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Case Report

Libman-Sacks Endocarditis: A Silent Threat Unveiled by Stroke in a Young Female with Antiphospholipid Antibody Syndrome – A Case Report and Review of Literature

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ABSTRACT

Libman–Sacks endocarditis (LSE) is a non-bacterial thrombotic endocarditis associated with systemic hypercoagulable states such as primary antiphospholipid antibody (APLA) syndrome and systemic lupus erythematosus. It is often missed due to its asymptomatic nature in the early stages. The vegetations in LSE are a potential source of embolism and can result in cerebrovascular accidents. Here, we report the case of a young female who presented with an embolic stroke and was diagnosed to have vegetation over the mitral valve. The patient was referred to our center for mitral valve replacement, but on detailed evaluation she was diagnosed as a case of LSE due to primary APLA syndrome. The patient was managed conservatively with anti-inflammatory drugs and anticoagulants.

Keywords: Libman–Sacks endocarditis, Antiphospholipid antibody syndrome, Rituximab, Young stroke, Autoimmune disease

INTRODUCTION

Libman–Sacks endocarditis (LSE) is a sterile thrombotic endocarditis of non-bacterial origin connected to systemic hypercoagulable states such as primary antiphospholipid antibody (APLA) syndrome and systemic lupus erythematosus.[1] The diagnosis may go unnoticed since the patient won't have any symptoms in the early stages of the illness. Here, we describe the case of a young woman who initially had an embolic stroke and subsequently developed LSE linked to primary APLA syndrome.

CASE REPORT

A 36-year-old female, in the immediate postpartum period, developed generalized tonic-clonic seizures, 2/5 power of the left-sided upper and lower limbs with associated facial weakness. There was associated motor aphasia. The patient had a known case of seizure disorder and was being treated with levetiracetam. After being brought to a nearby hospital, she underwent brain magnetic resonance imaging (MRI). There was an ill-defined focal area of altered signal intensity in MRI. T1-weighted images appeared as hypointense, and T2-weighted images were hyperintense. This

area showed restricted diffusion on diffusion-weighted imaging/apparent diffusion coefficient maps involving both cortical gray and subcortical white matter in the right frontal region, including the insular cortex, suggesting an acute infarct. Non-specific ischemic changes were seen in the bilateral frontoparietal region's subcortical periventricular white matter. The MRI angiogram showed no flow-related enhancement in the right middle cerebral artery (MCA) distal M1 and M2 segments, suggesting occlusion. The rest of the cerebral vessels and the neck vessels were normal. After denying consent for mechanical thrombectomy, the patient underwent thrombolysis at the same hospital with Alteplase (10% of the total dose due to thrombocytopenia, platelet count – 48,000/cu.mm).

An echogenic structure measuring 1.2 × 1 cm, likely vegetation, was visible on the underside of the mitral leaflet's P2 during echocardiography. There was severe mitral regurgitation. The ejection fraction was 55%. There was no regional wall motion abnormality. There were no other valvular lesions. The patient was started on intravenous antibiotics for treating infective endocarditis (IE) and referred to our hospital. Over 48 hours before coming to our hospital, the hemiparesis had a waxing and waning course.

During our evaluation, the patient gave a history of treatment for migraine-like headaches. She has been on antiseizure medication since 2014. She had a history of thrombocytopenia and increased menstrual bleeding for the past 10 years. She gave a history of one abortion at 12 weeks gestation 5 years back and infertility treatment since then. She developed preeclampsia during this pregnancy but carried the pregnancy to full term. She delivered twins by lower-section cesarean section complicated by postpartum hemorrhage due to placenta accreta 2 months ago. One of the twins expired on day four of life following surgery for duodenal atresia.

On examination, the patient was afebrile, with normal higher mental functions. She had a heart rate of 78 bpm, sinus rhythm, SpO_2 of 98% on room air, and warm peripheries. There was a livedoid rash over both the foot. There was no raised jugular venous pressure. On auscultation, a pan systolic murmur of 4/6 intensity was audible with radiation to the axilla at the mitral area. Upper motor neuron (UMN) facial palsy with 2/5° of power in the left upper and lower limbs was discovered during a neurological examination. The right limbs had a 5/5 power [Table 1].

