

## **Case report**

### **Successful treatment of chronic lupus myocarditis with prednisolone and mizoribine**

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## **Abstract**

A 36-year-old female patient who was diagnosed with chronic myocarditis as an initial manifestation of systemic lupus erythematosus (SLE) was admitted to our hospital. At her third occurrence of heart failure we performed an endomyocardial biopsy and proved chronic myocarditis with SLE. Subsequently, she was treated with prednisolone (PSL) and the immunosuppressive agent mizoribine (MZR), and improved her cardiac function. We describe for the first time treatment with MZR for chronic cardiac involvement of SLE.

## Introduction

In clinical studies, cardiac manifestations in systemic lupus erythematosus (SLE) may involve the pericardium, myocardium, endocardium, heart valves and coronary or pulmonary arteries [1]. Although cardiopulmonary symptoms are common in SLE, symptomatic lupus myocarditis is uncommon, especially in chronic phase. Severe myocardial dysfunctions are more often associated with coronary atherosclerosis, longstanding hypertension and corticosteroid therapy. This article describes a case of SLE patient complicating with severe heart failure due to chronic pericarditis and myocarditis. The diagnosis of myocarditis was proved by endomyocardial biopsy, which showed diffuse fibrinoid degeneration of collagen fibers, deflection of myocytes and infiltration of lymphocytes, indicating chronic myocarditis. Our patient was responded to PSL and immnosuppressive agent, MZR with diuretics, angiotensin-converting enzyme (ACE) inhibitor, digitoxin and  $\alpha/\beta$ -brocker, and successfully improved her cardiac function. She has been no recurrence of heart failure during 2 years follow up. We considered that corticosteroid and MZR might have suppressed the deposition of the immune complexes and the complements in the walls and perivascular tissues of myocardial blood vessels, and also the inflammatory cell infiltrates in the myocardial tissue as previously reported [1-5] .

## Case report

A 36-year-old female was admitted to our hospital in May, 2006 presenting malaise, exertional dyspnea and palpitation due to progressive heart failure. She had a family history of SLE. Ten years earlier, she had been diagnosed with pericarditis because she had experienced chest pain and shown ST segment elevation in a wide area on an electrocardiogram. Pericardial effusion was observed in an echocardiographic examination. Four years later (Fig. 1), she had begun to feel dyspnea and underwent an examination by cardiac catheterization that demonstrated normal coronary arteries, but hypokinesis in the anterior, posterior and inferior walls. The chest X-ray showed no remarkable findings of lung diseases including interstitial pneumonia. She was treated with a diuretic (furosemide, 40 mg/day) and an ACE inhibitor (enalapril maleate, 5 mg/day) for heart failure due to impairment of myocardial tissue after pericarditis. Eight months before her admission, she presented with refractory exertional dyspnea despite her ongoing treatment (diuretics, ACE inhibitor,  $\alpha/\beta$  blocker [carvedilol] and metildigoxin). In her admission, physical examination revealed butterfly rash, alopecia, pansystolic murmur with a third heart sound in the apex and a fourth heart sound in the right sternal border. Chest x-ray disclosed symmetrical enlargement of the heart (cardiothoracic ratio [CTR], 64%) and pulmonary congestion. An electrocardiogram revealed an inversion T-wave in I and aVL and a wide S-wave in II, III, aVF and V1-5. The echocardiogram (Fig. 3a) demonstrated dilation of all chambers (LVDd, 68mm; LVDs, 58mm) and severe impairment of ventricular contraction (ejection

fraction, 31%). In cine cardiac magnetic resonance imaging (MRI) showed severe left ventricular dilatation, severe global systolic dysfunction, myocardial thinning, and severe hypokinesis in anterior wall of apical segment and inferiolateral wall of middle and basal segment. Late Gadolinium enhancement MRI (LGE MRI) showed hyperenhancement in the subepicardial quartile of the left ventricular wall, especially in anterior wall of middle and basal segment (Fig. 2b). Besides, anterior wall of apical segment and inferio-lateral wall of middle and basal segment showed transmural enhancement which had no systolic function in cine MRI.(Fig. 2a). A cardiac catheterization demonstrated no segmental or diffuse narrowing or obstruction in the cardiac artery, but it did show severe global hypokinesis in the left ventricle. Initial laboratory studies revealed a hemoglobin level of 12.9 g/dl. The white blood cell count was 3200/mm<sup>3</sup> with 66% neutrophils, 19% lymphocytes, 3% eosinophils and 1% basophils. Platelet count was 114,000/mm<sup>3</sup>. Creatinine kinase was normal. Troponin T was negative. Levels of C3 and C4 were within normal limits. Antinuclear antibody (ANA) with a homogeneous pattern was detected at a dilution of 1:40; anti ds-DNA antibody was 17.2 IU/l (normal range: <12 IU/l), respectively. All other immunologic markers, including anti-Sm antibody, anti U1-RNP antibody, anti SS-A (Ro) antibody, anti SS-B (La) and anti-phospholipid antibody, were negative. There were no proteinuria and abnormal urinary sediment. Titers for influenza, coxsackie, echo and adenovirus were also negative. She was diagnosed as having SLE based on 5 out of 11 of the American College of Rheumatology (ACR) criteria, including butterfly rash, pericarditis, hematologic disorder, positive antinuclear antibody, and positive

