

Diagnosis and Symptomatic Treatment of Early Reactive Cardiac Amyloidosis in Systemic Sclerosis

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Systemic sclerosis as a connective tissue disease could affect all internal organs of the body and could also manifest as a cutaneous lesion. Cardiac involvement leading to cardiac manifestations in systemic sclerosis patients is not rare. However, cardiac amyloidosis combined with systemic sclerosis is extremely rare. Although there were no definite treatment options in this case, symptomatic treatment is the cornerstone of the management plan. In this case report, we described a correct diagnosis and symptomatic medical care of early reactive cardiac amyloidosis with systemic sclerosis and summarize the current state of the relevant literature. (*J Rheum Dis* 2015;22:132-136)

Key Words. Systemic scleroderma, Restrictive cardiomyopathy, Cardiac amyloidosis

INTRODUCTION

Systemic sclerosis (SSc) or systemic scleroderma is a connective tissue disease characterized by excessive fibrosis and vascular dysfunction [1,2]. SSc with myocardial involvement leading to cardiac manifestations usually presents as a restrictive pattern [3,4]. However, restrictive cardiomyopathy resulting from cardiac amyloidosis in patients with SSc is extremely rare [5,6]. Delayed or misdiagnosis could lead to late stage heart failure, a complication associated with high mortality rates [7]. For this reason, maintaining of high clinical index of suspicion, vigorous diagnostic efforts and therapeutic interventions are required. In this case, we present a patient with an 8-year history of SSc with early reactive cardiac amyloidosis who had a favorable clinical outcome attributed to correct diagnosis and symptomatic medical care.

CASE REPORT

A 34-year-old female presented to the emergency department with dyspnea on exertion and at rest. The patient's dyspnea severity was class III according to New York Heart Association (NYHA), and had been accompanied by generalized edema for the previous two weeks. The patient was diagnosed with SSc eight years earlier, when she presented with Raynaud phenomenon, arthralgias, a fever, a digital ulcer with sclerodactyly, and a skin rash with truncal involvement. However, there were no symptoms of heart failure or pulmonary hypertension. Also, the patient's chest x-ray and echocardiography showed no abnormalities. After being diagnosed with diffuse SSc, the patient was treated with prednisolone, hydroxychloroquine, and aspirin. In spite of taking these conventional medications, she suffered from severe arthritis and sclerotic symptoms. Therefore, we also used methotrexate for a short period. The patient had no other significant medical history and had never undergone a

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surgery. There were no specific findings in her family history.

On admission, the patient was alert but appeared uncomfortable and anxious. The physical examination revealed a grade I pretibial edema. On auscultation, there was no murmur, and the cardiac sound was clear. Her blood pressure was 90/50 mmHg, pulse rate was 118 times/min, and temperature was 36.0°C. The chest x-ray showed mild pulmonary congestion and significant cardiomegaly. The initial laboratory evaluation showed that the white blood cell count was 9,370 cells/mm³ (reference range, 5,000 to 10,000 cells/mm³) including 86% neutrophils; serum C-reactive protein (CRP), 1.90 mg/dL (reference range, 0 to 0.5 mg/dL); erythrocyte sedimentation rate, 39 mm/h (reference range, 0 to 20 mm/h); blood urea nitrogen, 32.8 mg/dL (reference range, 7.0 to 20.0 mg/dL); creatinine, 0.92 mg/dL (reference range, 0.6 to 1.2 mg/dL); albumin, 3.5 g/dL (reference range, 3.5 to 5.2 g/dL); lactate dehydrogenase, 1,435

U/L (reference range, 250 to 450 U/L); and serum creatine kinase, 144 U/L (reference range, 26 to 200 U/L). No urinary abnormality was observed. Electrocardiography showed normal sinus rhythm. Echocardiography revealed hypertrophied left ventricular wall with global hypokinesia, and an ejection fraction of 35%. The E wave of the dominant mitral filling pattern with rapid deceleration time suggested a restrictive physiology (Figure 1). Meanwhile, a cardiac catheterization study to exclude ischemic heart disease was normal. Magnetic resonance imaging (MRI) which was performed to discriminate cardiomyopathy demonstrated a poor contraction of the left ventricle during the systolic and diastolic phases with diffuse wall thickening, and the ejection fraction was approximately 25% (Figure 2). These echocardiography and MRI findings were consistent with restrictive cardiomyopathy. To determine the cause of the restrictive cardiomyopathy, we performed a transcatheter endomyocardial biopsy, which showed a hypertrophied myocardium and inter-

