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CASE REPORT

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Recurrence of valvular involvement in Libman–Sacks endocarditis associated with antiphospholipid syndrome: A case report

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Key Clinical Message

Recurrence of valvular involvement may occur after Libman–Sacks endocarditis surgery, emphasizing the need for frequent multivalvular evaluations with echocardiography or more sensitive methods to optimize surgical outcomes.

Abstract

This report presented a 32-year-old woman, complaining of recurrent fever and chills. Physical examination revealed the presence of a third heart sound (S_3), a pan-systolic murmur (III/VI) at mitral and tricuspid foci, tachycardia, and fine pulmonary crackles. Transesophageal echocardiography (TEE) revealed severe mitral regurgitation (MR) and moderate tricuspid regurgitation (TR) with vegetations on the mitral valve. Initially, intravenous antibiotic therapy was started simultaneously with diagnostic studies. Despite a positive TEE, negative blood cultures on three separate occasions precluded meeting the diagnostic criteria outlined in the modified Duke criteria. Moreover, the patient's condition continued to deteriorate after antibiotic therapy, leading to the diagnosis of Libman–Sacks endocarditis. The patient was considered a candidate for mitral valve surgery. All vegetations were completely debrided and then the mitral valve was reconstructed. Follow-up post-surgery echocardiography revealed the absence of MR and mitral stenosis (MS). Four months later, the patient presented again complaining of fatigue, dyspnea, lower extremity edema, and ascites with evidence of pulmonary hypertension and right heart failure on physical examination. TEE was performed, which revealed severe MR, severe TR, detached artificial chordae, and blood leak from the perforated pericardial patch. Therefore, she was necessitated for valvular surgery and underwent mitral and tricuspid valve surgery. The mitral ring and perforated pericardial patch were removed, and a mitral prosthetic valve was implanted. In addition, the tricuspid valve was repaired. Follow-up post-surgery echocardiography revealed the absence of MR and TR.

To our knowledge, this is the first case of LSE recurrence with multi-valvular involvement.

KEYWORDS

antiphospholipid syndrome, case report, heart valve diseases, Libman–Sacks endocarditis

1 | INTRODUCTION

Libman–Sacks endocarditis (LSE) is a rare disorder typically identified postmortem, with an estimated prevalence ranging from 0.9% to 1.6%.[1] It is a form of non-bacterial thrombotic endocarditis characterized by small sterile vegetations and valvular thickening, which can lead to valvular dysfunction and an increased risk of critical complications such as thromboembolic events, heart failure, pulmonary hypertension, and infective endocarditis.[1,2] It is commonly detected in individuals with antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE), given the strong association with antiphospholipid antibodies (aPLs), including anticardiolipin antibodies (aCL), anti-β2-glycoprotein I (β2-GPI) antibodies, and lupus anticoagulant. These antibodies lead to a hypercoagulable state and promote the deposition of fibrin-platelet thrombi on the heart valves.[1–3] LSE is asymptomatic in its early stages, with patients occasionally experiencing symptoms such as fatigue, shortness of breath, chest pain, and heart failure-related symptoms. Therefore, it is often misdiagnosed and subsequently mismanaged.[3] This report presents a rare and challenging case of LSE in an APS patient that highlights the complexity of the diagnosis and management.

2 | CASE HISTORY/EXAMINATION

A 32-year-old woman, previously diagnosed with APS 4 years ago due to triple positive aPLs on two separate occasions 12 weeks apart, along with a history of deep vein thrombosis (DVT) and two miscarriages, presented to the emergency room complaining of 4 weeks of recurrent fever, characterized by a nocturnal pattern with a peak of 38.4°C, and chills. She also reported a three-month persistent anemia. The patient has been following a prescription from prior doctor visits, taking prednisolone 5 mg in the morning and 1.25 mg in the evening, along with hydroxychloroquine 200 mg every 12 h for 3 months.

