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CASE REPORT

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Recurrent nonbacterial thrombotic endocarditis and stroke on anticoagulation

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ABSTRACT

We present a rare case of recurrent nonbacterial thrombotic endocarditis (NBTE) and stroke despite anticoagulation. A 48-year-old man with history of antiphospholipid syndrome, prior nonbacterial aortic valve endocarditis status post valve replacement and prior stroke was found to have acute ischemic stroke while on apixaban and nonbacterial thrombotic endocarditis of mitral valve. This was initially managed conservatively with therapeutic dose of enoxaparin, but the patient later underwent mitral valve replacement. Unfortunately, the patient later passed away with hemorrhagic stroke while on enoxaparin.

1. Introduction

Nonbacterial thrombotic endocarditis (NBTE), usually discovered postmortem, is a rare noninfectious cause of endocarditis and is characterized by fibrinoplatelet deposition on heart valves [1,2]. Its prevalence ranges between 0.3% and 9.3% [1]. NBTE is most commonly associated with primary antiphospholipid syndrome (APS), malignancy, hypercoagulable states, and systemic lupus erythematosus (SLE) [2,3]. NBTE in the setting of APS or SLE is also called Libman-Sacks endocarditis [4]. We present a rare case of recurrent NBTE characterized by mitral valve endocarditis complicated by stroke despite therapeutic anticoagulation in the setting of primary APS and previous aortic valve endocarditis status post aortic valve replacement.

2. Case description

The patient is a 48-year-old man brought to the Emergency Department in March 2019 from a nursing home with new right-sided facial droop. The patient had baseline cognitive impairment with left-sided weakness and visual field deficit from previous strokes. He was last known well the day earlier before he went to bed the previous night. He did not have any new arm or leg weakness. His past medical history was significant for antiphospholipid syndrome, NBTE of his aortic valve status post aortic valve replacement with Trifecta bioprosthetic valve 5 years back, occipital stroke with residual inferior visual field deficits, and multiple prior pulmonary embolisms and deep vein thromboses with inferior vena cava filter placement. He had previously failed warfarin and rivaroxaban and was on apixaban 10 mg two times daily. He had failed warfarin at another hospital as his international normalized ratio was never therapeutic from suspected Protein C or Protein S deficiency. Therefore, he was placed on rivaroxaban in September 2014. He was changed to apixaban during a hospitalization for a stroke in June of 2015 while on rivaroxaban. He was on apixaban 5 mg two times daily with last dose an hour prior to presentation. On examination, his temperature was 97.2°F and he was noted to have bilateral inferior visual field deficits from previous stroke. He performed one task correctly, answered one question correctly, had flattened nasolabial fold with asymmetry while smiling, and loss of fluency with National Institute of Health Stroke Scale of 4. Rest of the examination was unremarkable.

He was deemed not a candidate for recombinant tissue plasminogen activator as he had received apixaban an hour prior to presentation. A stat computed tomography of head showed encephalomalacia along bilateral superior and posterior parietal lobes with age indeterminate areas of low attenuation along the superior left frontal lobe extending to the cortex which were concerning for infarcts. Diffusion-weighted magnetic resonance imaging of the brain showed acute versus subacute punctate foci of hyperintensity within the left medial occipital lobe and bilateral superior parietal lobules along with remote infarcts involving the superior middle frontal gyri, left frontal opercular regions

and extending into bilateral occipital regions. Magnetic resonance angiogram of the head and neck did not show any hemodynamically significant stenoses in intracranial circulation, cervical carotids, and vertebral arteries. Electrocardiogram showed sinus rhythm with first-degree AV block. He was started on aspirin 81 mg daily and atorvastatin 40 mg daily. Hematology was consulted who recommended lifelong anticoagulation with enoxaparin 104.3 mg two times daily based on his weight.

