CLINICAL PRACTICE

*Clinical Vignettes***Mitral Valve Perforation in Libman–Sacks Endocarditis: A Heart-Wrenching Case of Lupus***Elizabeth S. Aby, MD¹, Zachary Rosol, MD², and Mengistu A. Simegn, MD³*

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Libman–Sacks (LS) endocarditis is one of the most common cardiac manifestations of systemic lupus erythematosus. Rarely, however, it can lead to serious complications, including severe valvular regurgitation or superimposed bacterial endocarditis. We describe the initial diagnostic challenges, clinical course, imaging studies and histopathological findings of a patient who presented with life-threatening lupus complicated by hemoptysis and respiratory failure secondary to a rare complication of LS endocarditis, acute mitral valve perforation. We review the current literature on valve perforation in the setting of LS endocarditis. In conclusion, although the disease is often asymptomatic and hemodynamically insignificant, it can result in serious and potentially fatal complications secondary to valve perforation, which may demand emergency surgical management.

KEY WORDS: Libman–Sacks endocarditis; valve perforation; vegetation; lupus carditis; endocarditis.

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CASE REPORT

A 30-year-old black woman presented with acutely worsening dyspnea. She had been well until 3 weeks earlier, when she developed polyarthralgia of the knees, hands and feet, with small violaceous papules along the anterior aspect of the shins bilaterally. She presented to an outside emergency department, where she was started on a 7-day course of steroids for a probable connective tissue disease, with instructions to follow up with a rheumatologist. Over the following days, she developed progressive shortness of breath, worsening cough and intermittent sharp pleuritic bilateral chest pain without associated fever or diaphoresis.

Her past medical history was significant only for depression and cocaine abuse. She smoked crack cocaine and had last

used 3–4 weeks prior to presentation. Her family history was notable for lupus in her maternal aunt.

On physical examination, she appeared acutely ill, with tachypnea and mild hypoxia, requiring supplemental oxygen. She was afebrile and had a blood pressure of 179/108 mmHg. Pulmonary exam was notable for diffuse coarse crackles with expiratory wheezes. She had tachycardia with normal heart sounds and a grade II/VI systolic murmur at the fifth left intercostal space. She had a diffuse 2–4-mm erythematous, non-blanching rash without palpable purpura involving her trunk and proximal lower extremities. Her neurologic exam was unremarkable.

An electrocardiogram on presentation showed sinus tachycardia with minimal diffuse ST depression without evidence of acute current of injury or abnormal Q waves. A chest radiograph (CXR) showed diffuse bilateral infiltrates with Kerley B lines (Fig. 1a). Shortly after chest computed tomography (CT) was obtained, the patient had frank hemoptysis and acute decompensation, developing severe hypoxemic respiratory failure and marked sinus tachycardia. She was intubated and mechanically ventilated. Copious frank blood was visualized with suctioning of the endotracheal tube. The chest CT performed prior to decompensation (Fig. 1b) showed patchy ground glass opacities and multifocal alveolar filling processes. A CXR (Fig. 1c) performed to evaluate endotracheal tube position showed rapidly worsening diffuse patchy interstitial and airspace opacities.

Hematologic and chemical laboratory test results are shown in Table 1. These revealed neutrophilic leukocytosis, mild normocytic anemia, elevated serum creatinine and low complement levels. Urinalysis was significant for pyuria, microscopic hematuria, active sediment and proteinuria.

Transthoracic echocardiography (TTE) revealed normal-sized cardiac chambers with hyperdynamic systolic function and severe eccentric mitral regurgitation. Transesophageal echocardiography (TEE) revealed that mitral valve leaflets were diffusely thickened, with a small, sessile echogenic mass on the atrial aspect of the anterior leaflet adjacent to a perforated A2 scallop (Fig. 2, Video A) with two adjoining regurgitant jets, one through the perforated segment and one across the malcoaptation point of the anterior and posterior valve leaflets (Fig. 2, Video B).

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Figure 1 Imaging studies of the chest. **a** Initial CXR with bibasilar pulmonary infiltrates and component of pulmonary edema. **b** Chest CT with contrast, with patchy ground glass opacities. **c** CXR taken after acute decompensation demonstrating rapid worsening of diffuse pulmonary infiltrates. **d** CXR after mitral valve replacement with improving pulmonary infiltrates.

