Aortic Valve Vegetation due to Nonbacterial Thrombotic Endocarditis in a Patient with Antiphospholipid Antibody Syndrome

Abdul Rasheed Bahar, MD, Tushar Mishra, MD, Yasemin Bahar, MD, Mahmoud Othman, MD, and Luis Afonso, MD, *Detroit, Michigan*

INTRODUCTION

Nonbacterial thrombotic endocarditis (NBTE) is a rare condition characterized by the development of sterile thrombotic vegetation(s) on cardiac valves that is most commonly associated with advanced malignancy and chronic inflammatory diseases including systemic lupus erythematosus and antiphospholipid antibody syndrome (APLAS).[1] Nonbacterial thrombotic endocarditis is most often found postmortem, with rates in autopsy series of approximately 1.2%.[2] In a study of 48 patients with NBTE, the condition was more prevalent in women.[3] The exact pathogenesis of the disease is still not known; however, endothelial injury in the setting of hypercoagulable states, hypoxia, immune complexes, and carcinomatosis is thought to be associated with the initiation of the disease.[4] Nonbacterial thrombotic endocarditis differs from culture-negative endocarditis, which has infectious origins based on clinical description that has not been readily identified or is difficult to culture. There are no pathognomonic signs and symptoms that allow for the diagnosis of NBTE, with most patients being asymptomatic until embolization occurs, which accounts for the majority of clinical manifestations, with up to 50% of patients with NBTE presenting with embolic phenomena.[5] The diagnostic approach to NBTE is mainly directed toward distinguishing NBTE from infective endocarditis (IE) and detecting the underlying cause as there are no laboratory tests that confirm the diagnosis of NBTE. In the past, postmortem examinations were required for the diagnosis of NBTE; however, currently, premortem diagnosis of NBTE is possible based on echocardiographic findings. Treatment of NBTE usually consists of systemic anticoagulation and treating the underlying associated condition. Surgery with valve debridement or excision is reserved mainly for patients with acute decompensated heart failure (due to valvular dysfunction) or the occurrence of recurrent thromboembolism despite therapeutic anticoagulation.[4]

In this report, we present a case of aortic valve (AV) vegetation due to NBTE in a patient with APLAS who developed an acute cerebrovascular event after an initial asymptomatic period. We also provide an updated literature review on the management of AV vegetations due to NBTE.

CASE PRESENTATION

A 47-year-old man with a history of triple positive APLAS, chronic lower extremity deep vein thrombosis, and thrombocytopenic purpura was transferred to the hospital due to abnormal findings on transthoracic echocardiography (TTE). On admission to the hospital, the patient denied any symptoms including fever, chills, shortness of breath, chest pain, rash, and bruising. However, the patient did report chronic fatigue and gradual weight loss. They denied intravenous drug use. On exam, normal S1 and S2 sounds along with an early diastolic murmur at the left sternal border consistent with aortic regurgitation (AR) were noticed. No abnormal lesions were noticed on the fingers or hands. Lab investigations revealed normal hemogram and chemistries including electrolytes, liver function tests, and kidney function tests. The patient was positive for lupus anticoagulant. Levels of IgA, IgG, and IgM anti-β2-glycoprotein (anti-β2GP) antibody were 21.41, 79.99, and 58.39 SAU, respectively, and IgG and IgM anticardiolipin (aCL) antibody levels were 150.4 and 143.1 units, respectively. Additional test results included ANA titer 1:640, positive RF, negative ENA screen, low complement C4, negative anti-dsDNA, negative syphilis EIA screen, CRP 8.2, ESR 47, and anti-smith negative. The TTE showed a highly mobile mass on the ventricular surface of the left coronary cusp (Video 1, Figure 1). These findings were confirmed with transesophageal echocardiography (TEE), which showed a 0.61 cm $\times$ 1.2 cm highly mobile mass on the ventricular surface of the left coronary cusp with moderate AR (Video 2, Figure 2).