Given history of aortic valve endocarditis and replacement and concern for embolic phenomenon, transesophageal echocardiogram (TEE) was performed. It showed a well-functioning stented bio-prosthetic aortic valve with trace aortic insufficiency and no evidence of thrombus or vegetation. However, a 0.7 × 1.1 cm mass noted on the tip of anterior mitral valve leaflet and 0.7 × 0.9 cm mass was noted on the tip of the posterior mitral valve leaflet with findings consistent with NBTE (Figure 1). He had moderate to severe, central mitral regurgitation (MR) and an intact interatrial septum with no evidence of a shunt by color Doppler or with injection of agitated saline. The left atrial appendage appeared normal. The mitral valve and bioprosthetic aortic valve were noted to have been functioning well at an outside hospital transthoracic echocardiogram (TTE) report a few years back. Other significant lab results are presented in Table 1. IgG B2 Glycoprotein 1 Antibody and IgG Cardiolipin Antibody were elevated consistent with his history of antiphospholipid syndrome. Mitral valve endocarditis was managed conservatively with anticoagulation. He was discharged to a subacute rehab on subcutaneous enoxaparin 100 mg two times daily.

Patient had a subsequent hospitalization 3 months later with a fever of 100.9°F and a low hemoglobin of 6.7 g/dl (reference range: 14–17.5 g/dL). He was noted
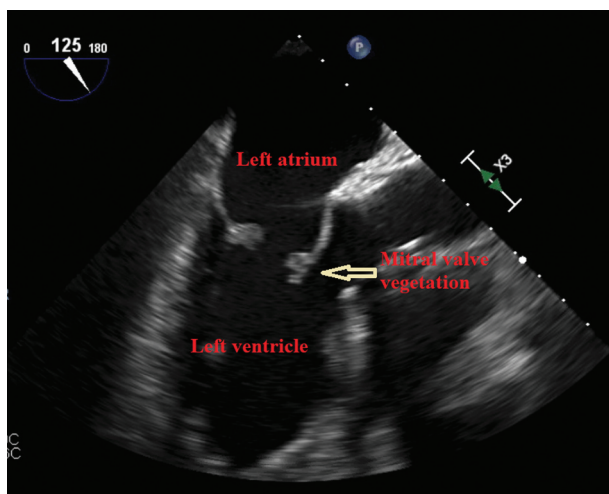

Figure 1. A 0.7 × 1.1 cm and 0.7 × 0.9 cm mass noted on the tip of anterior and posterior mitral valve leaflets respectively consistent with nonbacterial thrombotic endocarditis.

Table 1. Workup for patient during his initial presentation with acute ischemic stroke.

Labs	Value	Reference range
Prothrombin Time (PT)	14.8 sec	12.0–13.7 sec
International Normalized Ratio (INR)	1.2	0.9–1.1
Partial Thromboplastin Time (PTT)	43 sec	24–35 sec
Antinuclear Antibody (ANA) Screen	NEG 1:40	NEG 1:40
Smith Antigen	Negative	Negative
RO Antibody	Negative	Negative
LA Antibody	Negative	Negative
Anti-Double Stranded Deoxyribonucleic Antibody (DSDNA)	Negative	Negative
Myeloperoxidase, Immunoglobulin G Antibody (MPO)	<0.3 U/mL	≤3.4 U/mL
Anti-Proteinase 3, Immunoglobulin G Antibody (PR3)	<0.7 U/mL	≤1.9 U/mL
B2 Glycoprotein 1 Antibody, Immunoglobulin G	142 SGU	0–20 SGU
B2 Glycoprotein 1 Antibody, Immunoglobulin M	1 SMU	0–20 SMU
Cardiolipin Antibody, Immunoglobulin G	147 GPL	0–14 GPL
Cardiolipin Antibody, Immunoglobulin M	11 MPL	0–12 MPL
Hepatitis C Antibody	Negative	Negative
Vitamin B1	86 nmol/L	70–180 nmol/L
Rapid Plasma Reagin	Non-reactive	reactive
Blood Cultures X 2	No growth	growth

