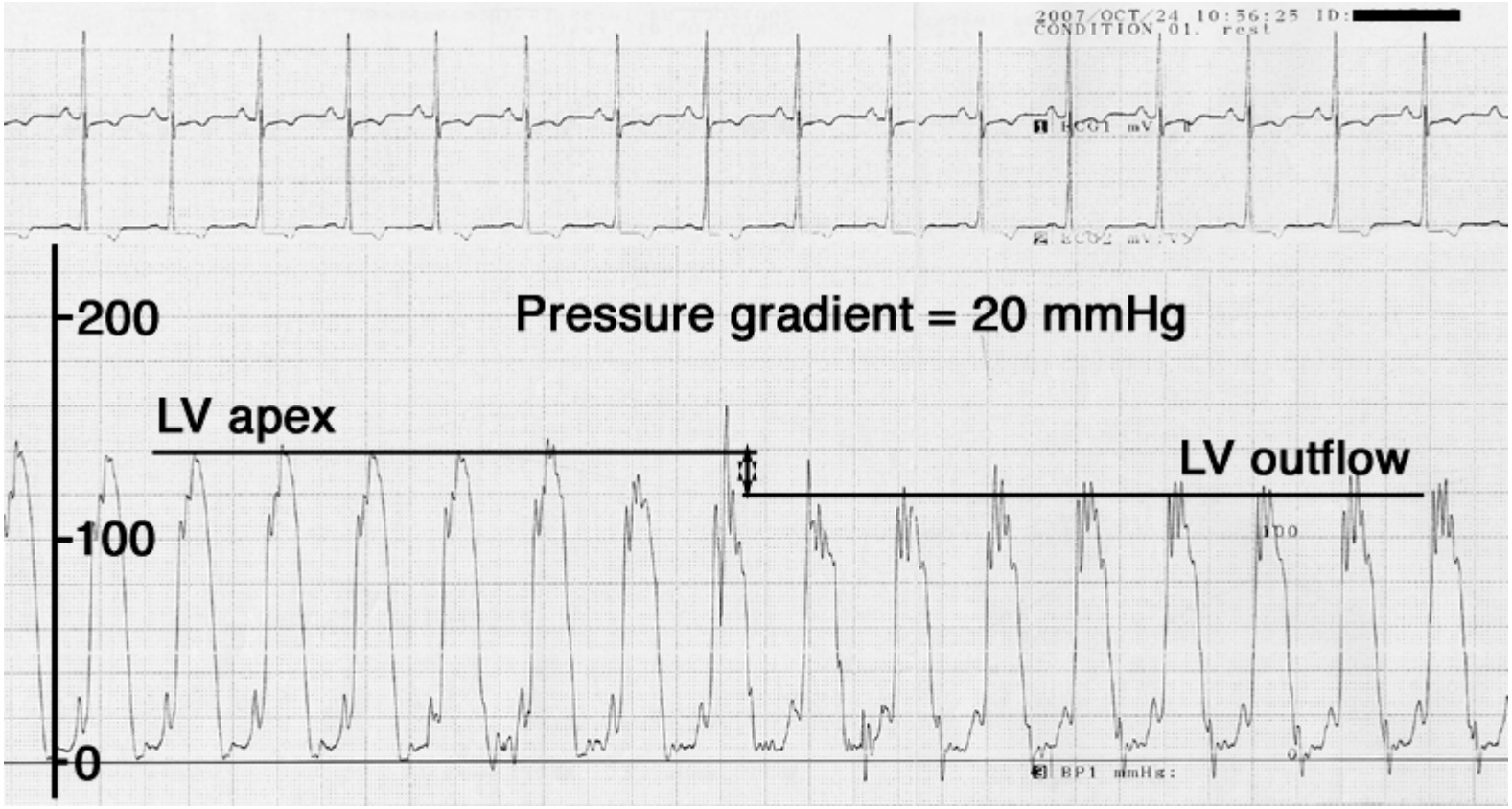
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