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VALVULAR HEART DISEASE

CLINICAL CASE

Nonbacterial Thrombotic Endocarditis of a Mitral Prosthesis After Warfarin, Enoxaparin, and Apixaban Failure

Andrew Nevin, MD, MED,[a] Samer Muallem, MD,[b] Michael Pfeiffer, MD[c]

ABSTRACT

Nonbacterial thrombotic endocarditis (NBTE) is an uncommon condition that carries significant morbidity and an in-hospital mortality rate of up to 36%. Involvement of a prosthetic valve with NBTE is even more rare. We present a case of prosthetic mitral valve NBTE that manifested 5 months after surgical mitral valve replacement. The patient's presentation was complicated by complex medical comorbidities and previous contraindications to multiple anticoagulant agents that included calciphylaxis secondary to warfarin and high concern for heparin-induced thrombocytopenia. The patient was taking apixaban when she developed prosthetic valve NTBE. The patient was transitioned to fondaparinux, with resolution of the mitral valve vegetations. Warfarin and heparin are first-line anticoagulant agents for antiphospholipid syndrome and NBTE, respectively. There is limited evidence for different anticoagulant agents in NBTE. Our case highlights nuance in the diagnosis of NBTE and complexities of anticoagulation decisions in patients with contraindications to various agents. (JACC Case Rep. 2025;30:103091) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 66-year-old woman was admitted to the cardiology service with a chief concern of exertional dyspnea and recent weight gain. Her vital signs on admission were notable for a temperature of 36.6 °C, a heart rate of 90 beats/min, blood pressure of 129/69 mm Hg, and an oxygen saturation of 95% on 2 L of oxygen. Examination was notable for inspiratory wheezes and crackles, as well as a grade II-VI holosystolic murmur at the lower sternal border.

PAST MEDICAL HISTORY

The patient's cardiovascular history included heart failure with preserved ejection fraction (EF),

TAKE-HOME MESSAGES

- Nonbacterial thrombotic endocarditis should be included on the differential diagnoses of patients with new valve dysfunction and/or embolic events of unknown origin, especially in patients with disease-level risk factors such as autoimmune disease or malignant disease.
- Similarly, endocarditis in the absence of infectious processes should prompt consideration of autoimmune or malignant disease diagnoses.
- Comorbid conditions, which may be common or uncommon with nonbacterial thrombotic endocarditis, can significantly affect the choice of appropriate anticoagulation.

From the [a]Department of Pediatrics, Penn State Children's Hospital, Hershey, Pennsylvania, USA; [b]Department of Medicine, McGaw Medical Center, Northwestern Memorial Hospital, Chicago, Illinois, USA; and the [c]Heart and Vascular Institute, Milton S. Hershey Medical Center, Hershey, Pennsylvania, USA.

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ABBREVIATIONS AND ACRONYMS

ANA = antinuclear antibody

APS = antiphospholipid syndrome

EF = ejection fraction

NBTE = nonbacterial thrombotic endocarditis

SLE = systemic lupus erythematosus

TEE = transesophageal echocardiogram

TTE = transthoracic echocardiogram

nonocclusive coronary artery disease, paroxysmal atrial fibrillation, and rheumatic mitral disease with mixed stenosis and regurgitation. Five months before this acute presentation, she had worsened mitral valve disease with severe stenosis and moderate regurgitation, associated with a reduction in left ventricular EF from 65% to 38%. She also developed significant tricuspid regurgitation during this window of decompensation. She underwent an open mitral valve replacement with a 29-mm St Jude Medical Epic bioprosthesis and simultaneous tricuspid annuloplasty repair with an Edwards Lifesciences MC3 annuloplasty ring for severe tricuspid regurgitation. On the first postoperative transthoracic echocardiogram (TTE), her EF normalized, the mean mitral gradient was 7 mm Hg, and tricuspid regurgitation remained moderate despite annuloplasty.

