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CASE REPORT
Cardiovascular imaging

Case report of culture-negative endocarditis in lupus nephritis

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Background Cardiovascular involvement is frequent in systemic lupus erythematosus (SLE). Valvular abnormalities are increasingly being recognized with the advent of echocardiography.

Case summary We present a case of a 46-year-old lady who presented to the emergency department with upper limb ischaemia. On examination, she had poor dentition and a short systolic murmur on auscultation. A blood workup revealed a diagnosis of SLE. Further investigations showed vegetations on the mitral valve. Initially, an infective endocarditis (IE) diagnosis was made, which was treated with antibiotics. High-dose steroids and immunosuppressants were initiated due to her clinical deterioration and biopsy-proven lupus nephritis. She improved clinically before being discharged home.

Discussion It can be difficult to distinguish between IE and Libman–Sacks endocarditis (LSE), especially in the setting of risk factors for both. Antibiotics and immunosuppressants might be started simultaneously in these cases. A multidisciplinary team is required to manage challenging cases of culture-negative endocarditis. Procalcitonin may have a role in differentiating bacterial endocarditis and LSE.

Keywords Case report • Endocarditis • Libman–Sacks • Procalcitonin

ESC Curriculum 2.1 Imaging modalities • 4.3 Mitral regurgitation • 4.11 Endocarditis

Learning points

- Beware that endocarditis can be the presenting feature of systemic lupus erythematosus.
- A multidisciplinary team approach is required to manage challenging cases of culture-negative endocarditis.
- Procalcitonin may have a role in differentiating bacterial endocarditis from Libman–Sacks endocarditis.

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with >50% of patients having cardiovascular involvement.[1] It can have a varied cardiac presentation manifesting as valvular disease, pericarditis, myocarditis, cardiomyopathy, or coronary artery disease. Prior studies on SLE have reported valvular lesions including endocarditis, valve thickening, valve stenosis, and regurgitation to be the most frequent cardiac manifestations[2] with the prevalence of valvular vegetations reported to be as high as 43%.[3] Although vegetations are commonly present, a symptomatic disease with haemodynamic alterations is rare,[4] sometimes leading to a delayed diagnosis.

Libman and Sacks[5] first described the verrucous, non-infective endocarditis (IE) in patients with SLE back in 1924. The advances in transthoracic echocardiography (TTE) techniques have aided in the assessment of structural and functional abnormalities in SLE.[6] Libman–Sacks endocarditis (LSE) can be seen in up to 10% of SLE patients.[7] The presence of vegetations in conjunction with a murmur mimicked IE in this instance.

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Timeline

Time	Events
Presentation	Patient presented with acute limb ischaemia; early systolic murmur on auscultation
Hospital day 1	Presumptive diagnosis of infective endocarditis made and intravenous antibiotics started
Hospital day 7	Patient diagnosed with culture-negative endocarditis as blood cultures persistently negative
Hospital day 10	Staged dental extraction and amputation
Hospital day 14	Worsening renal function, positive anti-dsDNA antibody; renal biopsy showing nephrotic syndrome. Patient started on immunosuppressants
6-month follow-up	Systemic lupus erythematosus is in control; renal function is stable (estimated glomerular filtration rate (eGFR) > 90 mL/min/m^2)

Case presentation

A 46-year-old lady, on anticoagulation for recent deep vein thrombosis (DVT), presented with severe pain in her left arm and was found to have necrotic left fingers with compromised blood supply to the left hand. On examination, the patient had poor dentition and a short systolic murmur at the apex. Her initial investigations were as follows: the white blood count (WBC) was 9×10^9/L (normal 4–11×10^9/L), C-reactive protein (CRP) 51 mg/L (normal 0.3–1 mg/dL), erythrocyte sedimentation rate (ESR) 31 mm/h (normal 0–29 mm/h), antinuclear antibody (ANA) 1:2560 (normal <1:160), anti-dsDNA 59 IU/mL (normal <30 IU/mL), C3 0.53 g/L (normal 0.88–2.01 g/L), and C4 0.05 g/L (normal 0.15–0.45 g/L). These results indicated the possibility of an ongoing inflammatory process. Blood cultures were negative.

Transthoracic echocardiography showed mild complex mitral regurgitation originating from this area (*Figure 1A*). Other valves were within normal limits. Transoesophageal echocardiography (TOE) showed an echogenic mass measuring 0.5 cm × 0.9 cm attached to the posterior mitral valve leaflet at the junction between P2 and P3 (*Figure 1B* and see Supplementary material online, *Video 1*). Further microbiological testing including viral panel, parasitic panel, respiratory cultures, and stool cultures was negative. Screening for antiphospholipid syndrome was negative. A renal biopsy revealed vasculitis glomerulonephritis with focal segmental proliferative lesions consistent with Class III lupus nephritis.

