Case Report
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Cardiac Complication in A Woman with Mixed Connective Tissue Disease

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ABSTRACT

Mixed connective tissue disease (MCTD) is a rare condition characterized by the presence of high-titer autoantibodies anti-U1 ribonucleoprotein (RNP) which symptoms are overlapped and varied. MCTD presentation in heart is not typical. Patients with cardiac complication may present with ventricular hypertrophy, abnormal heart conduction and pericarditis. We herein report a rare presentation of MCTD in a 62-year-old woman who had prominent cardiac symptoms. Echocardiogram demonstrated right ventricular enlargement, slight pericardial effusion, Holter ECG monitoring revealed cardiac arrhythmia. The patient was given methylprednisolone, Lei Gongteng, mycophenolate mofetil and recovery was apparent.

Keywords: *Mixed Connective Tissue Disease, Pericardial Effusion, Ventricular Enlargement*

Introduction

Mixed connective tissue disease (MCTD) is a rare systemic autoimmune disease characterized immunologically by the presence of high-titer autoantibodies anti-U1 ribonucleoprotein (RNP) against the U1 small nuclear RNP auto-antigen (Ortega-Hernandez and Shoenfeld, 2012; Tani *et al*., 2014). Clinically, it has overlapping features such as systemic lupus erythematosus (SLE), cutaneous systemic sclerosis (SSc), rheumatoid arthritis, polymyositis (PM), and dermatomyositis (DM) (Faden *et al*., 2018). MCTD can begin with any clinical manifestations of rheumatoid arthritis, SLE, or DM (Ortega-Hernandez and Shoenfeld, 2012).

MCTD will involves multiple organs and systems of the body, including joints, skin mucosa, blood vessels, muscles, lungs, heart, digestive system and blood system. The guideline of MCTD pointed out that the entire heart layer can be involved, and 20 % of patients have abnormal electrocardiograms, the common changes are right ventricular hypertrophy, right atrium dilatation, and abnormal heart conduction. Pericarditis is the most common clinical manifestation of heart involvement, it is found in 10 % -20 % of patients (Sapkota and Al Khalili, 2021). Pericardial filling is rare. Myocardial involvement is getting more and more attention, some of patients are secondary to pulmonary arterial hypertension,

which is often asymptomatic in the early stages (Sapkota and Al Khalili, 2021).

However, cardiac complication is not prominent in the MCTD, it become the primary or major symptom of MCTD is rarely reported. Herein, we reported a case of MCTD which presents typical cardiac symptoms at the early course of the disease.

Case Report

History

A 62-year-old woman admitted to our hospital with general fatigue, muscle pain in the proximal extremities and multiple joint pains which mainly involved in the interphalangeal joints, palm-phalangeal joints, elbow joints and knee joints. And also she revealed that, symptoms of joint pain were suffered more than 20 years, when there are no other presentations. The local hospital diagnosed as "rheumatoid arthritis" and methotrexate, Lei Gongteng, hydroxychloroquine, Lefluomet, and Kunxian capsules were used successively. Moreover, 1 or 2 years after onset, she went to local hospital again because of palpitation, the doctor told her that her heart rhythm was irregular and the heart was a litter bit dilatation, then metoprolol (5 mg/d) was given. Unfortunately, the results of the examination at that time were not obtained. Raynaud's phenomenon in both hands was appeared in the course of the disease and no facial rash or erythema was showed. All the drugs related rheumatism was discontinued 5 months ago due to stomach discomfort, which leaded to this attack. She has hypertension for more than 20 years, amlodipine glutamate was administrated regularly (1 mg/d), which was stopped 1 year ago, because of low blood pressure (100/57 mmHg). No history of Cardiovascular disease. She was diagnosed with interstitial lung disease through a computed tomography (CT) examination of chest for cough and phlegm 1 year before she was admitted to our hospital.

Physical Examination

On admission, blood pressure was 126/78 mmHg, and her body temperature was 37.2℃. The muscle strength was grade 4/5 in bilateral upper extremities and was normal in bilateral lower extremities. A physical examination revealed coarse crackles audible from the lower lung.