The patient was receiving amiodarone in the perioperative period for control of her atrial arrhythmia. Previous laboratory testing had demonstrated the presence of anticardiolipin antibodies and lupus anticoagulant on a single occasion, concerning for, but not diagnostic of, antiphospholipid syndrome (APS). She had previously been taking warfarin for her paroxysmal atrial fibrillation but had recently developed severe, biopsy-proven calciphylaxis on therapeutic warfarin and had been treated with sodium thiosulfate. She also had a positive platelet factor 4 immunoglobulin G antibody result during a workup for thrombocytopenia in the setting of heparin exposure with a negative serotonin release assay. However, avoidance of heparin-containing products was previously recommended by hematology. Ultimately, she was taking apixaban for stroke prophylaxis for atrial fibrillation with no confirmed hematologic indication for anticoagulation at the time of this admission.

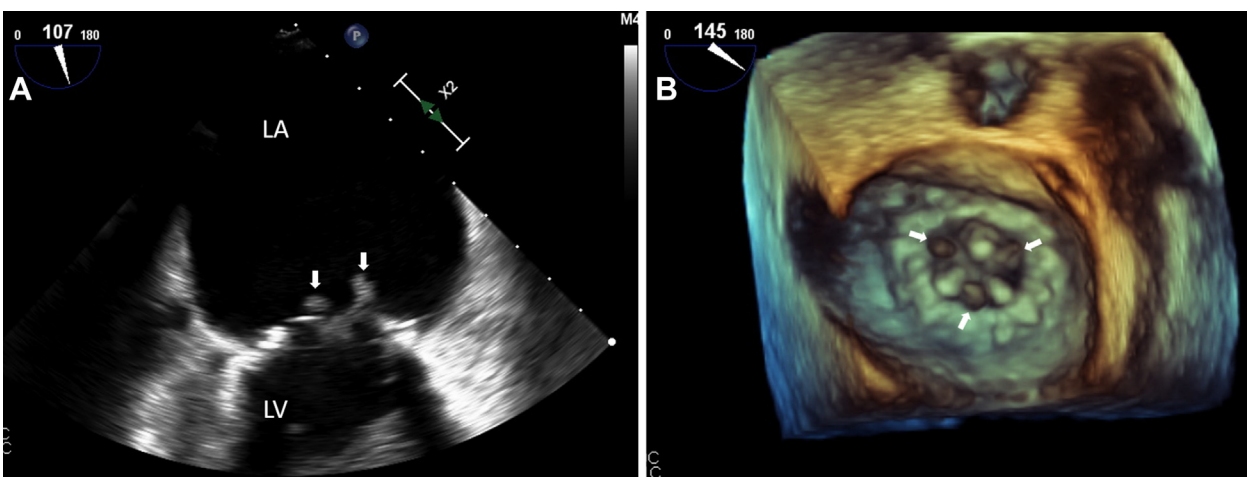
DIFFERENTIAL DIAGNOSIS

The differential diagnosis on admission was quite broad and included drug-induced hypersensitivity pneumonitis from sodium thiosulfate or amiodarone, interstitial lung disease, and pneumonia. In terms of cardiac causes, acute heart failure exacerbation and valvular dysfunction, given recent mitral and tricuspid surgery, were included in the differential diagnosis.

INVESTIGATIONS

Out of concern for acute decompensated heart failure and valvular dysfunction, the patient underwent TTE, which demonstrated an increased mean mitral valve gradient of 12 mm Hg, increased from her initial postoperative TTE. She subsequently underwent right-sided heart catheterization, demonstrating increased pressures: right atrial pressure of 16 mm Hg, mean pulmonary artery pressure of 54 mm Hg, pulmonary capillary wedge pressure of 36 mm Hg, and pulmonary vascular resistance of 4 WU. A transesophageal echocardiogram (TEE) visualized multiple echodensities on the atrial side of the

FIGURE 1 2- and 3-Dimensional Transesophageal Echocardiogram Views of Mitral Valve Pretreatment

