Case report

Infective endocarditis in a patient with lupus nephritis who was undergoing immunosuppressive therapy: A case of survival

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Abstract

Systemic lupus erythematosus is an autoimmune disease associated with mild valvular regurgitation. However, there have been no detailed reports of infective endocarditis in patients with systemic lupus erythematosus. Here, we describe a case of a 55-year-old woman without any cardiac abnormalities who was diagnosed with lupus nephritis by renal biopsy; she contracted infective endocarditis while receiving immunosuppressive therapy. Our case emphasizes that special consideration of the occurrence of infective endocarditis, and its early diagnosis and treatment are mandatory for patient survival. We propose that echocardiography should be performed before treating patients with systemic lupus erythematosus who have an uncertain cardiac status.

Key words: systemic lupus erythematosus, lupus nephritis, infective endocarditis, immunosuppressive therapy

(J Rural Med 2017; 12(2): 139–145)

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that can damage the heart, kidneys, joints, skin, lungs, blood vessels, liver, and nervous system. One major complication of SLE is valvular thickening and valve vegeta-

tion, commonly involving the mitral valve[1], which can lead to mild valvular regurgitation that is clinically irrelevant in most patients[2]. Among patients with SLE, the prevalence of valvular abnormalities ranges from 18% to 61%, with a median prevalence of 33%[3–5]. The co-occurrence of valvular disease and abnormalities in the reticuloendothelial system and complement pathway in SLE can place patients at a risk for developing infective endocarditis (IE)[1, 6]. However, the prevalence of IE among patients with SLE who receive immunosuppressive therapy is unknown.

Here, we describe the case of a middle-aged woman with SLE complicated by IE who survived owing to early detection and proper treatment of IE. Similar strategies could be employed to effectively treat other patients in the future.

Case Report

A 55-year-old Japanese woman was admitted to our hospital for suspected glomerulonephritis. Proteinuria, as shown by a urine protein/creatinine ratio of 1.8 g, was identified 4 months before admission, which was confirmed by the subsequent findings of abnormal leukocyte and granular casts by renal biopsy. The patient had previously been diagnosed with mixed connective tissue disease (MCTD) 17 years ago. Echocardiography performed at that time had shown pulmonary hypertension, with an estimated right ventricle pressure of 51 mmHg, without any valvular abnormalities. In addition, autoimmune hepatitis had been identified by liver biopsy 14 years prior to the present admission. Thus, a daily dose of 8-mg oral glucocorticoids (GC) had been administered for MCTD and autoimmune hepatitis in the rheumatology department. Positive anti-Smith antibody and a high titer of anti-double strand (ds) DNA antibody (920 IU/mL) at the present admission indicated a more like-

Table 1 Laboratory tests on admission

Blood tests	Values	(Continued)		(Continued)	
RBC	397×10^4 /μL	CK	31 IU/L	anti-dsDNA Ab	920 IU/mL
Hb	11 g/dL	AST	37 IU/L	anti CCP Ab	< 0.6 U/mL
Ht	35%	ALT	17 IU/L	anti GBM Ab	< 10 EU
Plt	24.8×10^4 /μL	LDH	174 IU/L	MPO-ANCA	< 10 EU
WBC	3,550 /μL	ALP	424 IU/L	PR3-ANCA	< 10 EU
St	0%	γGTP	156 IU/L	ASL	77 IU/mL
Sg	75.2%	HbA1c	6% (NGSP)	KL-6	275 U/mL
Mono	2.5%	FBS	121 mg/dL		
Lym	22%	T-C	119 mg/dL		
Eosi	0.3%	LDL-C	71 mg/dL	urinalysis	values
Baso	0%	TG	178 mg/dL	protein	2+
TP	7.1 g/dL	CRP	2.43 mg/dL	occult blood	±
Alb	2.2 g/dL	IgG	2,470 mg/dL	glucose	−
BUN	19 mg/dL	IgM	66.4 mg/dL	RBC	10–19 /hpf
Cr	0.72 mg/dL	IgA	892 mg/dL	WBC	10–19 /hpf
eGFR	65 mL/min/1.73 m^2	IgE	177.8 IU/mL	protein (collection)	3.87 g/day
UA	6.8 mg/dL	C_3	36.2 mg/dL	NAG	29.6 U/gCr
Na	141 mEq/L	C_4	3.2 mg/dL	$β_2MG$	6.4 mg/gCr
Cl	109 mEq/L	CH_{50}	< 12.0 U/mL	hyaline casts	2+
K	3.8 mEq/L	ANA	≥ 1,280 fold	epithelial casts	1+
Ca	8.1 mg/dL	RF	≤ 5 IU/mL	leukocyte casts	1+
iP	3.2 mg/dL	C1q	< 1.5 μg/mL	granulocyte casts	1+