Vital signs were unstable with a blood pressure of 115/80 mmHg, pulse rate of 140 beats per minute, body temperature of 39°C, respiratory rate of 18 breaths per minute, and oxygen saturation of 94% without oxygen supplementation. On physical examinations, the third heart sound (S_3) and a pan-systolic murmur (III/VI) at mitral and tricuspid foci, accompanied by noticeable tachycardia in cardiac auscultation, and fine crackle in pulmonary auscultation were detected.

TABLE 1 Initial laboratory tests.

Test	Result	Unit	Reference value
WBC	9.4	$\times 1000/mm^3$	4.5–11
RBC	**3.4**	$\times 10^6/mm^3$	3.8–5.2
HB	**10.8**	g/dL	11.6–15
HCT	38	%	36–48
MCV	93.2	FL	80–98
MCH	28	Pgm	27–31
MCHC	30.1	%	32–36
Platelet	**149**	$\times 1000/mm^3$	150–400
INR	**1.1**	Index	0.9–1.0
PT	12	s	11–13
PTT	**89**	s	21–35
Blood glucose	110	mg/dL	90–130
Urea	**31**	mg/dL	6–24
Creatinine	1.3	mg/dL	0.7–1.4
Sodium	139	mmol/L	136–145
Chloride	101.7	mmol/L	96–106
Potassium	4.4	mmol/L	3.7–5.5
Bicarbonate	22.1	mmol/L	22–32
CPK	58	IU/L	25–200
CK-MB	**2.30**	IU/L	5–25
ESR	**77**	mm/h	0–20
CRP	**14.5**	mg/dL	0–0.3

Note: The bold values presented the significant lab tests abnormality in this patient.

3 | METHODS (DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS, AND TREATMENT)

The patient's initial laboratory tests indicate acute inflammation due to high ESR and CRP, as shown in Table 1. According to the clinical findings, transesophageal

echocardiography (TEE) was performed, which revealed severe posterior-directed mitral regurgitation (MR) with partially flail mitral valves and moderate tricuspid regurgitation (TR). Additionally, a 30 × 5 mm mass at the base of the anteromedial side of the posterior mitral valve leaflet (PMVL) extending into the left atrium wall, with mobile components, and a large multilobulated, calcified, 26 × 12 mm mass adjacent to the tip of the anterior mitral valve leaflet (AMVL) on the atrial surface, extending into the left ventricle were detected (Figure 1).

Considering the patient's signs and symptoms and TEE results, the diagnosis of endocarditis was made, and due to the importance of early treatment of infective endocarditis, antibiotic therapy was started intravenously with vancomycin, ciprofloxacin, and ampicillin-sulbactam. However, the modified Duke criteria still needed to be met for infective endocarditis. Therefore, she underwent blood cultures three times on three separate occasions, which all were negative. PCR was used to determine whether HACEK organisms were infected; however, no organism from this group was discovered. Furthermore, despite aggressive medical treatment for 14 days, the patient's condition continued to deteriorate and severe MR did not improve, so LSE was diagnosed considering the history of APS. Meanwhile, the direct Coombs test was performed, which reported positive results, and as a result, persistent anemia was explained with immune hemolytic anemia, which is a manifestation of APS.

Computed tomography (CT) scans of the lungs and abdomen were performed, revealing a hypodense wedge-shaped mass (29 × 25 mm) and a smaller mass in the middle and lower part of the spleen. In addition, imaging revealed increased echogenicity in the left peri-renal area and consolidation in the left lung, accompanied by an air bronchogram. Neurological assessment, including magnetic resonance imaging (MRI) and cerebrospinal fluid analysis, did not reveal any embolic strokes or central nervous system involvement.

