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Myocarditis in Mixed Connective Tissue Disease: A Case Report

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Abstract

Myocarditis is a serious manifestation of systemic lupus erythematosus. It is reported that 5-10% of the patients present symptomatic myocarditis. However, myocarditis in mixed connective tissue disease is uncommon. Only a few cases with mixed connective tissue disease patients who presented symptomatic myocarditis were reported. We herein describe a patient with mixed connective tissue disease who developed acute myocarditis and responded rapidly to steroids. Physician should be aware of myocarditis as one of the serious complications of mixed connective tissue disease.

Keywords: Myocarditis; Mixed connective tissue disease; Systemic lupus erythematosus; Cardiac involvement

Introduction

Mixed Connective Tissue Disease (MCTD) is an autoimmune syndrome characterized by overlapping features including systemic lupus erythematosus (SLE), systemic sclerosis and polymyositis in association with a high titer of autoantibody to U1 ribonucleo protein (RNP). It has been reported that a prevalence of cardiac involvement in MCTD was 13% to 65% [1]. The most frequently observed cardiac manifestations were pericarditis in 30% to 43% of the patients and mitral valve prolapse in 25% to 32% [1]. The other manifestations included conduction disturbance and pulmonary hypertension. However, myocarditis in MCTD is uncommon [2-7]. A few cases were described during past the 30 years [8-13]. Here, we describe a case with MCTD who developed acute myocarditis and responded rapidly to steroids. Also, we review eight other reported cases with MCTD that developed myocarditis.

Case Report

In October 2012, a 32 year-old woman was diagnosed with MCTD on the basis of the following diagnostic criteria of Japanese MCTD committee: Raynaud's phenomenon, swollen hands, a high titer of anti-U1 RNP antibody, arthritis and cytopenia as SLE-like manifestation and myalgia as myositis-like manifestation. She was receiving 15 mg/day oral prednisolone. The patient had remained stable except for mild arthritis, and prednisolone was tapered to 11 mg/day. Creatine kinase (CK) level was within normal range all through the course of disease.

In November 2014, she was hospitalized because of muscle weakness, arthritis, fever, general fatigue and headache. She did not complain of cough, phlegm, dyspnea and chest pain. Physical examination showed bilateral cervical lymphadenopathy. CK level was 261 U/L (normal: <188 U/L). C-reactive protein (CRP) was 4.01 mg/dl (normal: <0.30 mg/dl). On admission, electrocardiography (ECG) showed sinus tachycardia and echocardiogram showed no abnormal findings (ejection fraction (EF): 64%). Chest X-ray also showed no abnormal findings. Pharyngeal antigen tests for adenovirus, mycoplasma and streptococcus were negative. Nasal antigen tests for influenza virus were negative. IgM antibody against parvovirus B19 was negative. It was unlikely that she had acute respiratory viral infection.

Six days after admission, she complained of dyspnea and chest pain. ECG showed sinus tachycardia and T wave inversions. Echocardiogram showed a decreased left ventricle ejection fraction (EF: 39%, left ventricular internal diameter end systole: 37 mm, left ventricular internal diameter end diastole: 46 mm) and pericardial effusion. Valvulopathy such as mitral valve prolapse and cavity thrombus were not found.

Troponin I was 0.667 ng/ml (normal: <0.045 ng/ml) and CRP was increased to 15.61 mg/dl. Brain natriuretic peptide (BNP) was 93.8 pg/ml (normal: <18.4 ng/ml). Arterial blood gas analysis showed acute respiratory failure (pH: 7.5, $PaCO_2$: 25.6 mmHg, PaO_2: 51.3 mmHg, HCO_3^-: 21.1 mmol/l). Chest X-ray showed cardiomegaly, pulmonary vascular redistribution and bilateral pleural effusions, suggesting the presence of congestive heart failure. Cardiac magnetic resonance (CMR) imaging could not be performed. Based on these findings, she was diagnosed with myocarditis with congestive heart failure. Therefore, methyprednisolone pulse (1 g × 3 days) and following oral prednisolone (60 mg/day) were started with prompt response. Also, furosemide and human atrial natriuretic polypeptide (hANP), azosemide as cardioprotective drugs was administered. Her dyspnea and chest pain disappeared 3 days later. Echocardiogram became normal (EF: 65%) 6 days later. Chest X-ray and ECG became normal 2 weeks later. CK level was decreased within normal range (78 U/L, 7 days later and 27 U/L, 10 days later). The dose of prednisolone was gradually tapered to 10 mg/day over 9 months.