Cardiac MRI showed mitral regurgitation. There was nodular thickening of the mitral valve leaflets [Figure 1]. Focal mid-myocardial late gadolinium enhancements were seen in the lateral wall of the basal to mid-left ventricle myocardium and in the tips of the papillary muscles. Left ventricular ejection fraction was 55%. A whole-body positron emission tomography (PET) scan was done to rule out any infective foci. Due to vascular sequelae, the PET

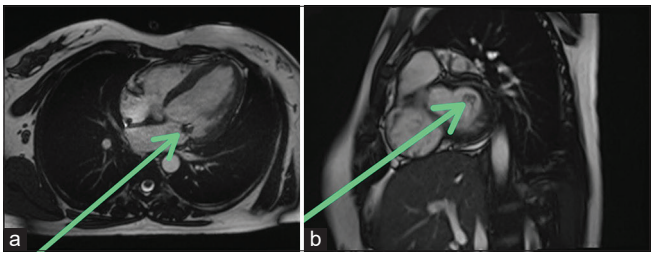

Figure 1: (a) Four-chamber balanced steady state free precession (bSSFP) image showing hypointense nodular lesion along the mitral valve leaflets. (b) Two-chamber bSSFP image showing hypointense nodular lesion along the mitral valve leaflets. Green arrows shows the vegetations.

Table 1: Laboratory investigations.

Laboratory tests	Report
Platelet count	46,000/cu.mm
APTT	68 s
C- reactive protein	3.8 mg/L
Procalcitonin	<0.1 ng/mL
ASO titer	55 Todd units
Liver function tests	WNL
Renal function tests	WNL
Anti-nuclear antibody by immunofluorescence	Negative
Anti-nuclear cytoplasmic antibody	Negative
Anti-ds-DNA	35 IU/mL
Lupus anticoagulant screening using a diluted Russell viper venom test	Strongly positive
Anti-cardiolipin antibody IgG	118.1 GPL units/mL
Anti-cardiolipin antibody IgM	6.6 MPL units/mL
IgG levels	1255 mg/dL
Aerobic blood culture (three sets)	All 3 negative
Anaerobic blood culture	Negative
Fungal blood culture	Negative

APTT: Activated partial thromboplastin time, IgG: Immunoglobulin G, IgM: Immunoglobulin M, ASO: Antistreptolysin O, WNL: Within normal limits, GPL: Ig G phospholipid unit, MPL: Ig M phospholipid unit

scan showed relatively reduced fluorodeoxyglucose (FDG) uptake in the right frontal lobe, basal ganglia, thalamus, and right temporal lobe. Physiological FDG uptake was noted in the myocardium. There was no definite scan evidence of increased FDG uptake in the mitral valve region to suggest an infective pathology.

The patient was diagnosed with LSE due to primary APLA syndrome [Table 2] and initiated on warfarin to maintain a target international normalized ratio (INR) between 2.5 and 3. Unfractionated heparin was used for bridging

Table 2: Revised Sapporo classification for diagnosing APLA syndrome.

Clinical criteria	
Vascular thrombosis	A minimum of one documented instance of venous, arterial, or small-vessel thrombosis
Pregnancy morbidity	(a) At least one death of a fetus with normal physical characteristics that cannot be explained occurred at a gestational age of 10 weeks or more.
	(b) One or more instances of giving birth to a structurally normal baby before reaching 34 weeks of pregnancy due to:
	(i) The standard definition of eclampsia or severe pre-eclampsia is used.
	(ii) Identifiable characteristics of placental insufficiency
	(c) Before 10 weeks of pregnancy, 3 or more consecutive miscarriages must occur, excluding any maternal or paternal factors such as chromosomal, hormonal, or anatomical abnormalities.
Laboratory criteria	The presence of one or more of the following characteristics, indicative of the detection of APLAs on at least 2 occasions, separated by a minimum of 12 weeks between each detection:
	(a) Lupus anticoagulant
	(b) IgG or IgM anticardiolipin antibodies with a titer between >40 (moderate) and >80 (high) GPL or MPL units or more than the 99th percentile as determined by the testing laboratory.
	(c) The testing lab found anti-β2GPI antibodies of IgG or IgM isoforms with a titer ranging from moderate to high, higher than the 99th centile.

APLA: Antiphospholipid antibody, IgG: Immunoglobulin G, IgM: Immunoglobulin M, β2GPI: Beta-2 glycoprotein 1

anticoagulation. The patient had high Immunoglobulin G (IgG) levels. Since it is associated with the risk of thrombosis, she received rituximab therapy 1 g on 0 and 14th day along with methylprednisolone.

The patient was discharged on warfarin, aspirin, amlodipine, and levetiracetam, with advice to maintain an INR between 2 and 3.

DISCUSSION

APLA syndrome symptoms include thrombocytopenia, venous or arterial thrombosis, recurrent miscarriages, and the presence of APLAs.[1] It can be primary without underlying conditions like systemic lupus erythematosus or secondary. According to the updated Sapporo classification criteria, at least one laboratory and one clinical criterion must be satisfied to diagnose APLA syndrome.[2]

Our patient had pregnancy loss in the past and right MCA thrombosis presenting with left-sided hemiplegia. Anticardiolipin (IgG) and lupus anticoagulant antibodies were detected in laboratory studies.