The patient's presentation with acute airspace disease, hemoptysis, lower extremity rash, recent polyarthralgia, nephritic urinary sediment and low complement levels was thought to be suggestive of systemic lupus erythematosus (SLE) with lupus nephritis, possible lupus pneumonitis/alveolar hemorrhage and complicated Libman–Sacks endocarditis. However, given her history of cocaine use and the finding of perforated mitral valve with a mitral valve mass, infectious endocarditis with immune complex glomerulonephritis, complicated by acute pulmonary edema, was also considered. Anti-glomerular basement membrane antibody disease (anti-GBM) and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, including granulomatosis with polyangiitis, were also in the differential diagnosis based on her clinical presentation.

Empiric broad-spectrum antibiotics and methylprednisolone were initiated after blood cultures were drawn. Following consultations with cardiology, infectious disease, nephrology and rheumatology, the patient underwent emergent bioprosthetic mitral valve replacement. Within hours of surgery, she showed remarkable clinical improvement, with resolution of her respiratory failure and hemoptysis. The rapid improvement in the patient's airspace disease visualized on CXR (Fig. 1d) and the absence of hemoptysis on presentation argued in favor of acute valvular failure as the primary etiology. Gram stain of the valve mass was consistent with

vegetation and showed neither organisms nor white blood cells. Histopathology of valve tissue revealed non-infectious mild acute endocarditis compatible with a diagnosis of Libman–Sacks endocarditis (Fig. 3). In light of the patient's rapid improvement, absence of fever, multiple negative blood cultures (aerobic, anaerobic and fungal), and absence of organisms on gram stain of vegetation, as well as negative

Table 1 Initial Laboratory Studies

Laboratory Test	Value
Sodium	138 mEq/L
Potassium	3.5 mEq/L
Chloride	106 mEq/L
CO ₂	19 mEq/L
Glucose	213 mg/dL
Blood urea nitrogen	20 mg/dL
Creatinine, serum	1.66 mg/dL
White blood cell count	24.13×10^9 cells/L
Hemoglobin, blood	8.9 g/dL
Hematocrit	26.2 %
Platelets	256×10^9 cells/L
C3	55 mg/dL (reference range: 90–180 mg/dL)
C4	8 mg/dL (reference range: 10–40 mg/dL)
Erythrocyte sedimentation rate	35 mm/h
C-reactive protein	30.90 mg/L
Urine analysis	Cloudy yellow, large blood, urine protein >300, negative ketones, specific Gravity 1.025, WBC >50, RBC >50, 6–20 hyaline casts, nitrite negative

Figure 2 Two-dimensional transesophageal echocardiography. AMVL, anterior mitral valve leaflet; LA, left atrium; LV, left ventricle; PMVL, posterior mitral valve leaflet; (*) vegetation; (**) perforated valve leaflet; (+) mitral regurgitation through perforated AMVL; (++) mitral regurgitation through malcoaptation point.

serology for *Brucella*, *Bartonella* and *Coxiella*, infectious endocarditis was deemed unlikely, and antibiotics were discontinued.

Further immunologic and autoantibody studies showed positive ANA and anti-dsDNA (Table 2). Skin-punch biopsy of leg lesions showed leukocytoclastic vasculitis. Kidney biopsy showed diffuse lupus nephritis (class IV-G), which suggests predominantly global proliferative lesions, and membranous lupus nephritis (class V) with a high index of activity (Fig. 4).

During her postoperative course, the patient developed right anterior cerebral artery (ACA) stroke with mild left leg paresis, most prominent with low systolic blood pressures. The etiology was presumed to be embolic stroke. The differential for her ischemic stroke included vasculopathy, thrombosis and, less likely, vasculitis based on cerebral angiography and the fact that central nervous system vasculitis in SLE is rare. She was treated with immunosuppressive therapy with high-dose systemic glucocorticoids, cyclophosphamide, and

hydroxychloroquine, and was discharged home with a plan for continued immunosuppression.