anti-DNA antibody. An endomyocardial specimen was obtained from the wall of apex segment and showed global fibrinoid degeneration of collagen fibers, defluxion of myocytes and infiltration of lymphocytes, indicating chronic myocarditis (Fig. 4). SLE was considered to be the origin of her chronic myocarditis. Soon after her admission, she received treatment for heart failure: diuretics (furosemide 80 mg/day, torasemide 8 mg/day), an ACE inhibitor (enalapril maleate 5mg/day), metildigoxin (0.1mg/day) and  $\alpha/\beta$ -blocker (carvedilol 5 mg/day). Her symptoms of heart failure gradually improved, and CTR had decreased to 55%. However CTR did not change since then and her dyspnea still remained. In addition to these cardiovascular agents, 30mg daily of PSL was started after an endomyocardial biopsy and two months later, she was supplemented with 50mg daily of mizoribine (MZR). MZR was gradually increased up to 200mg daily, and the dose of PSL gradually was tapered to 15mg daily over 4 months. Follow up MRI after 10 months showed an improved contraction of anterior ventricle wall (ejection fraction, 48%) and LGE MRI showed a decreased hyperenhancement in anterior wall of middle and basal segment (Fig.2c). However, hyperenhanced lesions were still remained in anterior wall of apex segment and inferio-lateral wall of middle and basal segment. Also those parts of contraction remained poor in cine MRI. After adding these therapies, her cardiac function and dyspnea had improved and butterfly rash had disappeared. Then, she was followed by an outpatient clinic, PSL was gradually tapered to 10mg daily. The follow up echocardiogram after 2 years treatment demonstrated that dilation of left ventricular (LVDd, 67.6mm; LVDs, 50.8mm) was still remained, but the impairment of ventricular contraction

was improved (ejection fraction, 48%) (Fig.3). Her clinical symptoms and laboratory data have been stable for 2 years since her admission, with no recurrence of heart failure.

## **Discussion**

We describe an SLE patient discovered with severe heart failure involving chronic myocarditis and pericarditis. Symptomatic myocarditis is relatively uncommon in lupus, with a prevalence of 10-14%. Bulkley and Roberts [6] identified fibrinous pericarditis in 53% of SLE patients, but myocarditis in only 3 out of 36. Initial manifestation of chronic myocarditis for SLE is so rare that it has never before been reported [1]. Signs and symptoms of myocarditis in SLE are similar to those due to other causes such as viral myocarditis, but no viral infection was detected in our case, and her 3 occurrences of heart failure could not be explained by other causes. No anti-myocardial or other circulating autoantibodies were detected in our case [1, 7].

In some reports, myocardial injury in SLE may be mediated by autoimmune disorder. Immunofluorescence studies have demonstrated fine granular immune complexes and complement depositions in the walls and perivascular tissues of myocardial blood vessels. Histologically, lupus myocarditis is characterized by interstitial edema, fibrinoid degeneration of collagen fibers, focal aggregates of plasma cells, monocytes, lymphocytes, and some neutrophils in the myocardial interstitium.[4, 5]

Recent advances in the MRI technology have made possible to show the detail image of myocardium in a variety of pathological conditions. It has been reported that myocarditis lesions often originate from the epicardial quartile of the ventricular wall and occur predominantly in the lateral free wall [8]. In a study by Mahrholdt et al [9] showed that contrast enhancement was never seen to originate from the subendocardium, which is typical for myocardial infarction. In our case, LGE MRI showed hyperenhancement in the subepicardial quartile of the left ventricular wall, especially in anterior wall of middle and basal segment and the immunosuppressive therapy decreased the enhancement lesions. Unfortunately, anterior wall of apex segment and inferio-lateral wall of middle and basal segment did not response to the therapy. These lesions were affected transmurally with fibrinoid degeneration of collagen fibers, defluxion of myocytes and infiltration of lymphocytes as shown in endomyocardial biopsy. We considered this finding was consistent with LGE MRI that showed hyperenhancement toward subendocardium (Fig.2a). This MRI finding was unlikely to myocarditis, but we speculated larger interstitial space between collagen fibers made larger volume of distribution of contrast.

