

Lupus Myocarditis: A Case–Control Study from China

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Abstract

Background: Myocarditis is an uncommon but serious manifestation of systemic lupus erythematosus (SLE). This study aimed to investigate clinical characteristics and outcomes of lupus myocarditis (LM) and to determine risk factors of LM in hospitalized Chinese patients with SLE.

Methods: We conducted a retrospective case–control study. A total of 25 patients with LM from 2001 to 2012 were enrolled as the study group, and 100 patients with SLE but without LM were randomly pooled as the control group. Univariable analysis was performed using Chi-square tests for categorical variables, and the Student's *t*-test or Mann–Whitney *U*-test was performed for continuous variables according to the normality.

Results: LM presented as the initial manifestation of SLE in 7 patients (28%) and occurred mostly at earlier stages compared to the controls (20.88 ± 35.73 vs. 44.08 ± 61.56 months, *P* = 0.008). Twenty-one patients (84%) experienced episodes of symptomatic heart failure. Echocardiography showed that 23 patients (92%) had decreased left ventricular ejection fraction (<50%) and all patients had wall motion abnormalities. A high SLE Disease Activity Index was the independent risk factor in the development of LM (odds ratio = 1.322, *P* < 0.001). With aggressive immunosuppressive therapies, most patients achieved satisfactory outcome. The in-hospital mortality was not significantly higher in the LM group than in the controls (4% vs. 2%, *P* = 0.491).

Conclusions: LM could result in cardiac dysfunction and even sudden death. High SLE disease activity might potentially predict the occurrence of LM at the early stage of SLE. Characteristic echocardiographic findings could confirm the diagnosis of LM. Early aggressive immunosuppressive therapy could improve the cardiac outcome of LM.

Key words: Echocardiography; Lupus Myocarditis; Prognosis; Systemic Lupus Erythematosus

INTRODUCTION

The heart is frequently involved in systemic lupus erythematosus (SLE), and the prevalence of cardiac involvement in SLE has been reported to be higher than 50%. All cardiac structures can be involved, including pericardium, endocardium, myocardium, coronary arteries, and conduction tissue.^[1] Myocarditis is an uncommon manifestation of SLE and presented in approximately 9% of patients with SLE in clinical studies. However, in 57% of postmortem studies from the 1950s and 1960s, indicating that subclinical myocardial involvement is common.^[2] Lupus myocarditis (LM) can lead to arrhythmias, conduction disturbances, dilated cardiomyopathy, heart failure, and even sudden death, thus this form merits clinical attention.

To the best of our knowledge, only three large case series in the literature^[3–5] have described the clinical characteristics of LM. Here, we conduct a case–control study of LM to improve the understanding of this rare manifestation in Chinese patients with SLE.

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METHODS

Patients

We identified hospitalized patients with LM admitted to Peking Union Medical College Hospital between 2001 and 2012. The identification was achieved through a diagnosis database search with International Classification of Diseases, 10th Revision diagnosis of LM (code M32.103+). For the control group, patients suffering from SLE, but free from LM, in the same institution during the same period and matched for sex and age were randomly retrieved from the database through the function of “select random sample of cases” in SPSS. The LM/non-LM patient ratio was 1:4. All patients fulfilled the revised American College of Rheumatology classification criteria for SLE. Myocarditis was defined as echocardiographic abnormalities including global or segmental wall motion abnormalities (WMAs) with/without decreased ejection fraction and the abnormalities were not attributed to other known causes. Cardiomyopathy due to coronary artery disease was excluded if the patients had risk factors or characteristic manifestations of electrocardiogram (ECG) or echocardiography of coronary artery disease. Viral myocarditis was excluded if the patient had a history of confirmed viral infection. Cardiomyopathy due to hypertension was excluded if the patient had a long history of hypertension. Uremic cardiomyopathy was excluded if the patient was at the end-stage renal disease. Cardiomyopathy due to valvular disease was excluded based on the echocardiographic results. Cardiomyopathy due to toxicity from medications was excluded if the suspected drug history was presented. The diagnosis of heart in every patient was assessed by an experienced attending cardiologist.