DISCUSSION

Systemic lupus erythematosus is a chronic autoimmune disorder characterized by autoantibody-initiated, complement-mediated multi-organ tissue injury. Cardiac involvement in lupus is estimated to occur in greater than 50 % of cases and to involve all three layers of the heart: the conduction system, coronary arteries, and valves.^{1,2} Valvular heart disease in SLE occurs along a spectrum from leaflet thickening to large vegetation, as in Libman-Sacks endocarditis.^{3,4}

Libman-Sacks (LS) endocarditis, initially described in 1924,⁵ is characterized by sterile fibrin-platelet thrombi vegetations and inflammatory valvular changes. It is detected in 43 % of patients with SLE using transesophageal

Figure 3 Mitral valve specimen. a Gross mitral valve specimen, arrow pointing to the flat tan vegetation on the mitral valve. b Microscopic appearance of mitral valve leaflet with focal areas of acute inflammation, fibrin and focal necrosis.

Table 2 Laboratory Studies

Laboratory Test	Value	Reference Range
ANA IgG titer	1:40	<1:40
Anti-dsDNA IgG	1:80	<1:10
Anti-RNP Ab	Negative	Negative
Anti-SM Ab	Negative	Negative
Anti-SSA Ab	Negative	Negative
Anti-SSB Ab	Negative	Negative
Total complement	<10 µ/L	22–60 µ/L
Beta 2 glycoprotein IgM titer	2	0–20
Beta 2 glycoprotein IgG titer	0	0–20
ANCA Ab IgG	<1:20	<1:20
Anti-GBM Ab IgG	<0.2	0–0.9
Cryoglobulin	Negative	Negative
Lupus anti-coagulant (DRVVT)	1.03	0–1.20
Anticardiolipin IgG titer	4.7	0–14.9 GPL units
Anticardiolipin IgM titer	4.3	0–12.4 MPL units
Anticardiolipin IgA titer	6.3	0–11.9 APL units
HIV serology	Non-reactive	Non-reactive

Ab, Antibody; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibodies; Anti-GBM, anti-glomerular basement membrane antibody; Anti-dsDNA, anti-double stranded DNA; Anti-RNP, anti-ribonucleoprotein antibodies; Anti-SM, anti-smooth muscle antibodies; Anti-SSA, anti-Sjögren's-syndrome-related antigen A; Anti-SSB, anti-Sjögren's-syndrome-related antigen B; HIV, human immunodeficiency virus; IgG, immunoglobulin G antibody; IgM, immunoglobulin M antibody

echocardiography (TEE).⁴ Three-dimensional TEE may have an additive and complementary value in the detection of LS endocarditis,⁶ which most commonly involves the mitral valve, followed by the aortic valve.⁷ LS endocarditis has been reported to be associated with higher disease activity, longer disease duration, and positive anticardiolipin and antiphospholipid antibodies.⁷ Although it characteristically

has negligible hemodynamic significance, when present, it is strongly associated with cerebrovascular and peripheral arterial embolism, cognitive dysfunction, acute and chronic valvular dysfunction, superimposed infective endocarditis, and the need for high-risk valvular surgery.^{2,8,9}

There is scant literature regarding the diagnostic and treatment dilemma providers face when valve perforation occurs in the setting of LS endocarditis. We conducted a systematic review of the literature on valve perforation caused by LS endocarditis, in which we performed a PubMed query with the keywords “Libman Sacks” and “perforation” as well as “Libman Sacks” and “repair.” Abstracts were reviewed and relevant papers were selected. Bouma and colleagues described a 49-year-old man with a history of SLE who presented with dyspnea, signs of cardiac decompensation, elevated C-reactive protein (CRP) (38 mg/l) and a normal white blood cell count (WBC, $4.6 \times 10^9/l$).⁸ He had severe mitral regurgitation and a small perforation in the P2 section of the posterior leaflet, with vegetation near the perforation. The mitral valve was repaired by resection of the P2 section and implantation of an annuloplasty ring. Takayama and colleagues described a 58-year-old man who presented with acute orthopnea, tachypnea, tachycardia, bilateral rales and a pansystolic murmur.¹⁰ He had mitral regurgitation with a mitral valve aneurysm rupture in the A2 scallop of the anterior mitral leaflet, which was treated with mitral valve valvuloplasty and annuloplasty. Yashiki and colleagues described a 40-year-old woman with SLE and severe aortic insufficiency secondary to

Figure 4 Kidney biopsy. a Hematoxylin and eosin [HE]. Jones stain (b) and periodic acid-Schiff [PAS] stain (c) with segmental peri-glomerular crescent. d Electron microscopy with subendothelial and mesangial deposits with effacement of the visceral podocytes; Immunofluorescence staining with diffuse granular glomerular capillary loop and mesangial immunoreactivity with antibodies to IgG (e) and Kappa (f).

leaflet perforation.¹¹ The patient had an elevated WBC ($10.9 \times 10^9/l$) and a normal CRP (0.4 mg/dl). In summary, the literature suggests that although LS endocarditis rarely leads to significant complications such as valve perforation requiring repair, clinicians should monitor cardiac and valvular function carefully after the diagnosis of LS endocarditis.