Radiological and Laboratory Examinations

The laboratory data were presented in Table: elevation of creatine kinase, creatine kinase-MB, C-reactive protein (CRP), erythrocyte sedimentation rate, rheumatoid factor, glutamic-oxaloacetic transaminase (153 U/L) and glutamic-pyruvic transaminase (72 U/L) were observed along with positive Troponin T (0.262 ng/ml). The level of anti-nuclear antibody was 1:3200 with a speckled pattern and

anti-double-stranded deoxyribonucleic acid (dsDNA) antibody (17.64 IU/ml), anti-Sm antibody (+++), anti-U1RNP Ab (+++) and anti-SS-A (R052) antibody (+++) were detected.

Table 1: Laboratory Findinds on Admission

Parameter	Result	Parameter	Result
Red blood cells	4.11×10^12 /L	PR3-ANCA	Negative
Hemoglobin	118 g/L	MPO-ANCA	Negative
Platelet	309×10^9 /L	IgG	30.6 g/L
White blood cells	4.5×10^9 /L	IgA	2.61 g/L
Albumin	29.6 g/L	IgM	1.02 g/L
Glutamic-oxaloacetic transaminase	153 U/L (13-35)	Complement 3	0.618 g/L
Glutamic-pyruvic transaminase	72 U/L (7-40)	Complement 4	0.146 g/L
Lactate dehydrogenase	722 U/L (120-250)	ANA	1:3200
Creatine Kinase	2284 U/L (40-200)	Anti-ds-DNA Ab	17.64IU/ml (<75)
Creatine Kinase-MB	101.3 U/L (0-24)	Anti-sm Ab	+++
C-reactive protein	1.2 mg/L	Anti-U1RNP Ab	+++
Erythrocyte sedimentation rate	43 mm/h	Anti-SSA (R052) Ab	+++
Troponin T	0.262 ng/ml (<0.014)	Anti-SSB Ab	Negative
N-terminal B-type natriuretic peptide	4760 ng/L (<125)	Anti-J0-1 Ab	Negative
Rheumatoid factor	497 IU/ml (<20)	Anti-Mi-2 Ab	Negative
Anticyclic citrulline peptide antibody	1.6U/ml (<5)	Anti-MDA5 Ab	Negative
HLA-B27	Negative	Cardiolipin Antibody	Negative

ANA: anti-nuclear antibody

MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibody

PR3-ANCA: proteinase 3-antineutrophil cytoplasmic antibody

HLA: Human leukocyte antigens

The electrocardiogram revealed sinus tachycardia, right axis, and paroxysmal ventricular premature beats with T wave repolarization abnormalities (Fig. 1). Holter ECG monitoring revealed atrial premature beats (1442 beats) with a few premature ventricular beats (228 beats). Echocardiogram demonstrated right ventricular dilation (RV 27 mm), slight pericardial effusion, RVSP: 34mmHg. Chest computed tomography confirmed the presence of interstitial pneumonia on the bilateral lung fields, while no serositis such as pleuritis or pericarditis was observed (Fig. 2). The respiratory function test showed mild restriction of lung ventilation dysfunction and sever restriction of lung diffuse function. The result of electromyogram was normal.

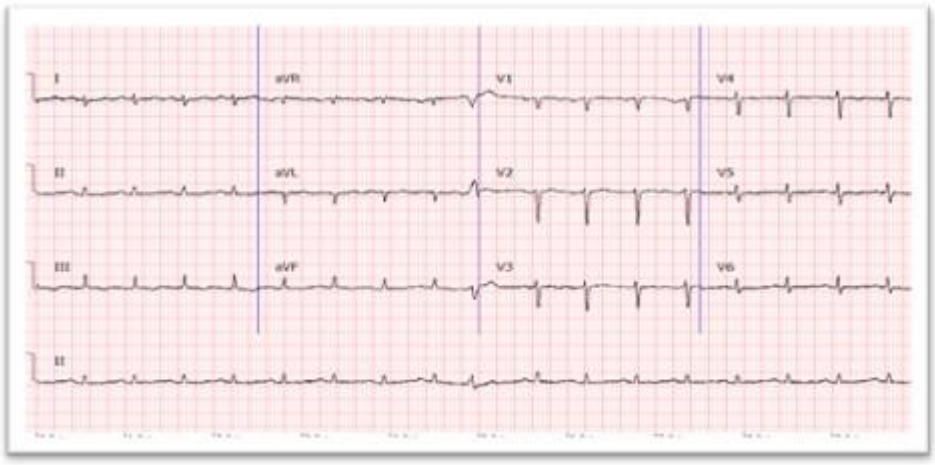

Figure 1: Electrocardiogram findings on admission which revealed sinus tachycardia, right axis, and paroxysmal ventricular premature beats with T wave repolarization abnormalities