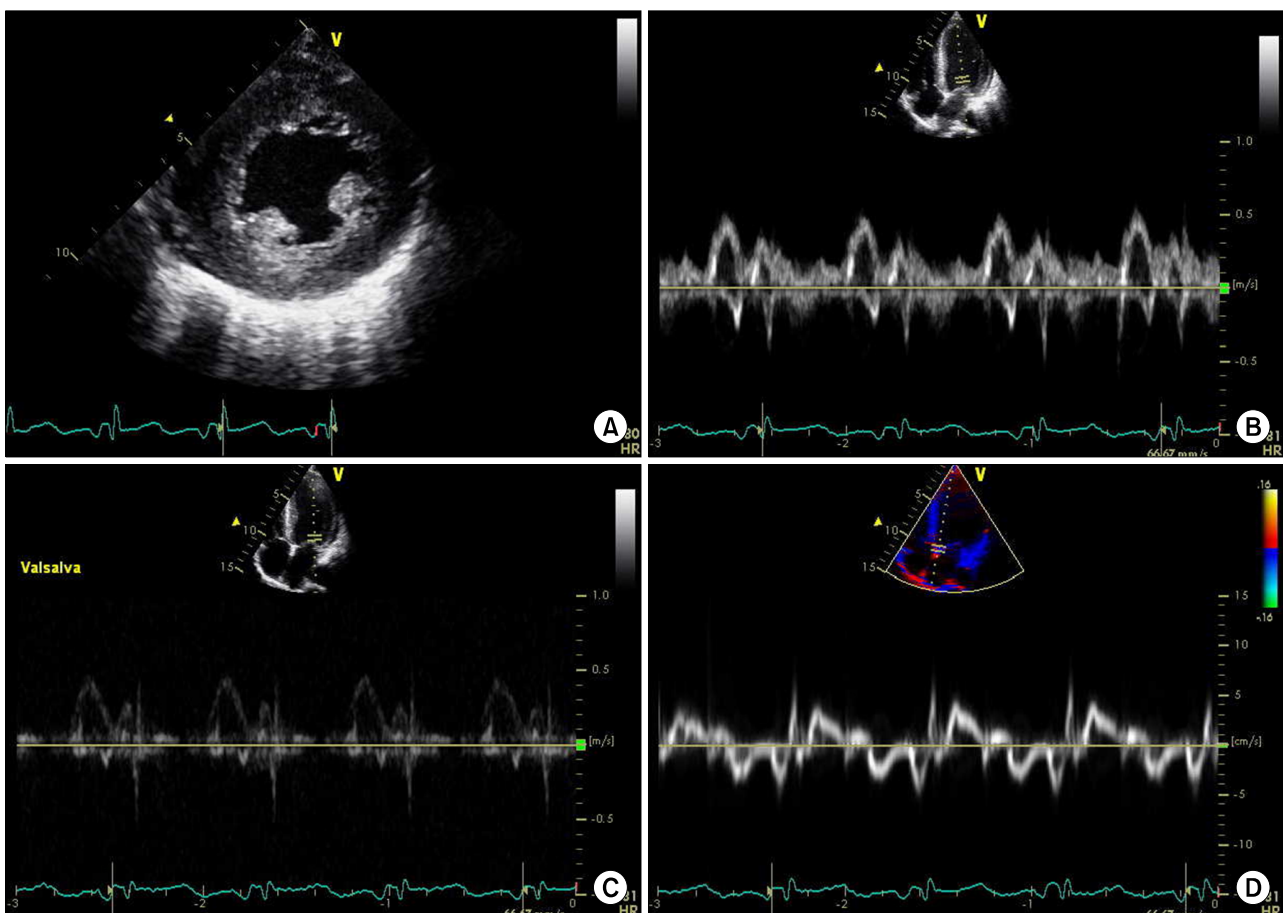


Figure 1. Echocardiography findings. Echocardiography shows global hypokinesia on left ventricle wall with concentric left ventricle hypertrophy (A), and E wave dominant mitral filling pattern with rapid deceleration time suggests restrictive physiology (B ~ D).