A patient who presents with a new cardiac murmur, fever and a history of known or suspected SLE represents a diagnostic dilemma. Since it is not uncommon for patients with LS endocarditis to develop superimposed bacterial endocarditis,¹² it is prudent to maintain a broad differential, perform a thorough history and physical, obtain blood cultures, and do further imaging. Consultation with an infectious disease specialist should be considered early on, as the consequences of treatment delay in infectious endocarditis can be grave. TEE is superior to TTE for the detection of LS endocarditis, because the echocardiographic findings on TTE are often non-specific.¹³ From an imaging perspective, LS vegetations are characteristically sessile with broad attachment, non-mobile, heterogeneous in echogenicity and uncommonly associated with significant valvular regurgitation. This is in contrast to the highly mobile, narrow-based infectious vegetations that tend to be homogeneous in echogenicity and associated with a variable degree of valvular insufficiency and perforation.^{4,6} The modified Duke criteria are sensitive for the diagnosis of infectious endocarditis. However, these criteria do not help in distinguishing infective from non-infective endocarditis, as multiple criteria are shared by these two conditions. Several laboratory markers, including WBC, CRP, ESR and antiphospholipid antibody (aPL) level, may be abnormal in both disease processes.^{14,15} White blood cell count tends to be elevated in cases of infection, while leukopenia is associated with active lupus. Very high CRP may be indicative of infection, but CRP levels may also be elevated in LS endocarditis, as it is a marker of inflammation.¹⁵ Elevated antiphospholipid antibody may be more suggestive of LS endocarditis.¹⁵ While these subtleties may be considered, no laboratory values have specificity high enough to distinguish LS endocarditis from infective endocarditis.

As was the case with our patient, the development of hemodynamically significant valvular insufficiency with valvular vegetation adds significant diagnostic uncertainty in a patient with lupus, particularly when fever is present. The patient in this case had a prominent leukocytosis, but ultimately had no infectious etiology identified. Confounding the initial evaluation was the fact that the patient had been on steroids for 5 days prior to presentation, and leukocytosis is a known side effect of steroid use. The TEE finding of mitral valve leaflet perforation and associated severe regurgitation, which is uncommon in LS endocarditis, added to the diagnostic uncertainty. However, a diagnosis of LS endocarditis was supported by the presence of active lupus based on renal biopsy and absence of evidence of infection. Ultimately, the diagnosis was confirmed with excisional biopsy of the valve tissue; however, this is not always an afforded luxury.

The literature regarding the treatment of LS endocarditis is scant. Because the disease is often associated with active SLE, treatment focuses on the management of active lupus using immunosuppressive agents. While steroids are thought to reduce inflammation, they may lead to scarring and valvular dysfunction.¹⁶ It is imperative to note that immunosuppressive therapy often used in this setting may lead to infection and poor wound healing and tissue integrity for those who need surgical valve replacement or repair. In patients with LS endocarditis associated with a positive aPL, antithrombotic therapy is recommended for the prevention of thromboembolic events.¹⁶ Supportive therapy for associated heart failure and arrhythmias may also be necessary.

Although LS endocarditis is typically asymptomatic or presents with only mild clinical symptoms, if left untreated it can lead to significant complications, including thromboembolic events and valve perforation. Greater awareness of these complications, close follow-up and careful cardiovascular examination are essential for earlier diagnosis and intervention. In addition, it is often difficult on initial presentation to distinguish between infective endocarditis and LS endocarditis. Diagnosis requires the integration of a diligent clinical history, exam, laboratory and bacteriologic data, and transesophageal echocardiography.

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Conflict of Interest: The authors declare that they do not have a conflict of interest.

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