Hb: hemoglobin, Ht: hematocrit, Plt: platelet, St: stab neutrophils, Seg: segmented neutrophils, Mono: monocytes, Lym: lymphocytes, Eosi: eosinophils, Baso: basophils, TP: total protein, Alb: albumin, BUN: blood urea nitrogen, Cr: serum creatinine, eGFR: estimated glomerular filtration rate, CK: creatine kinase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactic acid dehydrogenase, ALP: alkaline phosphatase, γGTP: γ-glutamyl transpeptidase, FBS: fasting blood sugar, T-C: total cholesterol, LDL-C: low-density lipoprotein cholesterol, TG: triglyceride, CRP: C-reactive protein, ANA: antinuclear antibody, RF: rheumatoid factor, Ab: antibody, CCP : cyclic citrullinated peptide, GBM: glomerular basement membrane, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase 3 anti-neutrophil cytoplasmic antibody, ASL: antistreptolysin, UP: urinary protein, UOB: urinary occult blood, UG: urinary glucose, NAG: N-acetyl-β-D-glucosaminidase, $β_2MG$: $β_2$ microglobulin.

ly diagnosis of SLE than MCTD. The patient was admitted to the nephrology department for evaluation and control of disease activity.

The medical history of the patient consisted of hypertension and positive hepatitis C virus antibody. No remarkable family history, alcohol use, smoking, or allergy was noted. Candesartan cilexetil/hydrochlorothiazide, famotidine, alendronate sodium hydrate, and loxoprofen sodium hydrate had been administered. Upon admission, the patient had a blood pressure of 126/80 mmHg, pulse rate of 99 beats per minute, body temperature of 36.7°C, and oxygen saturation of 99% at room air. Physical examination revealed the absence of heart murmur, crackles in lungs, edema, cutaneous, or articular findings. Findings of the head, neck, chest, abdomen, and extremities were unremarkable. The results of laboratory exams are shown in Table 1. The cardiothoracic ratio of the patient was 58% by chest radiography, and reticular shadows in both lower lung fields were visualized on computed tomography (CT). No abnormalities were indicated on electrocardiogram, and echocardiography detected no valvular abnormalities, dysfunction, or right ventricular load. The size of the kidneys was normal (right: 8.8 × 4.2 cm, left: 9.2 × 5.1 cm). A diagnosis of lupus nephritis (LN) with nephrotic syndrome was made based on the clinical course and the results of laboratory tests, and intravenous pulse GC therapy (1,000 mg methylprednisolone daily for 3 doses) was started, followed by daily oral administration of 60 mg of GC (1 mg/kg/day). The patient underwent renal biopsy on Day 7 and was classified as IV-S (A) + V type according to the International Society of Nephrology/Renal Pathology Society classification. She was prescribed 1 g of trimethoprim-sulfamethoxazole per day for prophylaxis of pneumocystis pneumonia; however, owing to a decline in platelets and an elevation in hepatic-cystic enzymes, trimethoprim-sulfamethoxazole was changed to pentamidine inhalation once a month. Although we planned to adminis-

ter intravenous pulse cyclophosphamide (CYC) along with GC, as recommended by the American College of Rheumatology guidelines for LN, we postponed its administration owing to esophageal candidiasis confirmed by upper endoscopy, which emerged during GC treatment. After treatment of the candidiasis by 200 mg of fluconazole per day, high-dose (800 mg) CYC (500–1,000 mg/m^2 IV once a month scheduled for six doses) was administered from Day 64. Estimated glomerular filtration rate was maintained above 60 mL/min/1.73 m^2 throughout the treatment course. LN activity was well managed, as judged by urine protein levels < 0.5 g per day, a decrease in anti-ds DNA antibody titers, and an increase in C3/C4 ratio (Figure 1). Therefore, the GC dose was gradually decreased, without subsequent administration of CYC.