Data collection

Patient information was obtained from medical records, including demographic data, the clinical manifestations of SLE (mucocutaneous involvements, arthritis, nephropathy, thrombocytopenia, and neuropathy), laboratory data (hypocomplementemia, anti-nuclear antibody, anti-dsDNA antibody, anti-Sm, anti-RNP, anti-SSA, anti-SSB, anti-rRNP, anti-cardiolipin antibodies, and lupus anticoagulant), and treatments. The activity of SLE was measured using the SLE Disease Activity Index (SLEDAI) 2000. LM information included data on symptoms, New York Heart Association (NYHA) classification, transthoracic echocardiography, ECG, creatine kinase (CK), CK-MB, cardiac troponin I (cTnI), brain natriuretic peptide (BNP), and N-terminal pro-BNP (NT-proBNP).

Statistical analysis

Univariable analysis was performed using Chi-square tests for categorical variables, and the Student's *t*-test or Mann-Whitney *U*-test was performed for continuous variables according to the normality. Fisher's exact test was used when indicated. Variables found to be significant at the 0.05 level were entered into a logistic regression model with LM as the dependent variable. All *P* values were two-tailed, and values of *P* < 0.05 were considered to be statistically significant. The SPSS for Windows, version 17.0 (Chicago, Illinois, USA), software package was used for analysis.

RESULTS

Our initial database search identified 35 patients with discharge diagnosis of LM out of 3744 patients with discharge diagnosis of SLE. Their charts were reviewed and 10 patients were excluded for the following reasons: (1) Seven without definite echocardiographic abnormalities of LM: 1 with increased echogenicity and thickening of myocardium but without WMAs, 1 with conduction defect only, 1 with likely myopericarditis, 1 with positive stress testing suggesting coronary artery disease, 1 with sinus tachycardia only, 1 with widened ascending aorta, and 1 with left atrial and ventricular enlargement; (2) One with echocardiographic abnormalities attributed to coronary atherosclerotic heart disease; and (3) Two with echocardiographic abnormalities attributed to coronary arteritis. Thus, 25 patients with definite LM were enrolled for the final analysis, with 100 matched patients as the control group who underwent echocardiography without any sign of LM.

Demographic, clinical, and laboratory profiles

The association of LM with demographic, clinical, and laboratory variables is shown in Table 1. There were no differences in age, sex, and flare-up age between the LM and control groups. The in-hospital mortality was not significantly higher in the LM group than in the controls (4% vs. 2%, *P* = 0.491). However, the disease duration was shorter in the LM group than in the controls (20.88 ± 35.73 vs. 44.08 ± 61.56 months, *P* = 0.008). Among the patients diagnosed with LM, 84% (21/25) had the disease duration of SLE < 3 years in our series. LM was the initial presentation of SLE in 7 patients (28%). A significantly higher prevalence of nephropathy and thrombocytopenia was observed in the LM group than in controls. However, anti-RNP was more frequent in the controls than in the LM group. Disease activity assessed by the SLEDAI was higher in the LM group than in the controls. There were no significant differences in other clinical and autoantibody profiles.

Multivariable analysis indicated that the independent risk factor associated with LM was SLEDAI (odds ratio [*OR*] = 1.322, 95% confidence interval [*CI*]: 1.178–1.483, *P* < 0.001), and the probable protective factor was anti-RNP (*OR* = 0.223, 95% *CI*: 0.056–0.888, *P* = 0.018).

Manifestations of lupus myocarditis

The presenting symptoms and signs of LM are shown in Table 2. Most patients presented with symptoms and signs consistent with congestive heart failure, and four patients did not have any cardiac symptoms including one patient with reduced left ventricular ejection fraction (LVEF) (34%). Eighty percent of patients were NYHA classification Class III or Class IV. Acute decompensated heart failure occurred in 12 patients, 10 of which had precipitating factors (infection, hypervolemia, hypertension, or anemia), and 6 of them accepted mechanical ventilation. Only 4 patients (16%) reported chest pain. Three patients had severe complication: One