Table 1 shows the representative cases of acute lupus myocarditis (except our case). Generally, acute lupus myocarditis requires urgent clinical therapy, including a high dose of oral PSL, intravenous methylprednisolone (mPSL), pulse therapy and/or immunosuppressive agents. Immunosuppressive agents such as azathioprine or cyclophosphamide may be beneficial [2, 10] In our case, fibrosis had already progressed in myocardial lesions together with infiltration of lymphocytes when we diagnosed as SLE. Commonly, the



treatment is focused to control blood pressure and water balance in the chronic state. However we considered the treatment with diuretics, ACE inhibitor and other cardiovascular agents might not be enough, because inflammatory cells still infiltrated into the myocardial tissue indicated as active myocarditis (Fig. 4) and this might be one of the reasons of her 3 occurrences of heart failure. We selected oral PSL 30mg (0.5mg/kg) daily and after 2 month we added MZR for the purpose of tapering the dose of PSL in earlier. It has also been reported that interaction between 14-3-3 proteins, known as MZR-binding protein and glucocorticoid receptors, may enhance the transcriptional activity of the receptor, thus suggesting a steroid-sparing effect of MZR [11]. Taking account of her general condition, we concerned about the recurrence of heart failure during the steroid tapering. Our patient responded successfully to this immunosuppressive therapy even in steroid tapering and recovered her cardiac function without any recurrences of heart failure for 2 years. We speculated that MZR might have enhanced the effect of steroid and suppressed the deposition of immune complexes and complements as well as inflammatory infiltrates in the myocardial and pericardial tissues.

In conclusion, we experienced a rare case of chronic myocarditis and pericarditis in an SLE patient who was successfully treated with a combination of PSL and MZR. We suggested that it was worth trying to treat an SLE patient even in the chronic phase of myocarditis and pericarditis.

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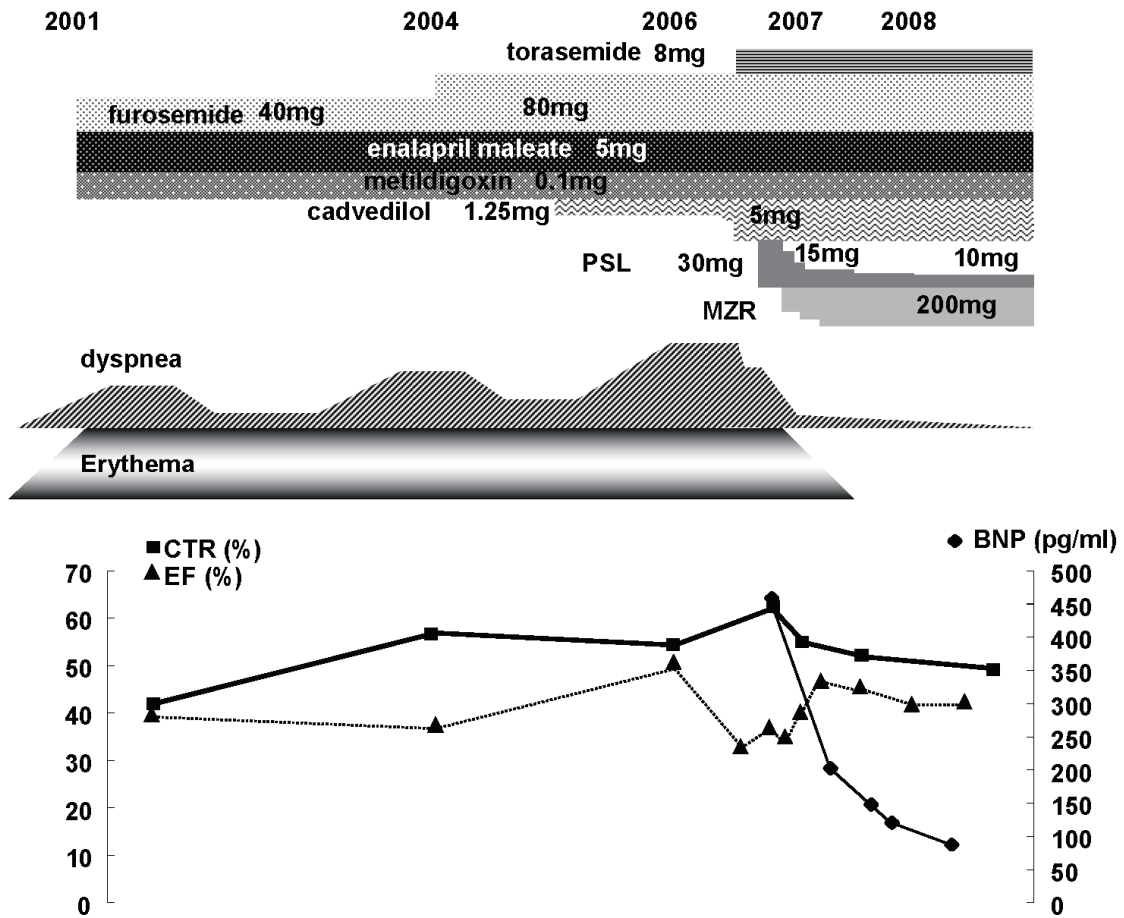
**Conflict of interest statement**