However, before her planned hospital discharge, the patient developed a fever owing to a urinary tract infection and bacteremia. Methicillin-sensitive Staphylococcus aureus (MSSA) was detected in four bottles from two sets of blood culture on Day 81. Administration of 1 g of ceftriaxone per day following amoxicillin-clavulanate for 2 weeks led to improvement; however, after the antibiotics were stopped, fever relapsed and MSSA was detected in four bottles from two sets of blood culture on Day 105. As IE was suspected as the possible cause of the consecutive bacteremia, antibiotic therapy was started with 4.5 g of ampicillin-sulbactam four times per day, and echocardiography was performed on Day 107, after excluding other foci of infections. Transthoracic echocardiography revealed an aneurysm in the chordae tendineae of the mitral valve and backward flow from the left ventricle, indicating new mitral valve regurgitation (Figures 2a, b, c, d). Transesophageal echocardiography performed the next day showed findings consistent with IE (Figures 2e, f). Although the patient had no abnormal neurological findings, diffusion-weighted magnetic resonance imaging revealed multiple fresh microinfarctions in the brain (Figures 3a, b, c, d, e). The patient did not have impaired vision, hemorrhage or Roth spots in the fundus of the eye, or Janeway lesions or Osler's nodes in her body. Brain CT did not detect cerebral hemorrhage on Day 110 (Figure 3f). A diagnosis of IE was made according to the Duke criteria, and administration of 60 mg of gentamycin twice per day was started in addition to 1.5 g of ampicillin-sulbactam three times per day. From Day 110, symptoms of congestive heart failure emerged, and the cardiorespiratory state of the patient worsened over time (Figures 4a, b). Although the temporary use of dobutamine, dopamine, and oxygen, and consecutive use of diuretics were partially effective in controlling the congestive heart failure, the condition of the patient worsened, with an exacerbation of mitral valve regurgitation. When it became obvious that the IE could not be controlled with conservative therapy alone, mitral valve surgery was deemed necessary. Replacement of the mitral valve with an artificial valve was performed in the cardiovascular surgery department after tapering the GC dose to 5 mg daily. The surgical findings were consistent with IE (Figures 5a, b, c). The postoperative clinical course was favorable, without worsening of renal function or LN activity, and the maintenance of adequate cardiac function with the artificial valve. The patient was discharged from the hospital with daily administration of 5 mg of GC, and warfarin as anticoagulant therapy (Figure 1).

Discussion

Our case highlights two important clinical issues: (1) special consideration of the occurrence of IE is required among patients with SLE, and (2) early diagnosis and treatment of IE are necessary for patient survival.