to have hemolytic anemia with reticulocytes of 10.9% (reference range: 0.5–2.0%), mild lactose dehydrogenase elevation of 287 IU/L (reference range: 140–271 IU/L), and elevated indirect bilirubin of 1 mg/dL (calculated by subtracting direct from total bilirubin). His direct Coombs test was positive for warm autoantibody IgG and C3 complement. His fecal occult blood test was negative. He received blood transfusion as necessary with goal hemoglobin > 7.0 g/dl and was started on intravenous methylprednisone that was tapered to hydrocortisone due to his adrenal insufficiency. Two out of 2 of his blood cultures from admission came back positive for *Enterococcus faecalis* which cleared on the sixth day of admission with antibiotics. Patient had a chronic indwelling Foley's catheter. Source of bacteremia was urine which grew >100,000 CFU/mL *E. faecalis* and >100,000 CFU/mL *Escherichia coli*. The patient was placed on intravenous vancomycin and ceftriaxone. Vancomycin was later changed to daptomycin due to persistent bacteremia. TTE showed focal thickening and calcification of the mitral valve leaflets and subvalvular apparatus, a small density on the atrial side of the mitral valve and moderate to severe mitral regurgitation. TEE further showed 0.6 × 0.5 cm and 0.4 × 0.3 cm masses attached to the tip of the anterior and posterior MV leaflets, respectively, with moderate to severe, central MR (Figure 2). No obvious vegetation was noted in the aortic valve. Given persistent bacteremia and severe MR, patient underwent redo sternotomy and mitral valve replacement with 27 mm Edwards bioprosthesis. Endocarditic breakdown of mitral valve was observed but no real vegetation was noted during the procedure. Histologic examination of the mitral
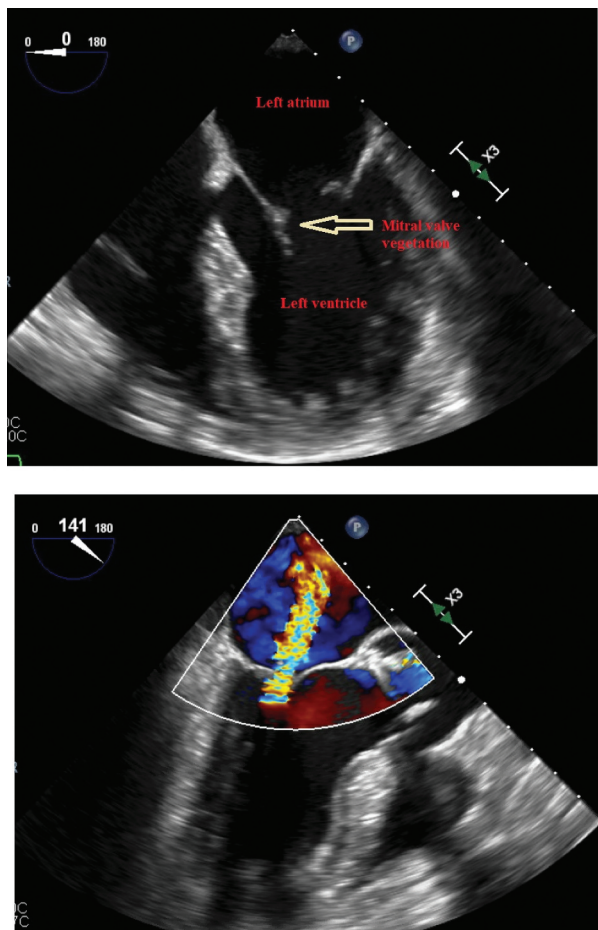
Figure 2. Transesophageal echocardiogram showing 0.6 × 0.5 cm and 0.4 × 0.3 cm masses attached to the tip of the anterior and posterior mitral valve leaflets respectively (a) with moderate to severe, central mitral regurgitation (b).

valve was consistent with vegetation, but bacterial, fungal, and anaerobic cultures were negative for definitive organisms. Post-operative stay was uneventful, and patient was discharged on IV daptomycin to complete a 6-week course.

The patient was hospitalized a month later with right temporal occipital intraparenchymal hemorrhage measuring 4.4 × 3.8 × 3.2 cm with adjacent edema but no midline shift. This was thought to be due to hemorrhagic conversion of prior stroke. Hemorrhagic stroke was managed conservatively by holding enoxaparin for 4 days and starting levetiracetam for seizure prophylaxis. He was again hospitalized a month and a half later with 3.8 × 3.4 × 2.7 cm large right cerebellar hematoma with mass effect on the fourth ventricle without hydrocephalus (Figure 3). Patient passed away later the same day thought to be from brain herniation.