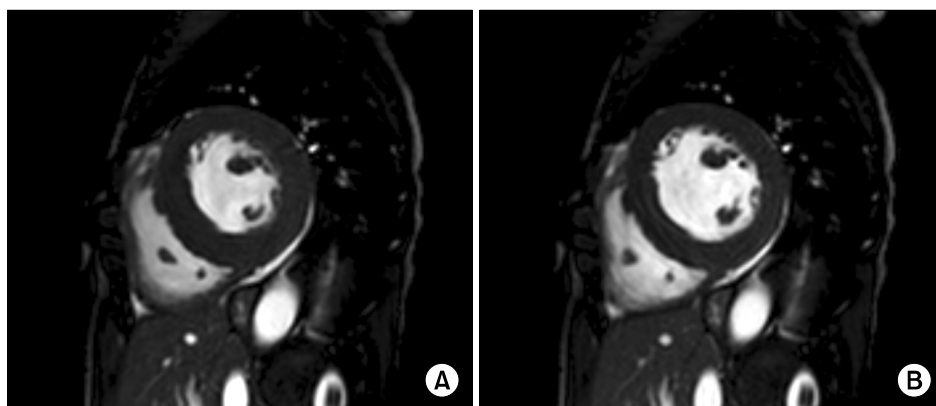


Figure 2. Radiologic findings of magnetic resonance imaging (MRI) of the heart. Cardiac MRI with cine image shows poor contraction of left ventricle during systolic (A) and diastolic phase (B). Note diffuse wall thickening and mild dilatation of left ventricle.

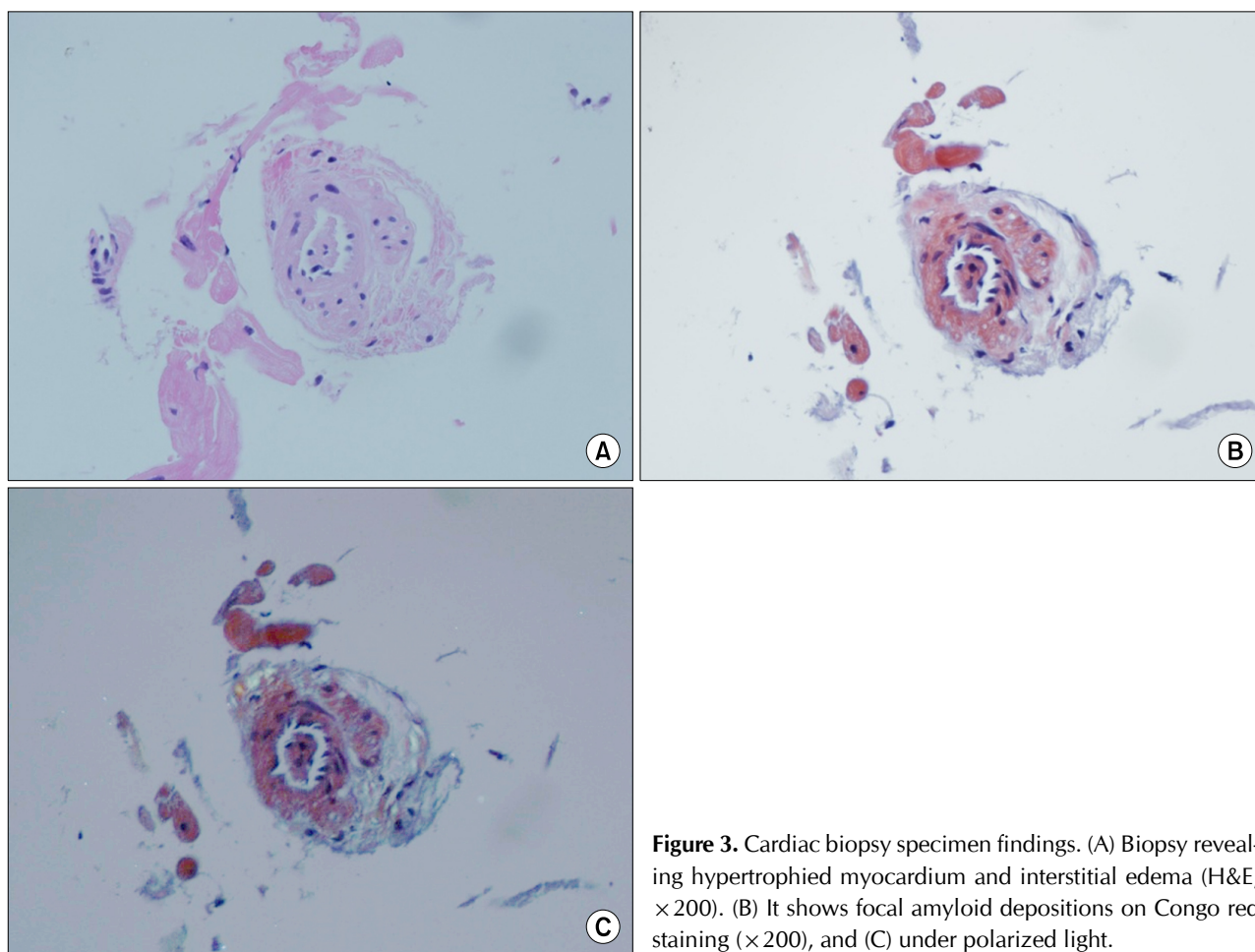


Figure 3. Cardiac biopsy specimen findings. (A) Biopsy revealing hypertrophied myocardium and interstitial edema (H&E, $\times 200$). (B) It shows focal amyloid depositions on Congo red staining ($\times 200$), and (C) under polarized light.