Table 1: Demographic and clinical characteristics of study population

Variables	LM cases (n = 25)	Controls (n = 100)	Z or χ^2	P
Female, n (%)	22 (88)	88 (88)	<0.001	1.000
Age (years), mean \pm SD	28.00 \pm 12.28	28.66 \pm 12.35	-0.173*	0.865
Flare-up age (years), mean \pm SD	26.28 \pm 12.33	25.20 \pm 11.54	-0.490*	0.627
Disease duration (months), mean \pm SD	20.88 \pm 35.73	44.08 \pm 61.56	-2.612*	0.008
In-hospital mortality, n (%)	1 (4)	2 (2)	0.342	0.491
SLEDAI, mean \pm SD	18.71 \pm 7.14	9.08 \pm 5.28	-5.294*	<0.001
Clinical manifestations, n/N (%)				
Mucocutaneous involvement	13/25 (52)	62/100 (62)	0.833	0.494
Arthritis	9/25 (36)	44/100 (44)	0.524	0.506
Nephropathy	21/24 (88)	50/100 (50)	11.121	0.001
Thrombocytopenia	13/25 (52)	17/99 (17)	13.201	0.001
Nervous system involvement	8/25 (32)	21/100 (21)	1.385	0.290
Antibody, n/N (%)				
ANA	25/25 (100)	100/100 (100)		1.000
Anti-dsDNA antibody	14/25 (56)	54/99 (55)	0.017	1.000
Anti-Sm antibody	7/25 (28)	32/98 (33)	0.199	0.811
Anti-RNP antibody	5/25 (20)	42/98 (43)	4.408	0.040
Anti-SSA antibody	10/25 (40)	49/98 (50)	0.798	0.502
Anti-SSB antibody	6/25 (24)	20/98 (20)	0.154	0.784
Anti-rRNP antibody	4/25 (16)	23/98 (24)	0.649	0.590
ACL	5/24 (21)	15/89 (17)	0.205	0.763
LA	6/17 (35)	16/79 (20)	1.792	0.208
Hypocomplementemia, n/N (%)	21/24 (88)	70/99 (71)	2.830	0.121

LM: Lupus myocarditis; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; ANA: Antinuclear antibody; ACL: Anticardiolipin antibody; LA: Lupus anticoagulant; SD: Standard deviation. *: Z values.

Table 2: Presenting symptoms and clinical signs of LM (n = 25)

Variables	Number of patients, n (%)
Symptom	
Asymptom	4 (16)
Dyspnea	21 (84)
Paroxysmal nocturnal dyspnea	19 (76)
Orthopnea	12 (48)
Chest pain	4 (16)
Palpitation	9 (36)
Sign	
Lung rales	14 (56)
Jugular venous distention	3 (12)
Gallop rhythm	5 (20)
Peripheral edema	10 (40)
NYHA classification	
NYHA I	4 (16)
NYHA II	1 (4)
NYHA III	7 (28)
NYHA IV	13 (52)
Acute decompensated heart failure	12 (48)
With precipitating factors	10 (40)
Without precipitating factors	2 (8)

LM: Lupus myocarditis; NYHA: New York Heart Association.

with complete atrioventricular block and cardiac shock, 1 with ventricular fibrillation, and 1 with left ventricular thrombus and arterial thromboembolism who was diagnosed with antiphospholipid syndrome (APS) because of the positive result of lupus anticoagulant.

Echocardiographic, ECG findings, and biomarkers of LM are shown in Table 3. Echocardiographic changes are characteristic. All patients had WMA. Eighty-four percent (21/25) had global hypokinesia, and 16% (4/25) had segmental hypokinesia. Eighty-eight percent (22/25) were WMA of left ventricle and 12% (3/25) were WMA of both ventricles. Reduced LVEF (<50%) was found in 92% of the patients, and 4 had LVEF <30% (3 had <20%). Approximately half (52%, 13/25) had ventricular dilatation. Nearly two-thirds (64%, 16/25) had valvular abnormalities, and all of the concurrent valvular abnormalities did not account for the reduced LVEF and ventricular dilatation. Eighty-four percent (21/25) had pericardial effusion.