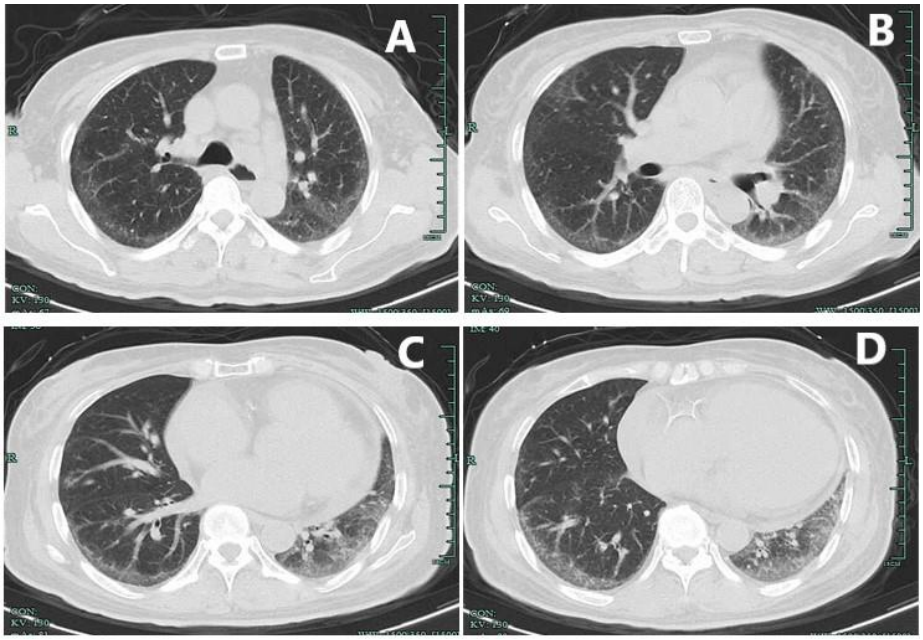

Figure 2: Chest computed tomography (CT) findings on admission. There was interstitial pneumonia on the bilateral lung fields and right ventricular dilation

Diagnosis

According to the aforementioned evidence, the patient had the clinical symptoms of Raynaud's phenomenon, rheumatoid arthritis and myositis. In addition, the examination revealed a high serum titer of anti-U1-RNP antibody and speckled antinuclear antibodies (ANA), which fulfilled the Kasukawa's diagnostic criteria for MCTD (Sapkota and Al Khalili, 2021). Although she was diagnosed with rheumatoid arthritis more than 20 years ago, it seems that this diagnosis is yet to be considered. Multiple joint pain at that time might be one of the initial manifestations of MCTD. Now we can explain all the symptoms with

one diagnosis. Echocardiogram demonstrated right ventricular enlargement (RV 27 mm), a slight pericardial effusion, and Holter ECG monitoring revealed atrial premature beats. In the present case, although MCTD itself and lung lesions can both lead to pulmonary hypertension, which in turn leads to the enlargement or hypertrophy of right ventricle. Primary performance of the disease rather than secondary to pulmonary hypertension was suspected for the following reasons: 1. cardiac symptoms precede pulmonary manifestations (1 or 2 years after onset, she was already feeling palpitation and doctor also told that her heart rhythm was irregular and the heart was a litter bit dilatation, while the symptoms of cough and phlegm were occurred by 1 year ago.); 2. echocardiogram showed pulmonary artery pressure was basically normal (34 mmHg); and cardiac examinations were in line with the performance of heart involvement under metoprolol was given for more than 10 years.