A previous study by Miller *et al.* reported that IE occurs in 3.3–4.4% of patients with SLE, regardless of valvular abnormalities and immunosuppression[1]. However, there have been no investigations regarding the prevalence of IE among patients with SLE who receive immunosuppressive therapy. Most patients with SLE do not have their cardiac status evaluated by transthoracic echocardiography. Asymptomatic cardiac diseases often remain undiagnosed, which increases the risk for and potentially results in a higher prevalence of IE[1]. Although the prevalence of Libman–Sacks endocarditis, a well-known valvular abnormality, is reported to be 40–60% by autopsy, it is diagnosed in only 4–6% of patients with SLE, because the majority of patients are asymptomatic[7]. In addition, a previous study has reported that the presence of high levels of IgG anticardiolipin antibodies is associated with the development of severe valvular regurgitation, a high incidence of thromboembolic events, and the need for valvular surgery in patients with SLE[2]. In the present case, antiphospholipid antibodies were not detected throughout the clinical course of the patient. However, in addition to the potential risk of IE among patients with SLE who have undiagnosed valvular abnormalities, major treatment for SLE (e.g., steroids) can increase the risk of IE with valvular dysfunction progressing to valvular fibrosis and atrophy[1, 6]. It was previously reported that IE has a prevalence of 3.9% among patients with SLE who develop valvular abnormalities during steroid therapy[1]. In the present case, immunosuppressive therapy probably produced a compromised state that caused MSSA bacteremia from a urinary tract infection, which contributed to the development of IE. In addition, steroid use can increase the risk of IE through hemodynamic changes due to valvular dysfunction, and a previous study has reported an associa-
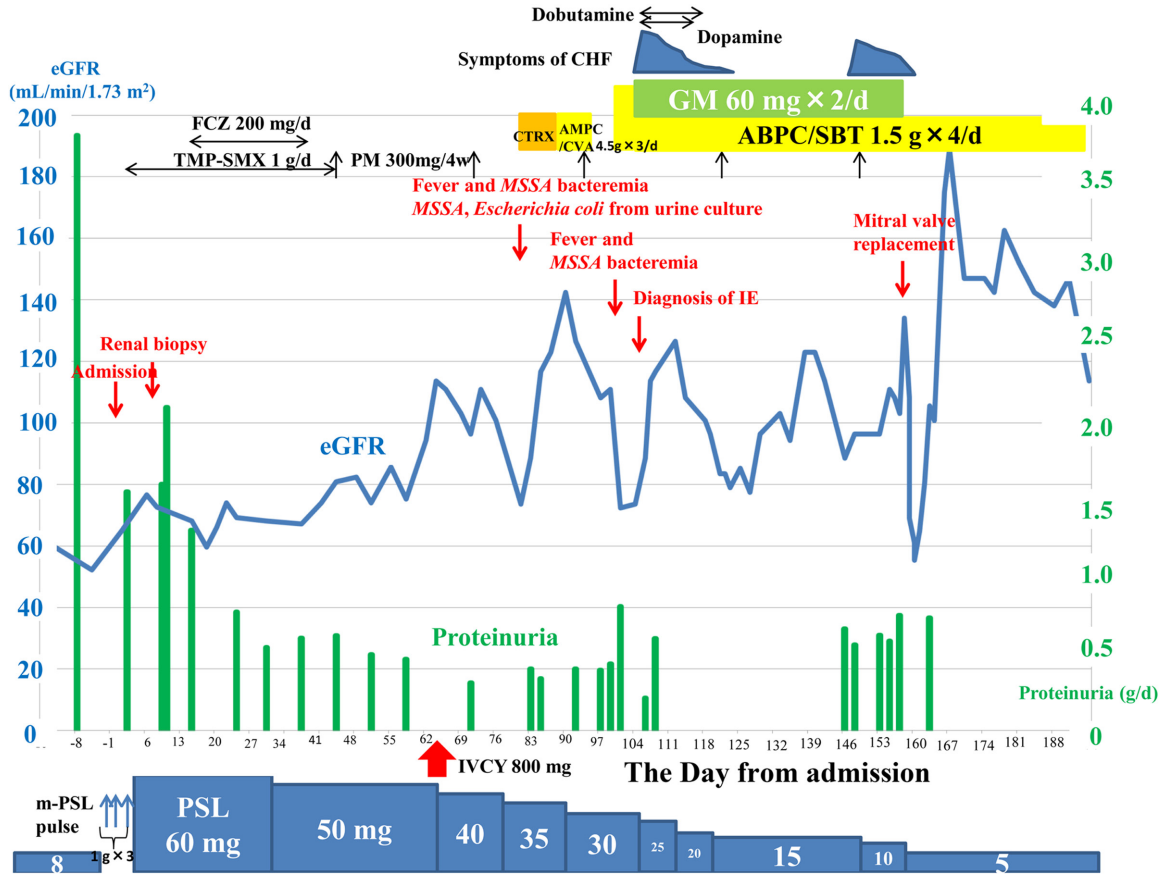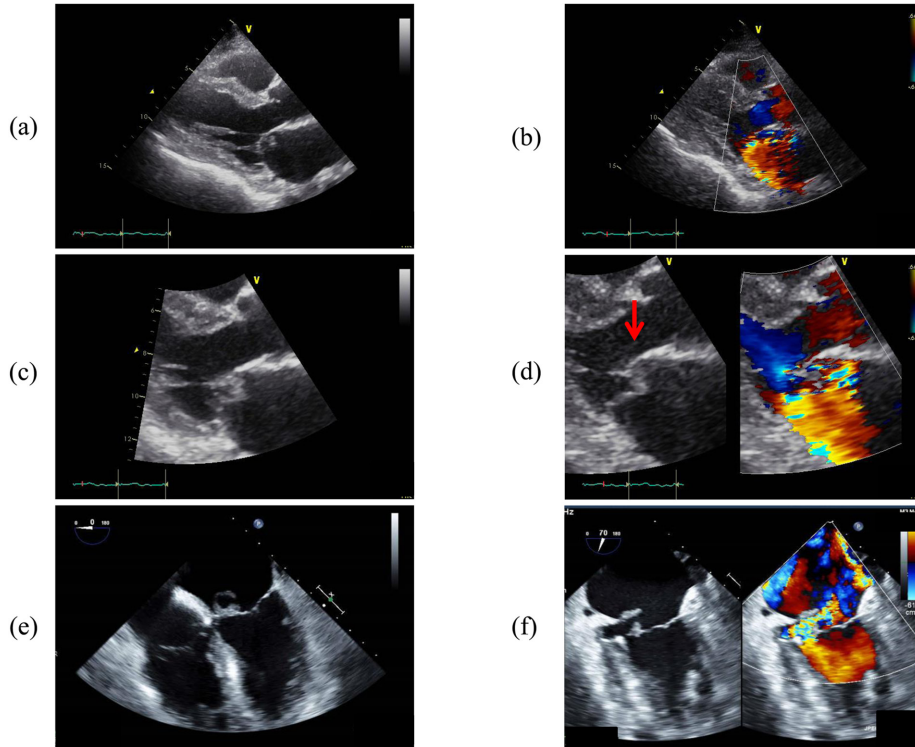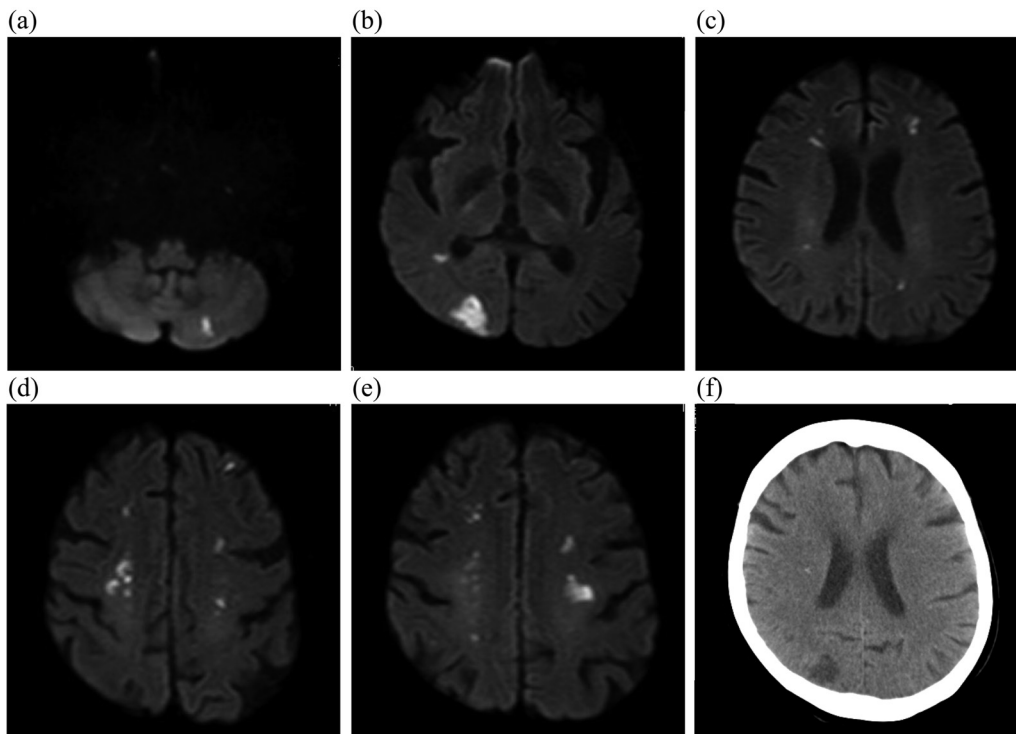
Figure 1