The most common finding on ECG was sinus tachycardia (80%). Six patients had other arrhythmia, which are depicted in Table 3, and 64% presented with nonspecific ST-T wave changes. In terms of biomarkers of myocarditis, a minority of the patients had elevated CK and CK-MB, but 55% (11/20) of the patients had elevated cTnI. Seven patients had BNP measured, and all had a BNP level of >400 ng/L. Nine patients had NT-proBNP measured, and eight had an NT-proBNP level of >10,000 pg/ml.

Treatment

All patients with LM received high-dose systemic corticosteroids with subsequent dose tapering. Twenty patients received 500 mg to 1 g daily intravenous methylprednisolone for 1–5 days. Twelve patients received intravenous immunoglobulin, and two patients received plasmapheresis. Twenty-two patients received

Table 3: Echocardiographic and electrocardiographic findings and biomarkers of LM (n = 25)

Variables	Number of patients, n (%)
Echocardiography	
Wall motion abnormalities	
Segmental hypokinesia of LV	4 (16)
Segmental to global hypokinesia of LV	3 (12)
Mild global hypokinesia of LV	3 (12)
Moderate global hypokinesia of LV	9 (36)
Severe global hypokinesia of LV	3 (12)
Global hypokinesia of both ventricles	3 (12)
LVEF	
<30%	4 (8)
30–39%	7 (28)
40–49%	12 (48)
≥50%	2 (8)
Chamber enlargement	
Left atrial enlargement	2 (8)
LV enlargement	2 (8)
Left atrial and ventricular enlargement	7 (28)
Whole heart enlargement	4 (16)
Valvular abnormality	
Increased echogenicity or thickening	5 (20)
Functional regurgitation	14 (56)
Pericardial effusion	
Mild	17 (68)
Moderate	4 (16)
Electrocardiography	
Sinus tachycardia	20 (80)
T wave change	16 (64)
Atrial premature beat	2 (8)
Ventricular premature beat	1 (4)
Q-T prolong	1 (4)
LBBB with ventricular fibrillation	1 (4)
III atrioventricular block	1 (4)
Serous biomarker	
Elevated CK	5/23 (22)
Elevated CK-MB	5/22 (23)
Elevated cTnI	11/20 (55)
Elevated BNP	7/7 (100)
Elevated NT-proBNP	9/9 (100)

LM: Lupus myocarditis; LV: Left ventricle; LVEF: Left ventricular ejection fraction; CK: Creatine kinase; cTnI: Cardiac troponin I; BNP: Brain natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide; LBBB: Left bundle branch block; CK-MB: Creatine kinase-myocardial band.

cyclophosphamide at a dosage of 0.4–0.6 g/w, 1 g/m or 0.1 g/d, and 1 deceased patient and 2 patients complicated with severe infection did not receive immunosuppressive therapy. Approximately half of the patients accepted traditional treatment of heart failure, including diuretics, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker, and β -blocker.

Outcomes

The details of the echocardiographic follow-up findings and overall outcomes of LM are shown in Table 4. In our series, there was one in-hospital death. The deceased patient died from

complete atrioventricular block, and cardiac shock attributed to LM. Three patients left the hospital before work-up and treatment were completed, so we could not tell their outcomes. Among the remaining 21 patients who underwent follow-up for at least 6 weeks, 1 patient suffered deterioration in WMA and symptoms of heart failure at the last follow-up, and all other patients achieved clinical improvement including 1 patient who did not undergo follow-up echocardiography but achieved definite clinical recovery from heart failure.

As to echocardiographic outcomes, 20 patients had first follow-up echocardiography within 10 weeks, and 12 of the patients had follow-up echocardiography for a mean duration of 15 months (range: 1.25–67). At the last echocardiographic follow-up, 80% (16/20) had improved LVEF including 70% (15/20) at the first follow-up and 65% (13/20) within 4 weeks; 70% (14/20) achieved complete recovery in WMA including 50% (10/20) at the first follow-up and 40% (8/20) within 4 weeks. In addition, the 15 patients got significantly improved LVEF (from $36.85 \pm 10.84\%$ to $55.27 \pm 9.15\%$, $P < 0.001$) at the first follow-up. With improvement in WMA and LVEF, 6 patients showed complete recovery in ventricular dilation. During follow-up, 1 patient suffered recurrence of WMA on the 10-month follow-up, 1 patient suffered deterioration in WMA and symptoms, and 2 patients suffered mild deterioration in LVEF but had no obvious symptom of heart failure. With the improvement of echocardiography, the BNP and NT-proBNP level decreased. Three patients reexamined BNP, and the level decreased from 2284 ± 1753 ng/L to 641 ± 258 ng/L. Six patients reexamined NT-proBNP, and the level decreased from 133360 ± 233083 pg/ml to 35752 ± 64086 pg/ml.