Discussion

Myocarditis in MCTD has been reported rarely. To our knowledge, eight cases have been reported (Table 1) [8-13]. Of all patients including our case, eight of 9 cases were female. The mean duration from the diagnosis of MCTD to the onset of myocarditis was 5.4 years. Seven of 9 cases were diagnosed with MCTD at least one year before myocarditis presentation. Four of 9 cases were treated with at least 11 mg/day prednisolone at the onset of myocarditis. These data suggest that we should consider the presence of myocarditis even in longstanding MCTD patients. Myocarditis is one of the potentially life-threatening complications of MCTD. We should promptly recognize the association of myocarditis with MCTD. However, myocarditis is often asymptomatic, even in patients who present myocardial necrosis with leukocytic infiltrations at autopsy [14]. It has been reported that 5-10% of the patients with SLE presented symptomatic myocarditis [15-18] and that 37 to 50% of the patients was diagnosed

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First author [ref]	Age/Sex	Onset myocarditis	Prior drugs	Treatments	Response	Final outcome
Whitlow et al. [8]	24F	2Y	PSL 40-60 mg	PSL 80 mg CY 100 mg, quinidine, Diuretics	Improvement	Death after 2 months (heart failure)
Grossman et al. [9]	35F	1Y	PSL 40 mg/5 mg	PSL 60 mg	No response	Death after 6 days
Nunoda et al. [10]	55F	A few months	None	PSL 30 mg	Gradual improvement	Alive
Lash et al. [11]	31F	12Y	None	PSL25 mg, Digitalis	Improvement	Alive
Lash et al. [11]	22F	11Y	Unknown	mPSL 64 mg	Improvement	Death after 3 years (vasculitis)
Lash et al. [11]	49F	10Y	PSL12.5 mg	PSL12.5 mg Digitalis, Diuretics	Improvement	Death after 2 years (vasculitis)
Hammann et al. [12]	30F	5Y	None	mPSL125 × 3 PSL 80 mg, IVCY	Improvement	Alive
Faieley et al. [13]	53M	Unknown	None	PSL40 mg, MMF 500 mg IVIG	Rapid improvement	Alive
Our case	34F	2Y	PSL11 mg	mPSL1 g × 3, PSL60 mg, Diuretics	Improvement	Alive

Table 1: Myocarditis of MCTD.

with myocarditis at autopsy [19,20]. It is likely that the frequency of myocarditis in MCTD has also been underestimated. The potential of higher incidence of undetected myocarditis depends on limitations of clinical and laboratory tools to detect subclinical forms of myocarditis. Also, even in patients with histologically diagnosed myocarditis, troponin level was elevated in 53%, CK and CK-myocardial band (CK-MB) levels were increased in only 8% and 2%, respectively [21]. Subtle cardiac symptoms and signs may be overshadowed by systemic manifestation of the underlying disease process and small amount of myocardial necrosis may not lead to increases laboratory variables [21]. Myocarditis is one of the most challenging diagnoses. Endomyocardial biopsy (EMB) is the gold standard for diagnosing myocarditis because EMB may provide information about its underlying cause such as virus, infiltrating cells, and fibrosis. However, EMB is an invasive with procedure-related risks and the utilization of the EMB is limited in clinical practice. In this respect, non-invasive alternative imaging methods such as echocardiogram and CMR are recommended in suspected myocarditis cases, although these methods have some limitations [22]. It has been reported that echocardiogram failed to provide a definite diagnosis in most cases [23] and that CMR had low sensitivity for the diagnosis of myocarditis [24]. New approaches are required for detecting myocarditis in early stage and elucidating the underlying cause.

The association between anti-RNP antibody and myocarditis in patients with MCTD or SLE has been described in some studies [18,25]. Zawadowski et al. reported that the frequency of anti-RNP antibody in SLE with myocarditis (62%) was greater than in published lupus populations (23%-40%) [18]. Singsen et al. reported that a high titer of anti-RNP antibody was detected in pediatric patients with MCTD-myocarditis [25]. Thus, anti-RNP antibody may correlate with myocarditis in patients with MCTD or SLE. Optimal treatment of myocarditis in MCTD remains unclear. In reported cases (Table 1), most common treatment was moderate-dose corticosteroids (Prednisolone: 30 mg to 80 mg/day). Six of 9 cases were treated with steroids alone. Three cases were administered with steroids alone without relapse (follow-up periods: 6 months to 12 years) [10,11, our case]. On the other hand, Lash et al. reported two cases of MCTD with myocarditis who improved through steroid therapy initially and developed vasculitis a couple of years later although their cardiac involvement was relatively stable [11]. Alternatively, the additional use of intraveneous immunoglobulin, cyclophosphamide, or mycophenolate mofetil (MMF) was also described in three of 9 cases. Fairley et al. reported a case of MCTD with myocarditis who responded rapidly to steroids, MMF and immunoglobulins, although the efficacy of immunoglobulins and MMF remains unproven [13]. Hammann et al. reported a successful case of MCTD with myocarditis treated with steroids and pulsed cyclophosphamide [12]. In contrast, it has been reported that glucocorticoid therapy did not reduce mortality in patients with viral myocarditis [26]. Also, no benefit from immunosuppressive therapy was found in acute myocarditis of unspecified etiology [27,28]. Further studies are needed to determine the optimal treatment of myocarditis in MCTD. The limitations of this study are a lack of direct evidence supporting the diagnosis of myocarditis. First, CMR imaging could not be performed because the patient was difficult to keep in bed due to dyspnea and chest pain. Second, cardiac biopsy could not be performed. Therefore, the diagnosis of myocarditis in our case is based on the findings in ECG, echocardiogram and laboratory test results.

Conclusions

Myocarditis is one of the life-threatening complications although it is often asymptomatic. Physician should be aware of myocarditis as one of the serious complications of MCTD.

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