Figure 2

Figure 3 (a)–(e) Diffusion-weighted magnetic resonance imaging on Day 108 confirmed multiple fresh micro-infarctions. (f) Brain CT on Day 110 showed no cerebral hemorrhage.
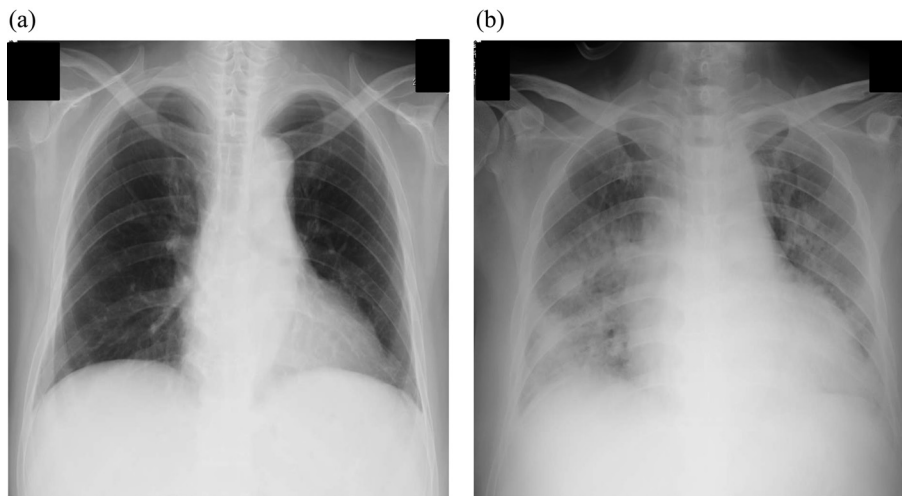

Figure 4 Chest radiograph on Day 61 (a) and Day 110 (b) confirmed exacerbation of cardiopulmonary congestion.

Figure 1 Clinical course. Changes in urinary protein levels and estimated glomerular filtration rate are indicated in parallel with clinical events. anti-ds DNA, anti-double-stranded DNA; GC, glucocorticoids; m-PSL, methylprednisolone; IVYC, intravenous pulse cyclophosphamide; IE, infective endocarditis; MSSA, methicillin-sensitive Staphylococcus aureus; TMP-SMX, trimethoprim-sulfamethoxazole; PM, pentamidine; FCZ, fluconazole; CTRX, ceftriaxone; AMPC/CVA, amoxicillin-clavulanate; ABPC/SBT, ampicillin-sulbactam; GM, gentamycin; CHF, congestive heart failure.

Figure 2 a)–(d) Transthoracic echocardiography on Day 107. Aneurysm in the chordae tendineae of the mitral valve and backward flow from the left ventricle indicated new mitral valve regurgitation. (e)–(f) Transesophageal echocardiography on Day 108.
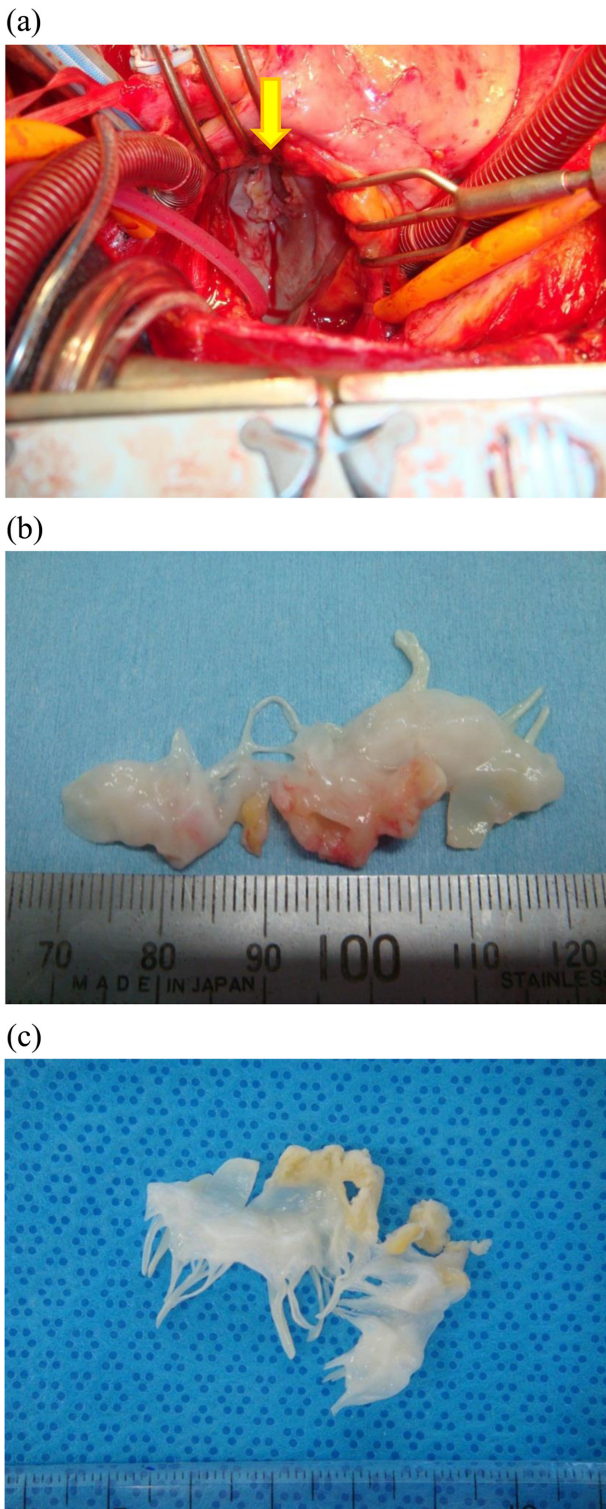
(a)