The patient was considered a candidate for mitral valve surgery. All vegetations on the AMVL and PMVL, destructing 2/3 of the leaflets, were completely debrided. The valve was then reconstructed using autologous pericardium patch and one pairs of artificial chordae. A size 30 mitral ring was implanted, and the AMVL was repaired using Gore-Tex PTFE thread. The histological analysis of the explanted valve tissue revealed characteristic features of LSE, including sterile vegetations, fibrin deposition, and inflammatory infiltration without evidence of bacterial infection. The microbiological analysis was negative for any bacterial growth. Follow-up post-surgery echocardiography revealed the absence of MR and mitral stenosis (MS) with moderate pericardial effusion. The patient was discharged in stable condition with warfarin, digoxin, furosemide, losartan, and propranolol medications.

Four months later, the patient presented again to the emergency room complaining of fatigue, dyspnea, lower extremity edema, and ascites. Vital signs were unstable with a blood pressure of 110/80 mmHg, pulse rate of 120 beats per minute, body temperature of 36.9°C, respiratory rate of 24 breaths per minute, and oxygen saturation of 93% without oxygen supplementation. A holo-systolic high-pitched murmur (IV/VI) on the mitral and tricuspid foci, fine crackles in the lung bases, and distended abdomen with notable bilateral lower extremity edema were detected in physical examination. Moreover, signs of jugular vein distention and the prominent pulmonary component of the second heart sound were also found. These clinical findings were in favor of pulmonary hypertension and right heart failure, which was probably due to mitral and tricuspid valve insufficiency. Therefore, TEE was performed, which revealed severe eccentric posterolateral directed MR, a flail AMVL with detached artificial chordae, and blood leak from the perforated pericardial patch. Moreover, severe multiple jet TR with non-coapted leaflets was also observed (Figure 2).

Mitral valve patch perforation was directly associated with LSE as histopathological examination confirmed the presence of sterile vegetations and fibrin deposition consistent with LSE, which likely contributes to structural weakening and subsequent perforation of the mitral valve patch. In the previous admission, no tricuspid valve

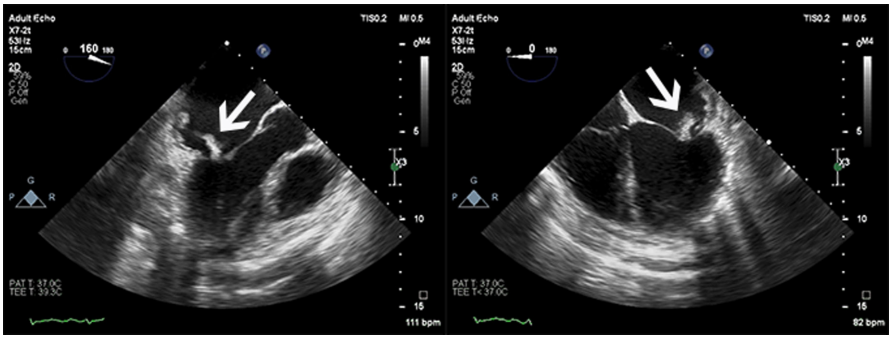

FIGURE 1 2D-TEE mitral valve view demonstrating vegetations (White arrows).

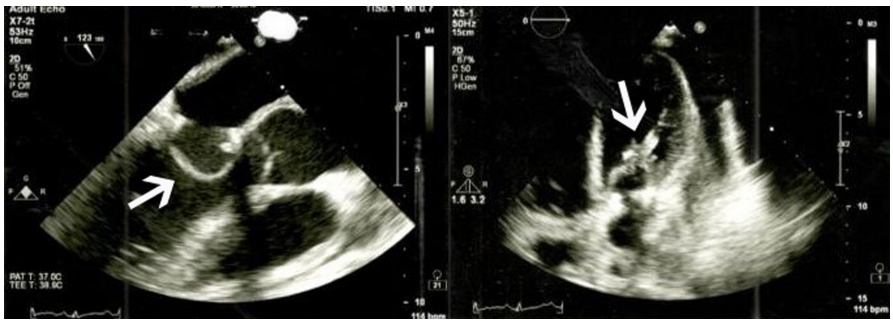

FIGURE 2 2D-TEE mitral valve view demonstrating perforated pericardial patch (White arrows).

involvement was detected during TEE, which could have been missed due to the limited sensitivity of TTE to detect minor valvular lesions, especially in non-bacterial thrombotic endocarditis.