Treatment and Outcome

Since she was diagnosed as MCTD, we decided to treat her with colchicine. 4 days after starting the administration of oral methylprednisolone at a dose of 20 mg/day and Lei Gongteng at a dose of 20 mg/day, the patient's symptoms were significantly improved. Considering she responded well to low-dose corticosteroids, we reviewed the blood index after 1 week of keeping the dose, however, the level of creatine kinase, creatine kinase-MB, C-reactive protein, erythrocyte sedimentation rate and rheumatoid factor were not decline significantly, therefore, mycophenolate mofetil (500 mg/day) was initiated and intravenous administration of methylprednisolone (40 mg/day) was performed for 6 days, related blood indicators were reviewed while the results were still not satisfactory. With that in mind, we continued to increase the dose. The final treatment is mycophenolate mofetil (750 mg/day), methylprednisolone (60 mg/day, intravenous administration) and Lei Gongteng (20 mg/day) and indicators were declined after 1 week: N-terminal B-type natriuretic peptide (593.9 ng/L), erythrocyte sedimentation rate (32 mm/h), IgG (23 g/L), glutamic-pyruvic transaminase (72 U/L), glutamic-oxaloacetic transaminase (85 U/L), lactate dehydrogenase (532 U/L), Creatine Kinase (1919 U/L), C-reactive protein (0.5 mg/L) and the symptoms did not recur during treatment.

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 (Lundberg, 2005) MCTD involves multiple organs and systems. The guideline of MCTD pointed out that the entire heart layer can be involved, and 20 % of patients have abnormal electrocardiograms, the common changes are right ventricular hypertrophy, right atrium enlargement, and abnormal heart conduction. Pericarditis is the most common clinical manifestation of heart involvement it is found in 10 % -20 % of patients,

pericardial filling is rare. However, heart involvement is not prominent in the MCTD and it become the primary or major symptom of MCTD is rarely reported. In our case, cardiac symptoms showed early in the course of the disease (Sapkota and Al Khalili, 2021).

It has been thought that MCTD has a relatively well prognosis previously and is effective in treating corticosteroids. Now it has been established that patients who with high titer antibodies is still less likely to cause severe renal complications and life-threatening neurological disorders. From this point of view, MCTD has a better prognosis than SLE. However, progressive pulmonary hypertension and cardiac complications are the leading causes of death in MCTD patients. Fukushima M, *et al*. (2018) reported a 14-year-old girl with myocarditis associated with MCTD, she was admitted to hospital with a 4 day history of rapidly worsening high-grade fever, chest pain and general malaise. Nakamura H, *et al*. (Nakamura *et al*., 2008) reported a case of MCTD complicated with hypertrophic obstructive cardiomyopathy (HOCM). In addition, MCTD can also involves macrovascular and increases cardiovascular (CV) risk, Triantafyllias K, *et al*. (2019) evaluated the effect of the gold standard assessment method of aortic stiffness carotid-femoral pulse wave velocity (cfPWV) in patients with this disease and to evaluate its associations with MCTD-associated markers and traditional CV risk factors. The results showed patients with MCTD have significantly higher aortic stiffness and thus CV risk. Since progressive pulmonary hypertension and cardiac complications are the leading causes of death in MCTD patients, and, accordingly, need attention in patients with MCTD. When there is an unexplained change in cardiac structure, an increase in myocardial enzyme accompanied with the elevated of muscle enzyme, it should be considered as rheumatoid-related diseases, especially when there are other rheumatic symptoms. On the other hand, symptoms such as palpitation and chest tightness in patients with MCTD may be a manifestation of cardiovascular system involvement, we should attach importance to the evaluation of cardiovascular system in patients with MCTD, early evaluation of electrocardiogram or Holter ECG monitoring, echocardiogram and cfPWV could be useful in such cases.

Conclusion

MCTD presentation in heart is not typical, such as ventricular hypertrophy, abnormal heart conduction and pericarditis. When there is an unexplained change in cardiac structure, an increase in myocardial enzyme accompanied with the elevated of muscle enzyme, it should be considered as rheumatoid-related diseases, especially when there are other rheumatic symptoms.

Author Contributions: C.Y.W. analyzed the data, prepared figures and wrote the manuscript. X.S.D. conceived the study, supervised the overall project.

Conflicts of Interest: The Authors declare that there is no conflict of interest.

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Abbreviations

- ds DNA: Double-stranded deoxyribonucleic acid
- MCTD: Mixed connective tissue disease
- PM: Polymyositis
- RNP: Ribonucleoprotein
- SLE: Systemic lupus erythematosus
- SSc: Systemic sclerosis
- DM: dermatomyositis

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