(b)

(c)

Figure 5 The mitral valve surgical findings in the mitral valve were consistent with infective endocarditis. (a) Intraoperative findings; (b) the mitral valve destroyed, and exhibiting infiltration of neutrophils and adhesion of vegetation; and (c) mitral valve with adhesion of vegetation removed.

tion between steroid use and IE[8]. Although we did not detect any valvular abnormalities by echocardiography before treatment of LN, we strongly recommend that echocardiography be performed in patients with SLE who show an uncertain cardiac status before treatment, considering the risk of IE owing to the prevalence of valvular abnormalities, and the risk of the treatment itself.

Although no studies have specifically focused on IE among patients with SLE, a Swedish study conducted from 1997 to 2007 reported a 30-day mortality rate of 10.4%, with a sudden decline in survival rate a few months after onset and a gradual stabilization of mortality rate over 5 years[9]. The same study also reported a 6.3-fold higher risk of mortality among patients aged under 65 years[9]. In addition to a sudden increase in mortality, embolus complications occur in 24–44% of patients with IE, 65% of which involve the central nervous system, often leading to death by cerebral hemorrhage[9]. A 7% prevalence of Staphylococcus aureus infection in the mitral valve is frequently associated with embolization, which is usually observed during the first 2–4 weeks after initiation of antibiotic treatment[6]. In our case, as there was no pathological state predisposing to thrombosis, such as vasculitis or antiphospholipid syndrome, we believe that embolization resulted from IE. No previously published reports have indicated that SLE is likely to cause infectious embolization. We confirmed that MSSA infection in the mitral valve was the cause of embolization and cerebral microinfarction at a very early phase, leading us to promptly initiate proper treatment and prevent further severe embolus complications. Surgery for valvular dysfunction due to IE should be considered in patients in whom IE cannot be cured or inactivated by conventional treatment. Ternhag *et al.* report that patients who underwent surgery had reduced mortality than that of patients who did not undergo surgery, across a 1-year follow-up after the onset of IE. Further, the 30-day mortality rate was significantly lower in the surgery group (6.3%) than in the non-surgery group (11.0%)[9]. When valve replacement is performed in patients who have been prescribed steroids for a long period of time, anticoagulant therapy should be considered owing to the instability of platelet function and coagulability. Our patient successfully recovered from IE and exhibited favorable cardiac function after mitral valve replacement. Hence, we strongly recommend surgical intervention for any cases involving congestive heart failure, treatment-resistant infection, or infectious embolization, as recommended by the Japanese clinical guidelines for IE.

In conclusion, special consideration of the possibility of IE, and its early diagnosis and treatment are required for reducing mortality among patients with SLE. We propose that echocardiography should be performed before treating

patients with SLE who have an uncertain cardiac status. Future studies should determine whether IE occurs more frequently in patients on SLE who receive immunosuppressive therapy, and whether routine echocardiography can successfully detect the occurrence of IE.

Conflict of interest: The authors declare no conflicts of interest.

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