Fig. 1

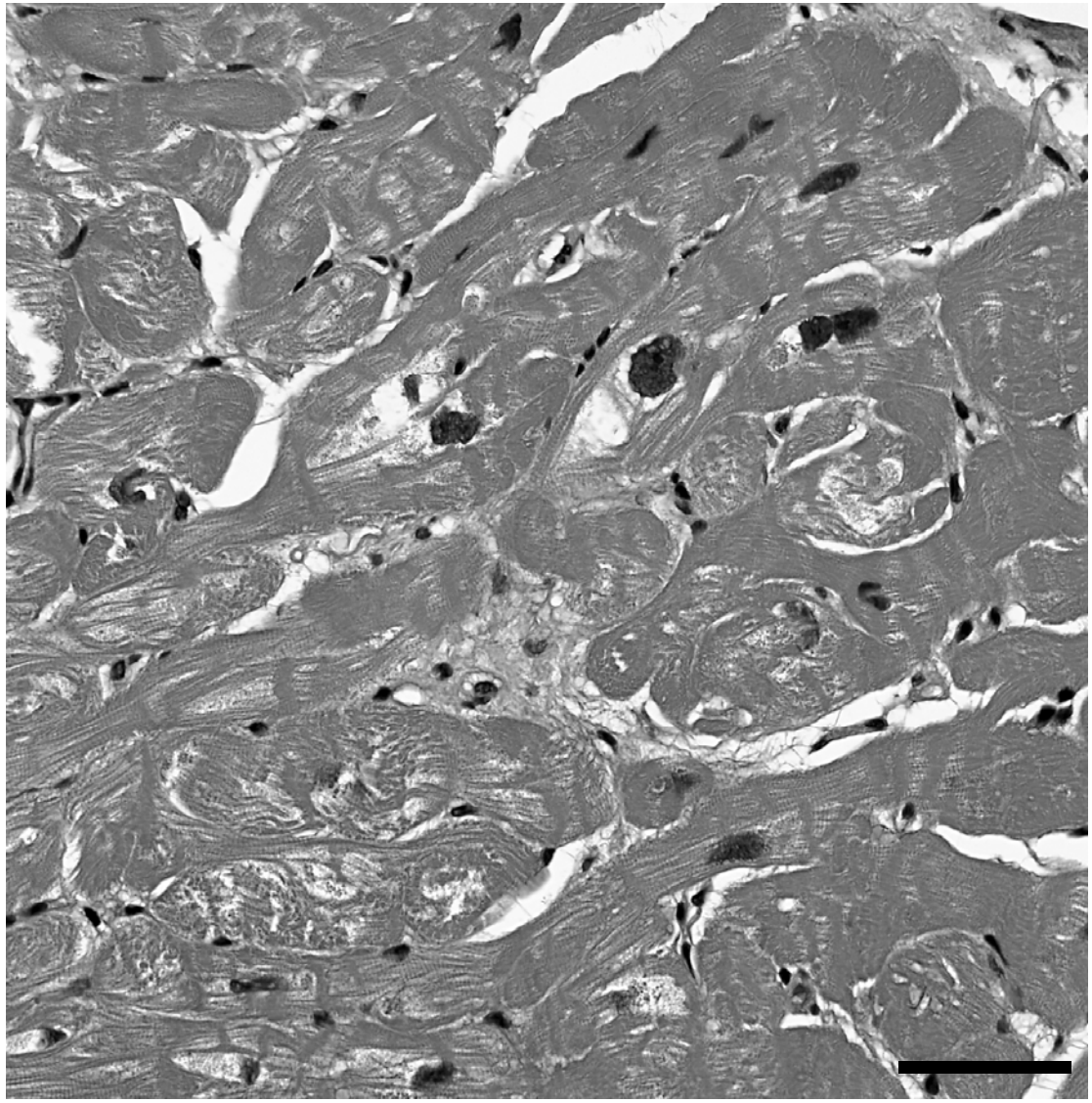

Fig. 2