Considering the patient's signs and symptoms and TEE results, she was a candidate for mitral and tricuspid valve surgery. The implanted mitral ring and perforated pericardial patch were removed completely, and size 28 Mitral St-Jude prosthetic valve was implanted. In addition, tricuspid valve was repaired with ring annuloplasty. Follow-up post-surgery echocardiography revealed the absence of MR and TR.

4 | CONCLUSION AND RESULTS (OUTCOME AND FOLLOW-UP)

After 2 weeks of hospitalization, the patient was discharged in a stable general condition, and the mentioned medical treatment was prescribed again. Over the 3-year follow-up, the patient's clinical condition has significantly improved since the initial presentation, and clinical complaints or significant clinical findings were not detected again. To our knowledge, this is the first case of LSE recurrence with multi-valvular involvement.

5 | DISCUSSION

Endocarditis refers to inflammation in the heart's inner lining, called the endocardium, characterized by vegetation development, mainly on the heart valves. These growths may arise from bacterial or fungal infections, termed infective endocarditis, or be associated with autoimmune diseases, malignancies, or hypercoagulable states, known as non-infective endocarditis.[4–7] Based on data analysis from the Global Burden of Disease (GBD) study in 2019, its incidence is estimated to be 13.80 per 100,000 individuals, with a substantial global burden that has increased in recent years.[8] Patients presenting with unexplained fever, chills, malaise, fatigue, night sweats, shortness of breath, and changes in heart rhythm should be evaluated for these disorders, especially when imaging studies reveal valvular involvements,[4,5] which in our case was considered due to the frequent fever and chills with nocturnal pattern and TEE results.

Despite the development of new imaging modalities, echocardiography remains the cornerstone and should be performed in all suspicious patients to examine the heart valves and chambers. While transthoracic echocardiography (TTE) is the primary method for detecting valve abnormalities, TEE is often preferred for its higher sensitivity in detecting small vegetation and providing more explicit images of the posterior cardiac structures.[9]

Given that infective endocarditis can affect various organs such as the lungs, kidneys, spleen, and brain, with embolism impacting up to 50% of individuals, prompt initiation of antibiotic therapy is crucial in suspicious patients, as it can significantly reduce the risk of embolism and systemic complications.[4] Therefore, we started antibiotic therapy simultaneously with diagnostic studies in this case. Despite a positive TEE, negative blood cultures on three separate occasions precluded meeting the diagnostic criteria outlined in the modified Duke criteria. Moreover, the patient's condition continued to deteriorate after antibiotic therapy, and the mitral valve involvement did not improve. So, the possibility of non-infective endocarditis was raised.

Non-infective endocarditis, also known as non-bacterial or sterile endocarditis, occurs as a result of abnormal immune-mediated response and disturbance in the natural balance of coagulation factors, leading to the formation and deposition of fibrin along with platelet aggregation on heart valves, ultimately contributing to the formation of vegetations.[6,7] It is a rare disorder, as Fournier et al.[10] reported the incidence of this condition in blood culture-negative endocarditis to be 2.5%, which is often misdiagnosed and typically diagnosed postmortem through autopsy, consequently not appropriately managed.[6] As mentioned, it is generally associated with autoimmune diseases, such as APS and SLE, in which case it is called LSE, strongly associated with aPLs, with Yoo et al.[3] reporting aPL triple positivity in 72.7% of LSE patients. Therefore, it is important to pay attention to these diseases in the past medical history of suspicious patients.