The patient had been using warfarin for APLAS, which was switched to rivaroxaban due to dietary restrictions and difficulty with monitoring the international normalized ratio. The patient was evaluated by cardiothoracic surgery, infectious disease, hematology, and cardiology teams, who advised against any surgical intervention for AV vegetation given the absence of heart failure symptoms and embolic phenomena. Also, given the absence of growth in 3 sets of blood cultures along with the negative Tropheryma whipplei, Bartonella henselae and Bartonella quintana IgG and IgM, and Brucella IgG and IgM results, the patient was not given antibiotic therapy for IE. Of note, the incubation periods of the blood cultures were further extended to improve the recovery of HACEK bacteria for culture-negative endocarditis. During the course of hospitalization, the patient remained stable, with no embolic events. The patient was switched from rivaroxaban to dabigatran due to the presumed failure of therapeutic anticoagulation with rivaroxaban. After extensive investigations, the patient was safely discharged with surveillance outpatient TTE scheduled. Repeat TTE (Video 3, Figure 3) in 2 months demonstrated resolution of the AV mass with mild AR.

Four months later, the patient presented to the hospital with complaints of word-finding difficulties. Computed tomography of the

From the Department of Internal Medicine, Wayne State University (A.R.B.), Wayne State University, Detroit Medical Center Heart Hospital (T.M., M.O., L.A.), and Wayne State University School of Medicine (Y.B.), Detroit, Michigan.

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Correspondence: Abdul Rasheed Bahar, MD, Department of Internal Medicine, Wayne State University, 4201 St. Antoine Street Suit 2E, Detroit, MI 48201. (E-mail: *rashidbaharr@gmail.com*).

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VIDEO HIGHLIGHTS

Video 1: Two-dimensional TTE, parasternal long-axis view, demonstrates normal left ventricular size and function with visualized vegetations attached to the ventricular surface of the left and right coronary cusps.

Video 2: Two-dimensional TEE, midesophageal long-axis (120°) view, demonstrates a large (1.2 × 0.6 cm), highly mobile mass on the ventricular surface of the left coronary cusp.

Video 3: Two-dimensional TTE, biplane, parasternal long-axis view, demonstrates normal left ventricular size and function with resolution of the previously noted vegetations.

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head without contrast was normal. Magnetic resonance imaging of the brain demonstrated acute infarction in the left parietal and posterior temporal lobes. The patient was started on a heparin drip for treatment of acute stroke with close monitoring for hemodynamic instability. A TTE was performed and did not show any vegetation, ventricular thrombi, or masses. After 5 days of bridging with heparin, the patient was transitioned to warfarin. After medical stabilization and clinical improvement, the patient was discharged home with close outpatient monitoring of the international normalized ratio and warfarin dose.

DISCUSSION

We report an unusual patient with NBTE attributable to primary APLAS who presented with a large mobile mass on the ventricular surface of the left coronary cusp with AR. Aortic valve vegetation is a clinically intriguing and infrequently encountered manifestation of NBTE. Nonbacterial thrombotic endocarditis is a rare condition that refers to a spectrum of noninfectious lesions of the heart valves in the absence of bloodstream bacterial infection, ranging from microscopic platelet aggregates to large vegetations, and is often diagnosed postmortem. However, the condition carries a high clinical significance due to its association with a high prevalence of valvular heart disease, leading to an increased risk of thromboembolic events, particularly cerebrovascular events.[6] It has been shown that in patients with NBTE, vegetations are most frequently found on mitral valves followed by AVs.[7] Our report, with its emphasis on a rare presentation, not only enhances our understanding of the condition but also provides a direction for further research and clinical considerations. This case is unusual in that it was diagnosed in an asymptomatic patient while on anticoagulation therapy, as most cases are discovered incidentally postmortem and are not well described in the literature. Furthermore, most of the previous cases of NBTE with AV vegetations have been reported in patients with underlying malignancy; however, data regarding nonbacterial thrombotic AV endocarditis in patients with primary APLAS are limited in the literature. The presence of mobile densities on valve structures in echocardiography usually indicates vegetation from subacute bacterial endocarditis, tumors, or thrombi. The finding of a large intracardiac mass caused by NBTE without known malignancy or connective tissue disease is rare.

Patients with NBTE are often asymptomatic, and cardiac murmurs, a hallmark of IE, are detected in less than half of the patients.[4] The most frequent presentation occurs when the vegetations dislodge and embolize, which ensues in approximately 50% of patients, rather than valvular dysfunction as the lesions do not usually produce sufficient valvular impairment to alter valve function.[5] However, on some occasions, the valve may be sufficiently damaged to cause heart failure necessitating valve replacement. Patients with NBTE frequently experience embolic events, particularly stroke, within 1 month of the diagnosis, and the overall prognosis is poor.[3]