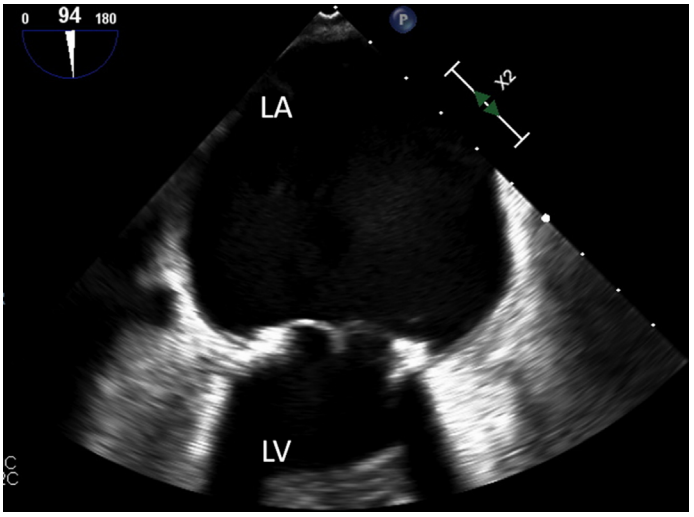


(A and B) Multiple vegetations are visualized on the atrial side of the prosthetic mitral valve (white arrows). LA = left atrium; LV = left ventricle.

mitral valve replacement, consistent with endocarditis (**Figures 1A and 1B**, Videos 1 and 2).

The infectious workup was unremarkable, with multiple sets of negative results of blood cultures that were grown for an extended period of time to exclude fastidious organisms. The patient remained afebrile, without other stigmata of an infectious process. Her ANA test result was positive at a titer of 1:2,560, with a high titer of anti-dsDNA antibody, low C4, and a positive direct antiglobulin test result. Given that a previous APS evaluation was both remote and unconfirmed, testing was repeated, and the results were positive for lupus anticoagulant, anticardiolipin, and β_2-glycoprotein, thus confirming a triple-positive subtype of APS. Her positive serologic results, APS diagnosis, and other medical comorbidities were consistent with a diagnosis of systemic lupus erythematosus (SLE). Valvular vegetations in the presence of a new SLE diagnosis and the absence of an infectious cause secured the diagnosis of nonbacterial thrombotic endocarditis (NBTE) with associated bioprosthetic valve dysfunction and acute decompensated heart failure with preserved EF.

FIGURE 2 2-Dimensional Transesophageal Echocardiogram View of Mitral Valve Post-Treatment



After 2 months of anticoagulation with fondaparinux, the previously visualized vegetations resolved. Abbreviations as in **Figure 1**.

MANAGEMENT

Shortly after admission, the patient received intravenous diuretic therapy with furosemide. She responded well, with resolution of her oxygen requirement. The patient was initiated on hydroxychloroquine for SLE. The NBTE of her bioprosthetic valve occurred during therapeutic anticoagulation with apixaban. Furthermore, the new diagnosis of triple-positive APS necessitated a change in anticoagulation therapy. Hematology was engaged to assist in this complex decision making. In light of her adverse events with warfarin, enoxaparin, and apixaban, the patient was transitioned to fondaparinux for long-term anticoagulation. Final decision making for anticoagulation occurred via multidisciplinary case review with cardiology, rheumatology, and hematology.

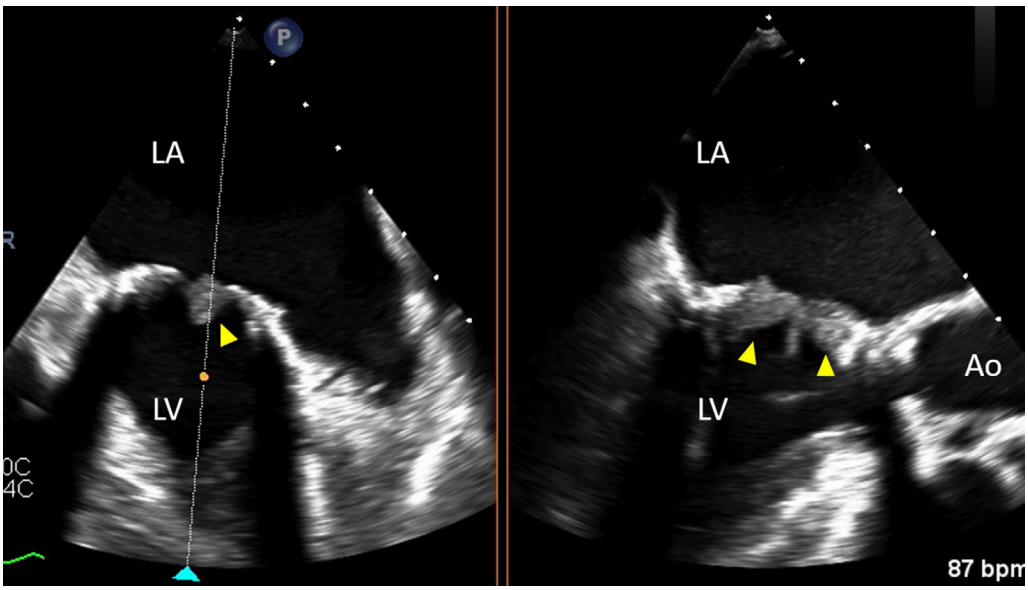
DISCUSSION: ASSOCIATION WITH CURRENT GUIDELINES/POSITION PAPERS/ CURRENT PRACTICE