None.

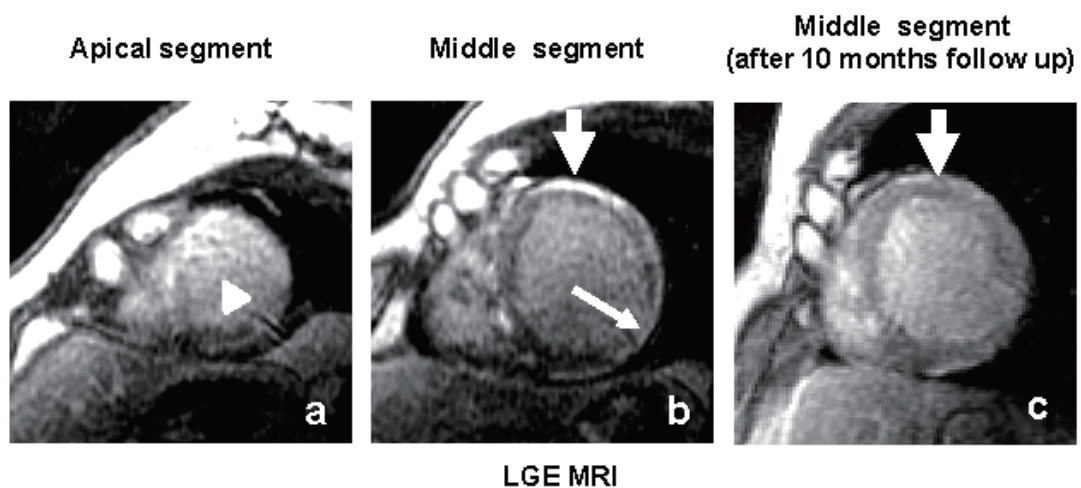
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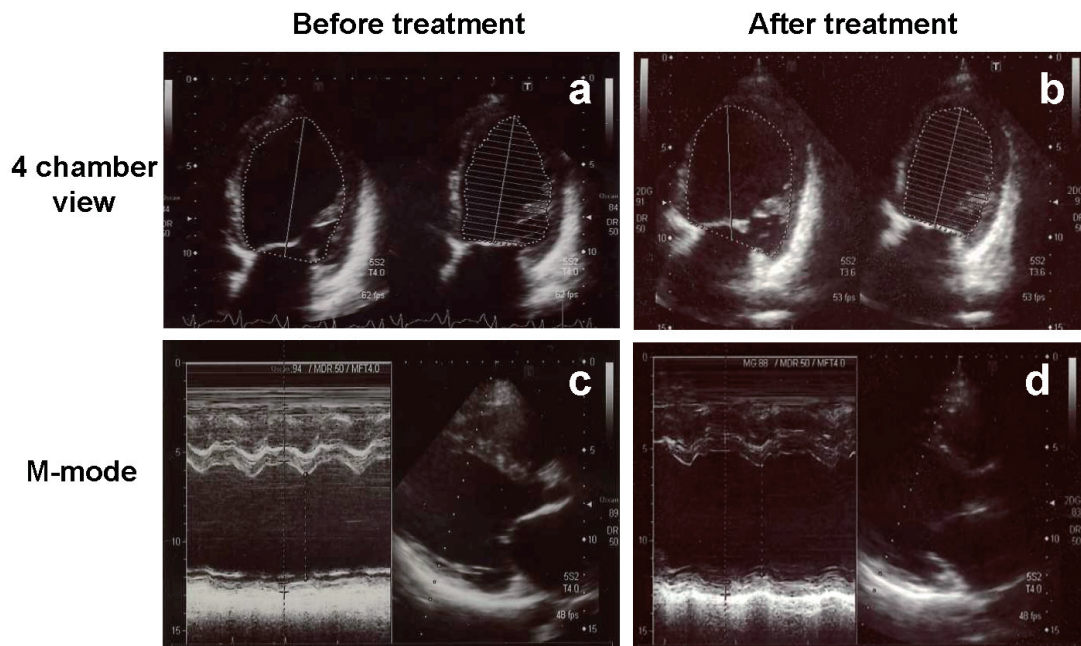
## Figure legends