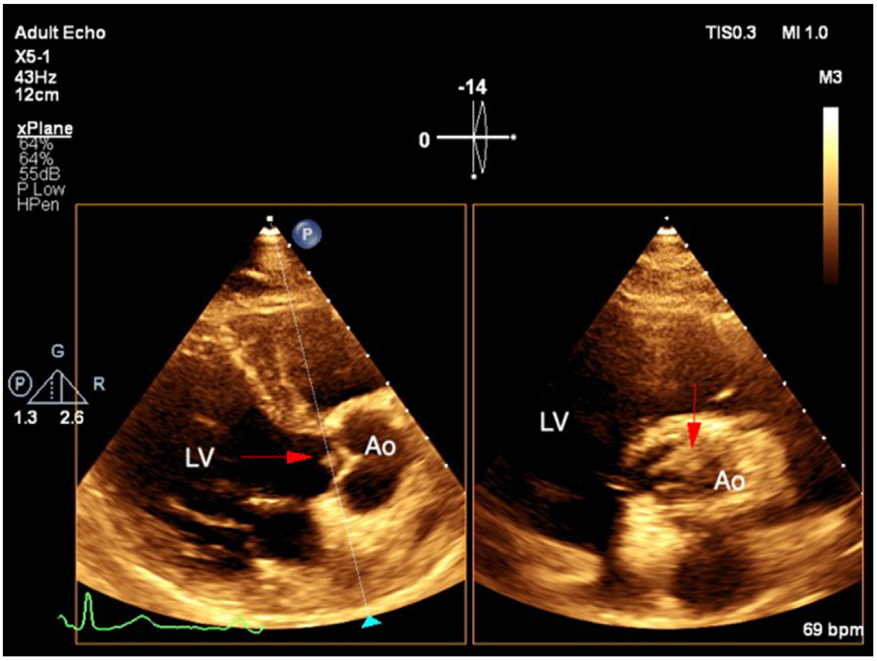

Figure 1 Two-dimensional TTE, biplane, parasternal long-axis diastolic view, demonstrates vegetations attached to the ventricular surface of the left and right coronary cusps (*red arrows*). *LV*, Left ventricle; *Ao*, Aorta.

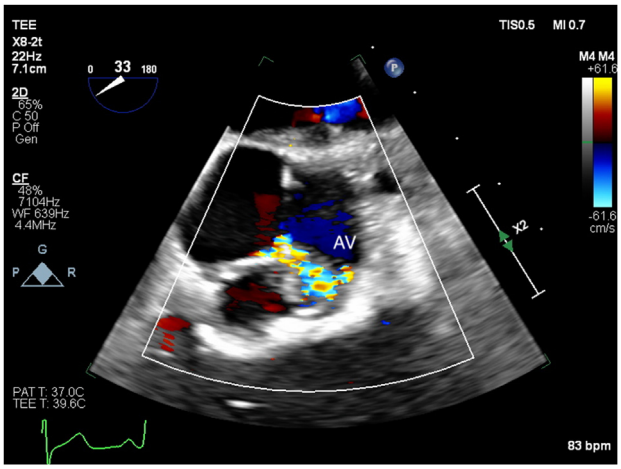

Figure 2 Two-dimensional TEE, apical short-axis (33°) diastolic view with color flow Doppler, demonstrates trileaflet morphology with moderate AR. *AV*, Aortic valve.

The diagnosis of NBTE is considerably more challenging than that of IE as there are no characteristic markers of the bloodstream, and the vegetations are small, easily friable, and frequently embolize, leaving very small remnants to be identified on the valve. Moreover, echocardiography is less sensitive for the detection of NBTE than for IE.[8] This was evident in our case given the initial incidental TTE finding followed by complete resolution of the vegetation and subsequent presentation with acute cerebrovascular event. The patient remained completely asymptomatic in the interim, making the clinical diagnosis even more challenging. Nevertheless, patients with suspected NBTE should be evaluated with two-dimensional TTE for the presence of valvular vegetations.[9] Despite being semi-invasive, TEE has demonstrated higher sensitivity, specificity, and predictive values for detecting NBTE compared to TTE as it provides better visualization of the posterior cardiac structures, exhibits higher resolution, and is considered more accurate in detecting valvular heart disease or masses.[10] In one study, the sensitivities of TTE in comparison to TEE for detecting vegetations, thickening, and regurgitation were 48%, 67%, and 73%, respectively.[3]