DISCUSSION

To the best of our knowledge, we report the first large case series of Chinese patients with LM in this study. The diagnosis of LM in our study is based on the definite diagnosis of SLE and characteristic echocardiographic abnormalities. Although the gold standard of diagnosing LM remains endomyocardial biopsy and exclusion of other causes, such as viral and ischemic cardiomyopathy, it is used infrequently because of perceived risks and the lack of specificity of the histology. The histological findings of LM resemble other forms of myocarditis, including viral-induced myocarditis. There is a perivascular and interstitial infiltrate of mononuclear cells (lymphocytes, plasma cells, and macrophages) and myocyte injury (myocardial degeneration, fibrosis, and scarring).^[6] Immunofluorescence studies demonstrated fine granular immune complex and complement deposition in the walls and perivascular tissues of myocardial blood vessels,^[7] which indicates that LM is an immune complex-mediated vascular phenomenon that leads to complement activation, inflammation, and myocardial injury.

In most recent clinical reports,^[1,3,5,8-10] the diagnosis of LM was based on echocardiographic evidence of impaired LVEF and/or WMA, and exclusion of myocardopathy/myocarditis

Table 4: Echocardiographic follow-up findings and overall outcomes of LM

Number	Sex	Age (years)	Echocardiography	First echocardiography follow-up	Last echocardiography follow-up (time)	Overall outcomes
1	Male	28	LVEF 19% global WMA of BV VD of BV	LVEF 44% PR in WMA PR in VD	LVEF 45% PR in WMA with more improvement PR in VD (7 months later)	Improved
2	Female	23	LVEF 20% global WMA of BV VD of BV	LVEF 50% PR in WMA CR in VD	LVEF 59% CR in WMA CR in VD (17 months later)	Improved
3	Female	24	LVEF 20% global WMA of BV VD of BV	LVEF 47% PR in WMA no change in VD	LVEF 50% CR in WMA CR in VD (4 months later)	Improved
4	Female	32	LVEF 28% global WMA of LV (severe)	LVEF 72% CR in WMA	NA	Improved
5	Female	23	LVEF 30% segmental to global WMA of LV	LVEF 29% deterioration in WMA	LVEF 33% more deterioration in WMA (6 weeks later)	Deterioration
6	Female	53	LVEF 30% global WMA of LV (severe) VD of LV	LVEF 41% PR in WMA PR in VD	LVEF 52% CR in WMA CR in VD (2 months later)	Improved
7	Male	34	LVEF 32% segmental to global WMA of LV VD of BV	LVEF 33% no change in WMA no change in VD	NA	Improved
8	Female	39	LVEF 33% global WMA of LV (severe) VD of LV	NA	NA	Leave the hospital
9	Female	27	LVEF 34% global WMA of LV (moderate) VD of LV	LVEF 37% no change in WMA	NA	Improved
10	Female	24	LVEF 36% global WMA of LV (moderate) VD of LV	LVEF 56% CR in WMA CR in VD	LVEF 55% CR in WMA CR in VD (63 months later)	Improved
11	Female	22	LVEF 38% global WMA of LV (moderate) VD of LV	LVEF 51% CR in WMA PR in VD	LVEF 54% CR in WMA CR in VD (4 months later)	Improved
12	Female	66	LVEF 40% segmental to global WMA of LV	LVEF 54% CR in WMA	LVEF 60% recurrence in WMA (10 months later)	Recurrence
13	Female	26	LVEF 42% segmental WMA of LV VD of LV	LVEF 47% no change in WMA no change in VD	LVEF 42% deterioration in WMA no change in VD (6 weeks later)	Improved
14	Female	17	LVEF 45% global WMA of LV (moderate)	LVEF 58% CR in WMA	NA	Improved
15	Female	13	LVEF 45% global WMA of LV (mild)	NA	NA	Leave the hospital
16	Female	32	LVEF 45% global WMA of LV (moderate)	NA	NA	Improved
17	Female	10	LVEF 46% global WMA of LV (moderate)	LVEF 63% CR in WMA	LVEF 64% CR in WMA (5 weeks later)	Improved
18	Female	23	LVEF 46% global WMA of LV (moderate)	LVEF 66% CR in WMA	NA	Improved
19	Female	26	LVEF 46% global WMA of LV (moderate)	LVEF 69% CR in WMA	NA	Improved
20	Female	25	LVEF 48% segmental WMA of LV VD of LV	LVEF 47% CR in WMA PR in VD	NA	Improved
21	Female	39	LVEF 48% global WMA of LV (mild) VD of LV	LVEF 57% CR in WMA no change in VD	NA	Improved
22	Female	20	LVEF 49% global WMA of LV (mild)	LVEF 45% no change in WMA	LVEF 73% CR in WMA (67 months later)	Improved
23	Female	19	LVEF 49% global WMA of LV (moderate) VD of LV	LVEF 54% PR in WMA no change in VD	LVEF 49% PR in WMA CR in VD (6 months later)	Improved
24	Male	39	LVEF 50% segmental WMA of LV			Died
25	Female	16	LVEF 56% segmental WMA of LV	NA	NA	Leave the hospital