3. Discussion

3.1. Pathogenesis

Epithelial injury is believed to be the inciting factor. This is followed by fibrin and platelet deposition of
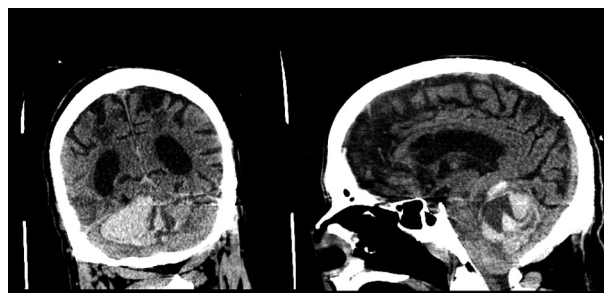

Figure 3. CT head showing 3.8 × 3.4 × 2.7 cm large right cerebellar hematoma with mass effect on the fourth ventricle.

the affected valve in the setting of a hypercoagulable state [2,3,5]. Antiphospholipid antibodies and complement have been noted on involved valves which suggests that APS is a risk factor for NBTE [6]. It is believed that these autoantibodies are directed against the phospholipids in the endothelium and not only damage the endothelium but also mediate activation and deposition of platelet and fibrin [2,5,7]. These lesions are more friable than the vegetations seen in infective endocarditis and are more prone to systemic embolization [1,2].

3.2. Clinical presentation

NBTE is typically clinically silent and patients commonly present with symptoms of embolization or valvular dysfunction. Patients may embolize to the brain, extremities, coronaries, spleen, and kidneys which manifests as focal neurological deficits, memory loss, painful extremities, and acute abdomen [2]. Cerebral embolization is the most common clinical manifestation of APS in patients with NBTE [8]. Vavlular dysfunction may present as heart murmurs, arrhythmias, and heart failure. Patients with primary APS may also have history of multiple miscarriages and arterial and venous thromboses [2].

3.3. Diagnosis

Anticardiolipin IgG or IgM, anti-B$_2$ glycoprotein IgG or IgM and lupus anticoagulant associated with history of thrombosis or pregnancy morbidity are required for a diagnosis of definite APS [7,9]. Patients may also have hemolytic anemia and thrombocytopenia. Schistocytes may also be present [10]. Positive antiphospholipid antibodies, negative blood cultures, and absence of systemic symptoms help differentiate NBTE from infective endocarditis [2]. Mitral valve followed by aortic valve are commonly affected valves. It can affect both normal valves and valves affected by rheumatic fever or endocarditis, chordae tendineae or the endocardium [2,3]. Valvular lesions are characterized by localized to generalized thickening with or without vegetations [3]. Vegetations are often rounded,

sessile, and heterogenous and are characteristically seen along the coaptation edge of the leaflets [2,11]. There may be associated valvular regurgitation or stenosis. All these findings can be detected on TTE or TEE [3]. Definitive diagnosis can be done by biopsy of the affected valve or postmortem. Histologic examination shows fibrinoplatelet deposition with mononuclear cell infiltration [2,11].

3.4. Management

No specific therapy exists for NBTE. Treatment should be directed at preventing systemic embolization and management of underlying malignancy or SLE [2]. Long-term anticoagulation is recommended by the American College of Chest Physician guidelines [12]. Unfractionated heparin is currently recommended to reduce rates of ischemic stroke in cancer patients [2]. Limited evidence exists on the use of direct oral anticoagulants in these patients [1,2]. Role of steroids is unclear but has shown to decrease the prevalence of Libman–Sacks endocarditis. Patients with severe symptomatic valvular dysfunction, recurrent systemic embolism, and large vegetations greater than 1 cm may undergo valve repair or replacement after assessing their individual risks and benefits. The prognosis of patients with NBTE is poor [2].

4. Conclusion

Our patient is a unique case of recurrent NBTE with multiple valve replacements that were complicated by recurrent ischemic strokes despite being on anticoagulation. We hope this case will help better understand treatment for similar cases of recurrent NBTE and strokes.

Disclosure statement

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