The mainstay treatment of NBTE is systemic anticoagulation with unfractionated heparin, reported to be the most effective anticoagulant by reducing the incidence of recurrent episodes of thromboembolism.[8] Warfarin is less effective than heparin in reducing the rate of recurrent embolization as the presence of non-vitamin K-dependent agents may induce thrombotic coagulopathy in NBTE treated with warfarin.[11] Anticoagulation with factor Xa or direct thrombin inhibitors has not

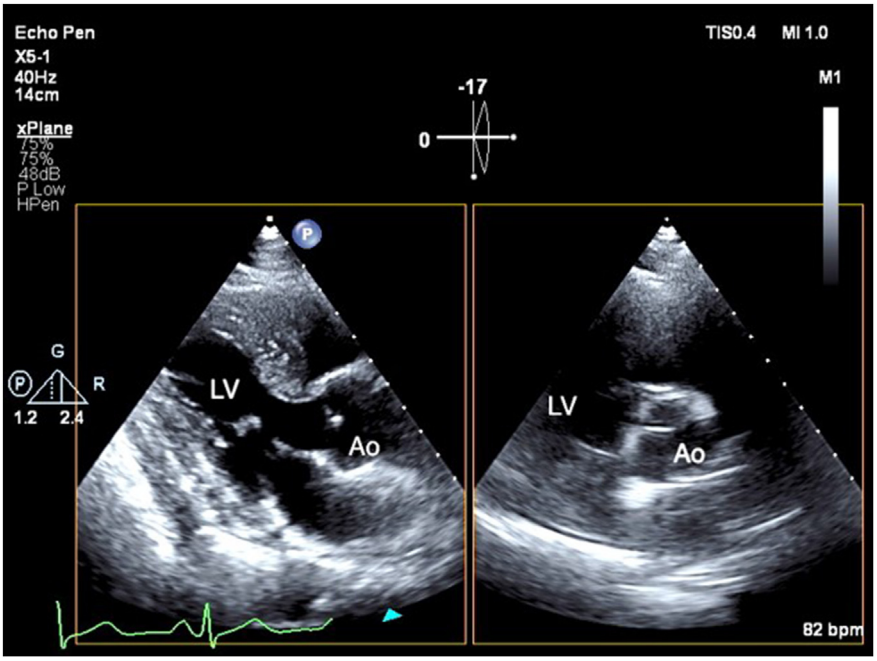

Figure 3 Two-dimensional TTE, biplane, parasternal long-axis diastolic view, demonstrates the resolution of the previously noted vegetations.

been evaluated to support their routine use as anticoagulants for NBTE.[12] However, it has not been shown that treatment with systemic anticoagulation fully prevents emboli from occurring in the future. Our patient developed a thromboembolic event while on appropriate anticoagulation therapy. Surgical intervention for NBTE-associated vegetation may be considered in select cases where the risk-benefit is favorable. Key considerations include the size and location of the vegetation, associated symptoms, risk of embolization, and overall health of the patient.[13] It is extremely difficult to presume that surgery of the initial AV vegetation in the first place could have prevented the subsequent stroke in our patient. However, we recommend close monitoring of similar cases with routine TTE even in the absence of clinical signs and symptoms. Valvular surgery can be an effective treatment for patients with large mobile vegetations or recurrent embolic events despite anticoagulation and patients with acute decompensated heart failure due to valvular dysfuntion.[4] The European Society of Cardiology guidelines recommend urgent surgical intervention for aortic or mitral valve vegetation >10 mm with severe stenosis or regurgitation and low operative risk (class IIa) or any vegetation >15 mm. On the other hand, the American College of Cardiology/American Heart Association guidelines recommend consideration for early surgery for left-sided mobile vegetations >10 mm without respect to lesion severity or operative risk (class IIb).[14]

CONCLUSION

This case report highlights a unique presentation of AV vegetation due to NBTE complicated by cerebrovascular events a long time after the resolution of the vegetation. The complexities of the diagnostic process and the challenging management outlined herein contribute valuable insights to the medical literature. The proper management of APLAS and prevention of thromboembolic events remain extremely challenging. Patients should be closely followed for potential complications of the disease.

ETHICS STATEMENT

The work did not include experiments on humans or animals. There are no patient identifiers mentioned in the report. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CONSENT STATEMENT

Complete written informed consent was obtained from the patient (or appropriate parent, guardian, or power of attorney) for the publication of this study and accompanying images.

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DISCLOSURE STATEMENT

The authors report no conflict of interest.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2024.05.002.

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