LM: Lupus myocarditis; LVEF: Left ventricular ejection fraction; WMA: Wall motion abnormality; BV: Both ventricles; VD: Ventricular dilation; LV: Left ventricle; PR: Partial recovery; CR: Complete recovery; NA: Not available.

induced by other causes such as coronary artery disease due to premature atherosclerosis, hypertension, renal failure, valvular disease, toxicity from medication, and viral infection. In the literature, it is suggested that wall hypokinesis, especially global hypokinesis, in the absence of other known causes is strongly suggestive of myocarditis. We followed this definition in our study. All of the patients in our series had echocardiographic evidence of WMA, and 92% of them had evidence of impaired LVEF. Cardiomyopathy due to coronary artery disease, viral infection, hypertension, chronic renal

failure, valvular disease, and toxicity from medication was excluded according to the rules mentioned in the method part. In addition, myocardopathy due to microthrombosis should be considered in a patient who had secondary APS. However, myocardial microthrombosis occurs more commonly in patients with catastrophic APS,^[11] so this diagnosis could be denied in this patient because she could not be diagnosed as catastrophic APS. In most cases, the WMAs were concurrent with pericarditis and valvular abnormalities, which could help to confirm the diagnosis of LM also.

The majority of patients with LM presented with symptoms and signs consistent with congestive heart failure, and 24% (6/25) required mechanical ventilation because of severe acute decompensated heart failure. Most patients of LM had resting tachycardia disproportionate to body temperature and more than half of the patients with LM had ST and T wave abnormalities. All of the above findings are consistent with previous reports.^[3,5,9,10] Therefore, LM should be suspected in patients with SLE presenting the above clinical characteristics. And then, echocardiography should be ordered to look for more evidence in these patients. Rarely, LM had severe complications such as cardiac sudden death and mortal cardiac shock.

The prevalence of LM in hospitalized patients with SLE in our center was 0.67% that was lower than the reported prevalence of LM in SLE.^[2] This may suggest that most LM was clinically neglected because of its asymptomatic presentation.

Most LM occurs at the early stage of SLE and can be the first presentation of SLE, which is consistent with the previous studies.^[3,5] Although univariable analysis indicated that renal involvement and hematological involvement were more frequent among patients with LM than among controls, multivariable analysis demonstrated that the independent risk factors for myocarditis in SLE was a high SLEDAI score, as the LUMINA^[4] study found. Therefore, we recommend that cardiac evaluation, especially echocardiography, should be done in patients with high SLE disease activity and in patients at early stage of SLE.