Differential diagnosis

The clinical dilemma here is about the aetiology of endocarditis, which would influence management. Although the lupus screen was positive, a diagnosis of LSE was initially not considered as it is very rare.[8] Starting steroids or immunosuppressants in patients with active systemic infection would also worsen the infection.

On the other hand, the patient had poor dentition, which is a portal of entry for infection. Thus, culture-negative endocarditis, constituting up to 2.5–31% of cases of endocarditis,[8] was one of the differential diagnoses. This justified our decision of treating her as having IE.

Treatment

Our patient was managed under a multidisciplinary team (MDT), involving cardiology, rheumatology, microbiology, vascular, and maxillofacial teams. The patient met one major clinical criterion (valvular vegetation on TTE) and two minor clinical criteria (arterial embolism causing acute limb ischaemia and glomerulonephritis), implying possible IE as per modified Dukes criteria. The initial consensus was to manage our patient as culture-negative IE with antibiotics. The patient was started on intravenous antibiotics (meropenem and piperacillin–tazobactam for 5 days followed by cotrimoxazole for 2 weeks) and a therapeutic dose of enoxaparin. Later, she proceeded to have a staged dental extraction and a left below-elbow amputation.

Despite 2 weeks of intravenous antibiotics, she deteriorated further and had multiorgan involvement, suggestive of active SLE. Her renal function declined to 45 mL/min/m^2. The urine albumin-to-creatinine ratio was raised to 105 mg/mmol (normal < 3.5 mg/mmol). A renal biopsy confirmed lupus nephritis (Classes IIIa and V) with nephrotic syndrome. Additionally, our patient also developed pancytopenia and loculated pleural effusions.

Given the clinical deterioration, two further negative blood cultures and a persistently low procalcitonin, the patient was started on oral prednisolone with antibiotics before stepping up to intravenous methylprednisolone and later intravenous cyclophosphamide. Ramipril was also initiated for nephrotic syndrome. The patient was discharged following a 2-month admission after her SLE was controlled and renal function reverted to baseline. At 6-month follow-up, her SLE remains under control and her renal function (eGFR) remains above 90 mL/min/m^2.

Discussion

Libman–Sacks endocarditis falls under the category of non-bacterial thrombotic endocarditis (NBTE). In SLE, immune complex deposition and complement activation are the primary mechanisms for valve damage causing inflammation, fibrosis, scarring, and calcification. These processes eventually lead to valvular vegetations, stenosis, or regurgitation.[9] Although any valve can be affected, studies show that almost 63% of LSE cases involve the mitral valve and 34% involve the aortic valve.[7]

Typically, LSE is asymptomatic, and a diagnosis is made when a patient presents with embolic complications, usually stroke.[5] Transthoracic echocardiography is a good initial test, although TOE is more sensitive for detecting valvular abnormalities.[10] The characteristics of valve disease can guide the diagnosis in some patients. Vegetations can be differentiated based on appearance, location, and mobility patterns. Lupus-associated valve masses are typically located near the leaflet base, whereas masses in IE are predominantly located at the leaflet's line of closure.[11] It is essential to remember that LSE can be complicated by IE.[7] Therefore, initiation of empirical antibiotics is essential, especially if differentiation is difficult. Procalcitonin, a marker of bacterial infection, has been studied as an early indicator of IE. Although a threshold for diagnosing or exclusion is yet to be determined, it was found to be more sensitive and specific for IE[12] and thus should be used in addition to traditional variables (age, presentation, ESR, and CRP).

Management of LSE involves treating the underlying disease and anticoagulation for thrombo-embolic events. Glucocorticoids have been used to counteract the inflammatory processes and facilitate healing.[9] Owing to anti-inflammatory and antithrombotic properties, hydroxychloroquine has shown benefits in patients with SLE.[13] As cerebrovascular disease accounts for the major cause of mortality and morbidity in SLE, anticoagulation is paramount.

Valve surgery is indicated in patients with severe symptomatic valvular dysfunction.[14] A recent study highlighted the role of anti-inflammatory and antithrombotic therapy for obviating surgery in patients with LSE and cerebrovascular disease.[15]

Our patient had risk factors for IE; she did fulfil the modified Dukes criteria for IE and was treated as a case of culture-negative endocarditis.