stitial edema with focal amyloid depositions on Congo red staining and no specific findings in the immunohistochemical analysis (Figure 3). Additional laboratory results showed both elevated urine and serum $\beta 2$ -microglobulin; $7.058 \mu\text{g/mL}$ (reference range, 0 to $0.3 \mu\text{g/mL}$); $5.112 \mu\text{g/mL}$ (reference range, 0.6 to $2.36 \mu\text{g/mL}$), respectively and an elevated serum amyloid A (SAA) level;

$29.5 \mu\text{g/mL}$ (reference range, 0 to $8 \mu\text{g/mL}$). However, monoclonal immunofixation was normal. The results were compatible with early reactive cardiac amyloidosis rather than primary amyloidosis. On the basis of these findings, she was diagnosed with SSc accompanied by early reactive cardiac amyloidosis and treated with diuretics, an angiotensin receptor blocker, and a beta-blocker.

Gradual clinical improvement, from NYHA class grade III to grade II, occurred after the medical therapy. Therefore, chemotherapy and bone marrow transplantation were excluded from the treatment plan. On the 14th day after admission, her CRP level normalized; 0.12 mg/dL (reference range, 0 to 0.5 mg/dL), and there were no signs of systemic inflammation. The patient was discharged on the 18th hospitalization day with medications. A chest x-ray conducted in the outpatient clinic in a month after discharge showed complete resolution of both pulmonary congestion and cardiomegaly. However, echocardiography still revealed restrictive cardiomyopathy with decreased left ventricular function. At the time of writing, four months after discharge, the patient has been doing well. There were no symptoms of heart failure. The laboratory test and chest x-ray showed also normal results.

DISCUSSION

SSc is an autoimmune or connective tissue disease characterized by a progressive thickening of the skin caused by an accumulation of collagen, and by injuries to the smallest arteries [1]. It can involve not only skin, but also various internal organs. Systemic manifestations of SSc may vary depending on the organs involved. Involvement of internal organs, especially the heart, the lung, and the kidneys, is associated with a poor prognosis [8]. Symptomatic cardiac involvement occurs in 15% to 35% of patients with SSc, but majority of patients with SSc are believed to have subclinical cardiac involvement [2,4,9]. An early comprehensive survival study found the two-and five-year mortality rates of patients with symptomatic cardiac involvement due to SSc were 60 and 75%, respectively [10]. However, somewhat surprisingly, a recent survival study shows that half of the patients with severe cardiac involvement survive for more than five years [3]. The improved survival is likely due the recent developments in non-invasive detective techniques and intensive symptomatic care [3].

As mentioned earlier, cardiac involvement is a common complication in SSc, while cardiac amyloidosis combined with SSc is extremely rare [5,6]. Amyloidosis comprises a group of diseases characterized by the extracellular deposition of insoluble fibrillar proteins. Amyloid A (AA) amyloidosis, also termed reactive amyloidosis or secondary amyloidosis, a subtype of SSc, is a potential complication of chronic rheumatic disease. A literature review showed that AA amyloidosis with cardiac involvement

occurs in rheumatoid arthritis patients about 10% of the time, and clinically overt heart failure often develops in the terminal phase of the disease [11]. However, to the best of our knowledge, only one case of cardiac amyloidosis combined with rheumatoid arthritis and SSc has been reported in the English literature [12].

The prognosis of cardiac amyloidosis is poor due to the lack of effective treatments [13]. The treatment of cardiac amyloidosis consists of two parts: management of heart failure and treatment of the underlying disease. Controlling the inflammatory activity of the underlying disease in order to maintain SAA levels below 10 μ g/mL may help improve the outcome [14]. However, in the case of SSc, no effective treatment has been introduced yet. Hence, we had only to treat the patient with conventional medical therapies for heart failure.

In this case, the patient showed restrictive cardiomyopathy. SSc patients with symptomatic restrictive cardiomyopathy are often considered as having myocardial fibrosis. However, like our patient, cardiac amyloidosis could be an unusual cause for restrictive cardiomyopathy. Physicians need to notice that cardiac amyloidosis might be a rare, but fatal complication of SSc. A vigilant and high clinical index of suspicion may be needed in order to diagnose it early in the disease course.

SUMMARY

We report an extremely rare case of reactive cardiac amyloidosis with SSc. In this case, the patient's symptoms were dramatically improved after conventional symptomatic treatment, an outcome attributed to early and correct diagnosis. Therefore, we report this case and summarize the current state of the relevant literature.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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