Our patient was a known case of APS, an autoimmune systemic disorder associated with arterial, venous, or small vessel thrombotic events across various organs and tissues mediated by aPLs. This disorder may result in critical complications, such as DVT, pulmonary embolism, stroke, and myocardial infarction.[11–13] Its prevalence is estimated to be 40–50 cases per 100,000, with an annual incidence of 1–2 cases per 100,000 individuals.[14] Diagnosis requires a comprehensive evaluation of multiple clinical, laboratory, and imaging studies, making it a challenging process. The persistent presence of aPLs, including aCL, anti-β2-GPI antibodies, or lupus anticoagulant, is crucial to confirm the diagnosis and assess disease severity. Additionally, a history of at least one thrombotic or recurrent early miscarriage, fetal loss, or pregnancy morbidity supports the diagnosis.[11,12,14] The diagnosis in our patient was based on the presence of triple positive aPLs on two separate occasions 12 weeks apart, along with a history of DVT and two miscarriages.

Cardiac involvements are prevalent and clinically significant in APS, including valvular disease, coronary artery disease, myocardial dysfunction, pulmonary hypertension, intracardiac thrombus, accelerated coronary atherosclerosis, and right or left ventricular dysfunction.[15,16] Valvular disease including LSE stands as the predominant cardiac manifestation in APS, with a reported prevalence ranging from 30 to 40% detected by TTE, to 82% by TEE.[16] LSE vegetations commonly impact left sided valves, particularly the mitral valve, especially the PMVL, followed by the aortic valve. Nevertheless, it may rarely extend to any of the four valves or multiple valves simultaneously.[17,18] In our case, mitral valve was affected first, and then after the surgery, tricuspid valve was also affected, which is a very rare condition. Moreover, valvular regurgitation is the dominant valvular dysfunction, as in our case, whereas, valvular stenosis is rare.[16] It should be noted that pulmonary embolism can be detected in echocardiography[19]; however, no special finding was seen in this patient.

Valvular involvement screening is not routinely conducted for all APS patients, leading to a delayed diagnosis of LSE in the early, asymptomatic stages. Typically, further evaluations including echocardiography are conducted when patients presented with symptoms or when a new murmur is identified during a physical examination.[15] Limited studies have been conducted on the management and treatment of this disease, and the optimal management approach remains poorly defined. Anticoagulation therapy plays a pivotal role in preventing thromboembolic complications associated with APS. In cases with severe valvular dysfunction or recurrent embolism despite anticoagulation therapy, surgical intervention for valvular repair or replacement might be indicated.[1,2,15,16] Chalvon et al.[20] conducted a study on APS patients with severe valvular involvements who underwent valvular surgeries, and reported normal postoperative valvular function in 78% of patients, early-onset post-operative complications in 39% of patients, and post-operative neurological sequelae in 43% of patients. However, destruction of repaired valve and involvement of another valve (tricuspid valve) after mitral valve surgery is an extremely rare event reported in our case. To our knowledge, this is the first case of LSE recurrence with multi-valvular involvement.

In conclusion, this report highlights the complexity of severe LSE management even after successful surgery, emphasizing the necessity of valvular involvement screening through echocardiography in APS patients and also LSE patients who have undergone valvular surgeries as part of a comprehensive management strategy to optimize patient outcomes.

AUTHOR CONTRIBUTIONS

Shahab Masoumi: Project administration; supervision; visualization; writing – original draft. **Razieh Parizad:** Conceptualization; methodology; validation. **Rezayat Parvizi:** Conceptualization; methodology; validation. **Amirreza Jabbaripour Sarmadian:** Writing – original draft; writing – review and editing. **Samira Jafarisis:** Writing – original draft; writing – review and editing. **Kia Seyed Toutounchi:** Data curation; investigation.

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CONFLICT OF INTEREST STATEMENT

The authors declare no financial and non-financial competing interests related to this work.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author on reasonable request.

ETHICS STATEMENT

This study was performed according to the principles outlined by the World Medical Association's Declaration of Helsinki on experimentation involving human subjects, as revised in 2000, and was approved by the Tabriz University of Medical Sciences ethics committee with the approval number IR.TBZMED.REC.1402.384 on 2023/08/28.

CONSENT

The patient was informed regarding publishing this case report, and written informed consent was obtained to publish this report under the journal's patient consent policy.

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