Warfarin is the first-line anticoagulant agent for triple-positive positive APS.[1] Unfractionated and low-molecular-weight heparin are suggested as first-line anticoagulation choices for NBTE; however, the evidence for this recommendation is limited, and warfarin may be used in non–malignancy-related cases.[2] Although the indications for direct oral anticoagulant agents have expanded, they remain unsupported in NBTE,[2] with emerging evidence of increased events with rivaroxaban, a Xa-inhibitor, in triple-positive and other high-risk APS.[3] Our patient lacked traditional anticoagulation options because of her presentation on apixaban, new diagnosis of high-risk APS, and history of serious reactions to warfarin and heparin-containing products. She was maintained on fondaparinux on discharge, despite the lack of comparative evidence in APS with other risk factors such as atrial fibrillation and mitral valve replacement.[4,5]

NBTE is a hazardous entity, carrying a mortality rate as high as 36% and significant morbidity associated primarily with embolic events.[2] Left-sided NBTE is far more common than right-sided NBTE. It is most closely associated with mucinous adenocarcinomas such as pancreatic and lung cancer.[2] Autoimmune diseases, most notably SLE and APS, are other major disease-level risk factors that contribute to a proinflammatory and procoagulant state and predispose to NBTE.[2,6] Studies demonstrate a female predilection, likely a reflection of the higher incidence of predisposing autoimmune disease in women.[6,7]

NBTE remains a challenge to diagnose. Its incidence is poorly understood, it does not have a distinct pathognomonic presentation, and it may not be readily apparent on more easily accessible imaging, such as TTE.[6,7] TTE has limited sensitivity for NBTE, reported as 45% for all NBTE and only 38%

FIGURE 3 2-Dimensional Transesophageal Echocardiogram View of Mitral Valve After Anticoagulation Change



Leaflet thickening (arrowheads), consistent with thrombosis, occurred approximately 90 days after transition to dabigatran. Ao = aorta; other abbreviations as in Figure 1.

for mitral valve vegetations, compared with 97% sensitivity with TEE.[2,7] A suggested diagnostic algorithm notes the following key aspects to suspect NBTE: female sex or age >39 years; an embolic event; a history of connective tissue disease, malignant disease, or APS; and relative exclusion of infective endocarditis.[7]

The cornerstone of therapy for NBTE consists of treatment of the underlying disease process (malignant or autoimmune process) and anticoagulation.[8] In practice, comorbidities frequently influence anticoagulation decisions.[2] In the case of our patient, fondaparinux was chosen given evidence of efficacy as a second-line medical therapy for APS.[9] Valve replacement is considered a secondary option for NBTE. Although there are no guideline-level recommendations, valve replacement may be reasonable for patients with severe valve regurgitation, recurrent emboli after anticoagulation initiation, large (>10 mm) vegetations, or prosthetic valve NBTE.[10]

FOLLOW-UP

A redo mitral valve replacement was deferred in our patient. She did not have any embolic events, tolerated her valve dysfunction relatively well, and desired conservative treatment if possible. The patient was discharged on fondaparinux, hydroxychloroquine, and an oral diuretic regimen. A TEE 2 months after discharge demonstrated complete resolution of mitral valve vegetations, improved leaflet mobility, and a reduced mitral valve gradient (**Figure 2**, Video 3). Her symptoms of heart failure significantly improved.