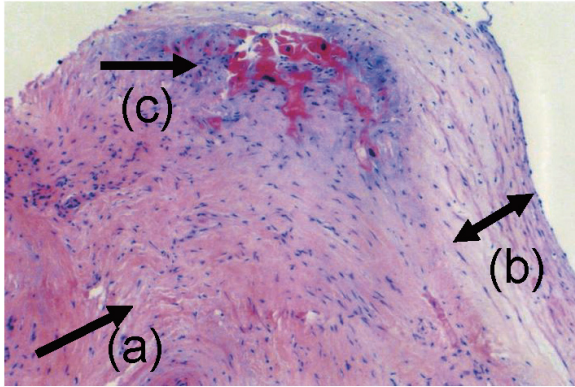
**Fig. 1** Clinical course. CTR; cardiothoracic ratio, EF; ejection fraction BNP; brain natriuretic peptide, PSL; predonisolone, MZR; mizoribine,



**Fig. 2** Late Gadolinium enhanced images (LGE) MRI in short axis view of apical segment (a) and middle segment(b, c). Anterior wall of apical segment (triangle) and infero-lateral wall of middle segment (narrow arrows) showed high signal intensity in transmural layer. Anterior wall of middle and basal segment (wide arrows) represented high signal intensity in the subepicardial quartile of the left ventricular wall.



**Fig. 3** Echocardiography showed the improvement of ventricular contraction. 4 chamber view (a, b), M-mode (c, d) before and after treatment.



**Fig. 4** Endomyocardial biopsy showed global fibrinoid degeneration of collagen fibers **(a)**, thickened endocardium **(b)**, and defluxion of myocytes and infiltration of lymphocytes **(c)**, indicating chronic myocarditis.

**Table1.**

Representative case reports of lupus myocarditis. IVCY, intravenous cyclophosphamide; mPSL, methylprednisolone; IVIg, intravenous immunoglobulin therapy. \* First onset of lupus. # Ejection fraction (EF) was evaluated by gated blood pool scintigraphy (GBPS). All the other cases were evaluated by echocardiogram.

Patients	Initial symptom	Complication	Treatment	Result	Ref.
*44 M	Dyspnea, edema	nephritis	PSL (1mg/kg/day)	EF: 40%→ 71% (14 days)	[12]
*26 F	Fever, anuria, dyspnea	nephritis	PSL (1mg/kg/day) + mPSL pulse(1g/day, 3days) +IVCY+ IVIg (0.4g/kg, 5days)	EF: 30%→ 72% (1 month)	[12]
*63 F	Chest pain, dyspnea	Neuropsychiatric lupus, enteritis (developed later)	PSL (1mg/kg/day)	EF: 38%→ 38% (11 days) → expired	[11]
23 F	Dyspnea, edema	nephritis	mPSL pulse(1g/day, 3days) + IVCY (1g/day, 6 courses)	EF: 40%→ 55% (19 days) → expired	[13]
43 F	Flu-like syndrome, dyspnea	none	PSL 20mg/day + hydrochloroquine 400mg/day	EF: 25%→ #34% (12 month)	[3]
15 F	Fever, polyarthritis	none	PSL (1mg/kg) +mPSL (500mg/day, 4 days)	EF: 30%→ 50% (5 days) → recurrence	[3]
22 M	Cutaneous flare, proteinuria	nephritis	PSL (60mg/day) + IVCY (1g/day, 4courses)	EF: 24%→ #53% (4 months)	[3]
18 M	Fever, malar rash, edema	Deep vein thrombosis (in past history)	PSL (60mg/day) + mPSL pulse(1g/day) +IVCY +IVIg (0.4g/kg, 5days)	EF: 30%→ 50% (7 days)	[14]
*our case	Dyspnea	none	PSL (0.5mg/kg/day) + MZR 200mg/day	EF: 31%→ 48%(24 months)	