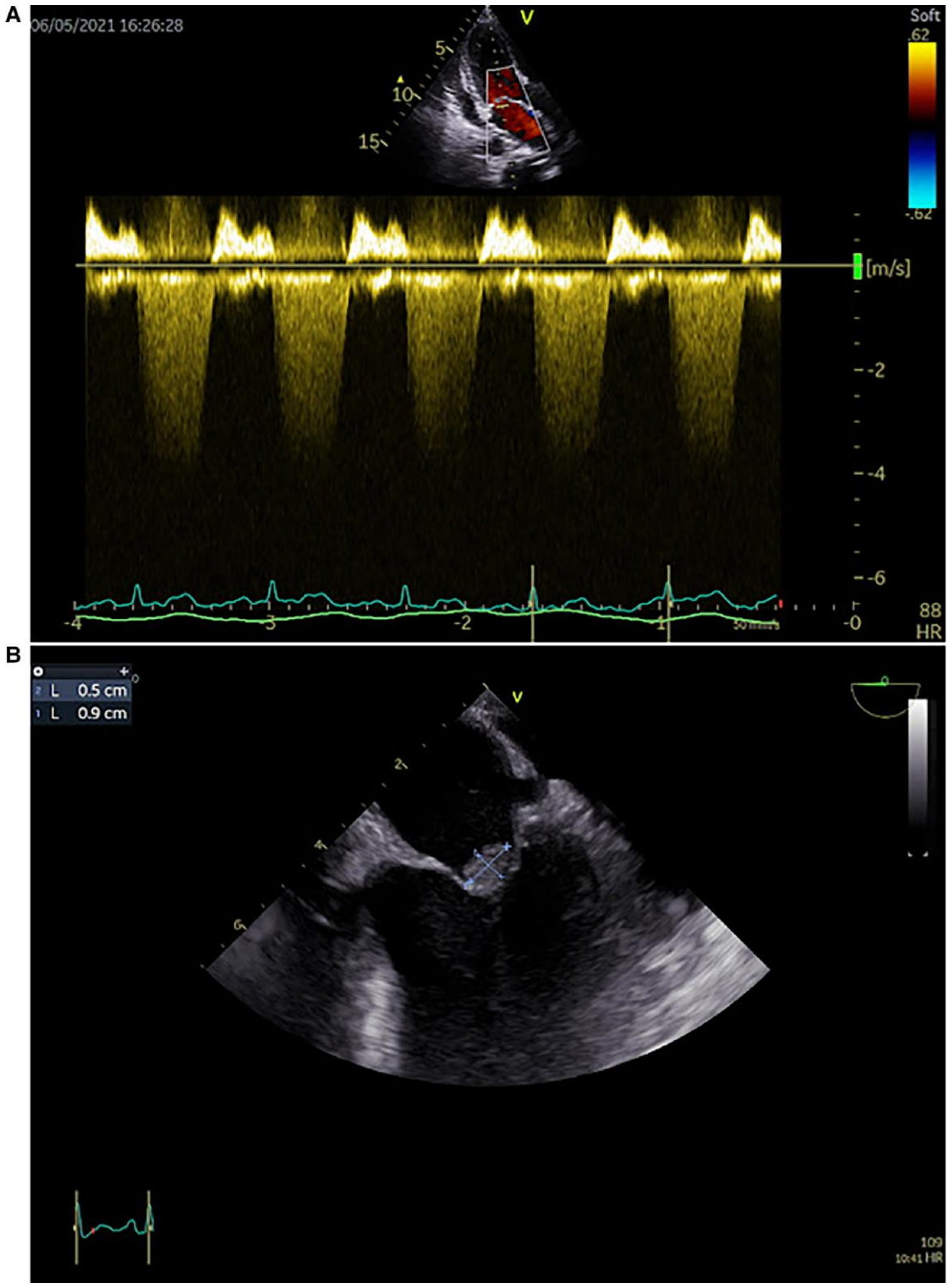
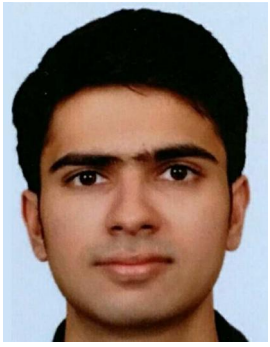


Figure 1 (*A*) Transthoracic echocardiography. Doppler trace showing mitral regurgitation. (*B*) Transoesophageal echocardiography. Mid-oesophageal view showing a mass attached to the posterior mitral leaflet measuring 0.5 cm × 0.9 cm.

Soon, the patient had systemic clinical involvement as well as laboratory features indicating a separate active disease process, eventually leading to a diagnosis of SLE. Systemic lupus erythematosus was suspected based on the patient's age, systemic presentation, lack of improvement with antibiotics, and elevated ESR and CRP despite low procalcitonin. As the patient's clinical condition worsened and she had biopsy-proven Class III lupus nephritis, she was treated with steroids and cyclophosphamide. Since both conditions were actively

contributing to the patient's illness, a combination of antibiotics and immunosuppression was used. The strength of our approach is targeting both disease processes. Predicting how each disease process will react to treatment was not known.

Lead author biography



I am a second-year internal medicine resident. After graduating from medical school in India, I started residency in the USA. The dynamic field of cardiology has always intrigued me. I plan to apply for a cardiology fellowship. My interests include interventional cardiology, structural heart disease, and the application of artificial intelligence in cardiology.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that witnessed verbal consent for submission and publication of this case report including images and associated text has been obtained from the patient detailed in this case report. This has been discussed with the editors.

Conflict of interest: None declared.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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