Heart valve involvement[3] is the most prevalent cardiac manifestation of primary APLA syndrome, affecting one-third of patients. The aortic valve and mitral valve are the most severely impacted and rarely are right-sided valves impacted. The predominant functional abnormality is regurgitation. LSE lesions are characterized by valve thickening and vegetation and have a prevalence of 0.9–1.6%. It is incidentally detected while evaluating for other heart diseases or at postmortem. Valvular lesions in LSE are sterile fibro fibrinous vegetations. It can appear anywhere on the left side of the heart's endocardial valve surface. These sessile vegetations resemble warts and range in size from a pinhead to 3–4 mm.[4] Complement deposition, autoimmune complexes, and fibrin-platelet thrombus formation on the valves bring on heart valve thickening.[5] Endothelial cell activation occurs due to APLAs. This results in monocyte and platelet activation, which results in aggregation of monocytes and platelets – this activation cascade results in thrombus formation in valves already damaged by immune complex deposition. APLA syndrome is a risk factor for recurrent pulmonary embolism, which in turn can result in chronic thromboembolic pulmonary hypertension.[6] Cerebrovascular accidents in APLA syndrome can be caused by embolization of fragile LSE vegetation or due to the hypercoagulable state caused by the APLAs. The vegetations in LSE are a potential source of embolism and can result in cerebrovascular accidents. If the underlying conditions are treated, the valvular lesions in LSE do not cause any symptoms and are of minor hemodynamic significance. If untreated, LSE vegetation easily embolizes systemically compared to IE vegetation due to the meager inflammatory reaction at the attachment site of the valve. Our patient was undiagnosed and untreated when she presented with an embolic stroke. MRI of the brain showed features of right frontal acute infarcts, and a magnetic resonance angiogram showed total occlusion of the M1 and M2 branches of the right MCA. In our patient, we ruled out IE before diagnosing LSE. We used the modified Duke's criteria to rule out IE.

Treatment of LSE mainly relies on anti-inflammatory therapy.[7] Research on treating LSE, particularly randomized controlled trials (RCTs), is limited. Most studies focus on observational data and case reports rather than RCTs. A chimeric monoclonal antibody that targets CD20 is called rituximab. It treats APLA syndrome complications such as thrombocytopenia and skin and heart valve involvement by targeting B-cells that produce antibodies. It is used for the treatment of a variant of APLA known as catastrophic APLA syndrome or Asherson's syndrome.[8] Multiple intravascular

thromboses in several organs, systems, or tissues can occur concurrently or continuously, and a high titer of APLAs characterizes Asherson's syndrome. It has a high mortality rate. No trials have shown the role of rituximab in LSE. A 75% response rate on receiving rituximab therapy was demonstrated in an analysis of 24 primary APLA syndrome patients. In addition, the study showed promise for ameliorating symptoms, including thrombocytopenia and skin and heart valve involvement.[9] However, IE has been reported in lupus patients treated with rituximab therapy. Recently, rituximab and a monoclonal antibody targeting CD38-Daratumumab have been used to treat autoimmune diseases, such as APLA syndrome.[10] Inducing B-cell depletion more effectively than rituximab, obinutuzumab is a humanized glycoengineered type II monoclonal antibody against CD20 that may be useful for patients resistant to rituximab.[11]

Consideration should be given to anticoagulation when LSE is linked to APLA syndrome. In people with APLA syndrome, warfarin is used to keep them from getting a thromboembolism in the future. According to a comprehensive review of the literature conducted by Dufrost *et al*., 16% of APLA syndrome patients treated with direct oral anticoagulants (DOAC) experienced recurrent thrombosis. This rate is 3.5 times higher in people who have triple-positive APLA syndrome, which means that they met all three laboratory criteria for APLA.[12] A total of 648 APLA syndrome patients from five RCTs have demonstrated that patients treated with DOAC had a higher incidence of arterial thrombosis than patients treated with warfarin (odds ratios = 5.168, 95% confidence interval = 1.567–17.04, $P = 0.007$).[13]

People with APLA syndrome should start taking warfarin with an INR goal of 2–3. This is the best treatment available. Even after achieving therapeutic INR values, patients with recurrent thrombotic events may benefit from low-dose aspirin, an INR of 3–4, or low-molecular-weight heparin. Heparin's anti-inflammatory effects and anti-thrombotic properties are beneficial against various inflammatory mediators. Insufficient evidence supports the safety and efficacy of these individualized drug regimens.

Surgery becomes the mainstay when there is an uncontrolled infection, severe valve dysfunction leading to heart failure, or recurrent embolic strokes.[14] The prognosis of LSE is considered poor if it is associated with recurrent thromboembolism.[15] While there is some evidence supporting the effectiveness of medical therapies, including immunosuppressants and antithrombotics, the lack of robust RCTs highlights a significant gap in the literature.

CONCLUSION

LSE is rare as the first presentation of APLA syndrome. Following a diagnosis, careful monitoring, stringent anticoagulation, and prompt identification and management of complications should be implemented.

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