In subsequent follow-up, the patient advocated for a transition to oral anticoagulation because of the undesired impact of long-term injections. The patient had previously experienced treatment failure with apixaban, and with confirmed high-risk APS, factor Xa inhibitors have known increased risks.[3] Under the guidance of hematology, she attempted a transition to dabigatran because of its different mechanism of action as a direct thrombin inhibitor. She developed progressive shortness of breath and volume overload within 3 months of dabigatran treatment. The patient was hospitalized and started on intravenous diuretic therapy. The TEE showed no vegetations, but it demonstrated stenosis of her prosthetic mitral valve with thickened leaflets concerning for layered thrombosis (**Figure 3**, Video 4). The patient was transitioned from dabigatran back to fondaparinux and started on a prednisone taper, as well as mycophenolate mofetil. The mycophenolate mofetil and fondaparinux were continued indefinitely. The

patient is currently more than 1 year from all the described events. She has had improved mitral valve function with reduced gradient on serial echocardiographic imaging. She has had no recurrent heart failure hospitalizations and retains NYHA functional class I status.

CONCLUSIONS

NBTE is an uncommon clinical phenomenon, especially when associated with a bioprosthetic valve. It should be considered in individuals with new valvular dysfunction or unexplained embolic events, and comorbid autoimmune disorders or malignant disease should increase the index of suspicion. Our case of prosthetic NBTE presented complex treatment decisions because of the association with the patient's triple-positive APS and contraindications to multiple anticoagulant agents. We highlighted safety concerns with both factor Xa inhibitors and direct thrombin inhibitors in high-risk APS subtypes. This case underscores the need for more investigation into NBTE and dissemination of unusual cases with complex management decisions.

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Dr Pfeiffer has served as a speaker and a proctor for Abbott Lifesciences; and has served as a consultant for Ancora Heart. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Andrew Nevin, Penn State Milton S. Hershey Medical Center, 500 University Drive, P.O. Box 850, MC H047, Hershey, Pennsylvania 17033, USA. E-mail: anevin@pennstatehealth.psu.edu.

REFERENCES

1. Tektonidou MG, Andreoli L, Limper M, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. *Ann Rheum Dis*. 2019;78:1296-1304.

2. Zmaili M, Alzubi J, Lo Presti Vega S, Ababneh E, Xu B. Non-bacterial thrombotic endocarditis: a state-of-the-art contemporary review. *Prog Cardiovasc Dis*. 2022;74:99-110.

3. Pengo V, Denas G, Zoppellaro G, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood*. 2018;132:1365-1371.

4. Mentias A, Saad M, Michael M, et al. Direct oral anticoagulants versus warfarin in patients with atrial fibrillation and valve replacement or repair. *J Am Heart Assoc*. 2022;11:e026666.

5. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. *Chest*. 2021;160:e545-e608.

6. Alhuarrat MAD, Garg V, Borkowski P, et al. Epidemiologic and clinical characteristics of marantic endocarditis: a systematic review and meta-analysis of 416 reports. *Curr Probl Cardiol*. 2024;49:102027.

7. Quintero-Martinez JA, Hindy JR, El Zein S, et al. Contemporary demographics, diagnostics and outcomes in non-bacterial thrombotic endocarditis. *Heart*. 2022;108:1637-1643. https://doi.org/10.1136/heartjnl-2022-320970

8. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e576S-e600S.

9. Bor B, Doyle AJ, Bartoli-Abdou JK, et al. Clinical outcomes of patients receiving long-term fondaparinux for thrombotic antiphospholipid syndrome. *Lupus*. 2024;33:1446-1454.

10. Liu J, Frishman WH. Nonbacterial thrombotic endocarditis: pathogenesis, diagnosis, and management. *Cardiol Rev*. 2016;24:244-247.

KEY WORDS anticoagulation, autoimmune, echocardiography, endocarditis, mitral valve, valve replacement

APPENDIX For supplemental videos, please see the online version of this paper.