The antibody profile of LM in our study was different to previous studies. We found that anti-RNP is the probable protective factor of LM, which was contrary to previous study.^[5,12] Nonetheless, the previous conclusion was drowned in a subset of patients with SLE who had both skeletal myositis and myocarditis in Bornstein's study.^[12] In our series, there were only 4 patients with incomplete myositis and none of them had positive anti-RNP. In consequence, the controversial findings need clarification in further studies. In addition, we failed to corroborate the associations of LM with anti-SSA and antiphospholipid antibodies,^[5,13,14] as the LUMINA^[4] study did not. However, both patients suffering from lethal arrhythmia were positive for anti-SSA, which supports the established association between anti-SSA and conduction defect again.^[15]

In our series, all patients with LM received high-dose systemic corticosteroids, most along with cyclophosphamide. Current treatment strategies of LM are based on clinical experience rather than randomized trials. In most of the literature, high-dose steroids have been used as a first-line treatment. Both intravenous immunoglobulin and immunosuppressive agents, such as cyclophosphamide, mycophenolate mofetil, and azathioprine, have also been used, often along with high-dose steroids. There is also a case report of successful therapy of refractory LM with rituximab,^[16] in which the patient still suffered from symptoms of heart failure after therapy of two courses of intravenous pulse

methylprednisolone and monthly cyclophosphamide pulses. Thus, in the context of success of rituximab in refractory SLE,^[17,18] if we encounter patients with refractory LM, we can attempt to treat it with rituximab.

After early immunosuppressive therapy, most patients got clinical and echocardiographic improvement, as reported in previous studies.^[3,5] We also noticed that these improvement would be observed rapidly. Most patients achieved it within 1–4 weeks after therapy. One deceased patient and one patient suffering recurrence were observed in our series. The deceased patient had the highest level of serous CK-MB (almost 40 times above than the high normal range) and troponin I (almost 300 times above than the high normal range), which indicate the severity of myocardial injury. In the other two studies,^[3,5] all the deceased patients with LM had long duration of SLE from 8 to 21 years. This may suggest that severe myocardial injury and long duration of SLE may be the predictors of mortality. In addition, the cohort of LM from Mayo Clinic^[5] suggest that a low LVEF on presentation which does not improve with treatment is an indicator of poor prognosis. And the LUMINA^[4] study indicate that the prognosis of patients with LM was comparable to those without LM for the first 5 years of disease, after which survival in the myocarditis group dropped drastically, and most death were not related to myocardial involvement.

Except for SLE, dermatomyositis/polymyositis, systemic scleroderma, and eosinophilic granulomatosis with polyangiitis are more commonly associated with myocarditis/cardiomyopathy.^[19,20] Unlike LM, cardiac involvement is the common cause of death in all of the above three diseases.^[21-25] In consequence, why is the outcome of LM good in most cases? We propose two probable reasons: First, aggressive treatment in a timely manner results in a good outcome. Since LM is accompanied by high SLE disease activity in most instances, it would be treated with aggressive immunosuppressive therapy without delay. Second, we speculate that myocardial necrosis is not severe in most patients with LM, because most patients had no elevation or low level of biomarkers of cardiac injury. In addition, a recent study^[26] of cardiovascular magnetic resonance of LM showed that the frequency of high T2 and early gadolinium enhancement abnormalities indicating myocardial edema and hyperemia was similar with myocarditis caused by other etiologies, however, the frequency of late gadolinium enhancement abnormalities indicating necrosis and fibrosis was lower than myocarditis caused by other etiologies, which also support our speculation.

The major limitations of our study are that most patients with LM had no information about coronary angiogram and biopsy of myocardium to exclude cardiomyopathy due to other causes. The strict differential diagnosis had been made based on the clinical information by an experienced attending cardiologist, and this is a common method for diagnosis in the real practice. And we had explanation about the diagnosis

in the second paragraph of this section in detail. Therefore, we think that would be acceptable in a retrospect study.

In conclusion, LM is an uncommon but serious organic involvement of SLE. Most LM occurs at the early stage of SLE. A high SLEDAI score was the independent risk factor of LM. Characteristic echocardiographic findings consistent with LM could help confirm the diagnosis. Although LM can result in death rarely, after aggressive immunosuppressive therapy, the outcomes of LM are good in most cases.

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Conflicts of interest

There are no conflicts of interest.

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