OMCR

Oxford Medical Case Reports, 2018;6, 190–194

doi: 10.1093/omcr/omy024
Case Report

CASE REPORT

Nonbacterial thrombotic endocarditis in a patient with primary antiphospholipid syndrome

Natee Sirinvaravong[1,*], Mary C. Rodriguez Ziccardi[1], Soumya Patnaik[2], Mahek Shah[3], Gustavo Fernandez[4], Jose-Nitram Aliling[5] and Alexander Rubin[6]

[1]Department of Medicine, Einstein Medical Center, Philadelphia, PA, USA, [2]Division of Cardiology, University of Texas Health Science Center at Houston, Houston, TX, USA, [3]Division of Cardiology, Lehigh Valley Healthcare Network, Allentown, PA, USA, [4]Division of Pulmonology, Temple University Hospital, Philadelphia, PA, USA, [5]Division of Rheumatology, University of California, Los Angeles, CA, USA, and [6]Division of Cardiology, Pennsylvania Heart and Vascular Group, Jenkintown, Philadelphia PA, USA

*Correspondence address. Natee Sirinvaravong; E-mail: Natee.sirin@gmail.com

Abstract

Nonbacterial thrombotic endocarditis (NBTE) is described in patients with mucin-producing cancers and connective tissue disorders (usually SLE). We report NBTE in the setting of primary antiphospholipid antibody syndrome (APS). A 65-year-old female with APS was incidentally found to have thickened mitral leaflets on transthoracic echocardiogram with no signs of infection. Transesophageal echocardiogram (TEE) showed a mobile mitral mass (1.4 × 0.7 cm) and moderate mitral regurgitation. Differential diagnoses included bacterial endocarditis, NBTE, thrombus or tumor. Given the history of primary APS, the absence of fever and negative blood cultures, NBTE was considered. Low-molecular-weight heparin, hydroxychloroquine and corticosteroid were initiated. Repeat TEE in a week revealed shrinkage of the mass (0.6 × 0.7 cm), indicating an inflammatory nature. Lifelong anticoagulation is indicated regardless of embolism occurrence. Hydroxychloroquine and corticosteroids may have roles in the treatment. Determining and treating the underlying etiology is important.

INTRODUCTION

Nonbacterial thrombotic endocarditis (NBTE) is a rare non-infectious cause of endocarditis in which there is deposition of sterile platelet thrombi on heart valves, particularly the mitral and aortic valves. This condition is described mostly in patients with advanced malignancy and connective tissue diseases. We report a case of NBTE in a patient with primary antiphospholipid antibody syndrome (APS) who had dramatic improvement after medical management.

CASE REPORT

A 65-year-old African American female presented to the hospital for a follow-up of a mitral valve mass seen on transthoracic echocardiogram (TTE) while being admitted to an outside hospital for diverticular lower gastrointestinal bleeding. Computed tomography (CT) of abdomen and pelvis showed colonic diverticulosis without evidence of cancer. Her past medical history was significant for APS (diagnosed by persistently positive antiphospholipid [aPL] antibody and recurrent

Received: November 27, 2017. **Revised:** March 9, 2018. **Accepted:** April 16, 2018

lower extremity deep vein thrombosis) for which she was on long-term rivaroxaban, non-obstructive coronary artery disease and hypertension. Rivaroxaban was held. She was hemodynamically stable. Hemoglobin level remained stable at around 10 g/dl (normal 11.5–16). The diverticular bleeding resolved spontaneously. TTE for elevated cardiac biomarkers (troponin-I 0.31 ng/ml [normal 0–0.04]) during the hospitalization incidentally showed mildly thickened anterior and posterior mitral leaflets. No murmur was appreciated on physical examination. Blood cultures were negative. She was discharged on therapeutic dose of enoxaparin instead.

She subsequently received transesophageal echocardiogram (TEE) at our institution which showed a large (1.4 × 0.7 cm) mobile, shaggy, echogenic mass located at the coaptation line on both leaflets of the mitral valve (Fig. 1). There was moderate mitral regurgitation. She was afebrile and did not have any signs of systemic embolization including petechiae, splinter hemorrhage, flank pain, or focal neurological deficits. Three sets of blood cultures were consistently negative. Blood tests revealed positive speckled-pattern antinuclear antibody (ANA) with a titer of 1:160. Magnetic resonance imaging (MRI) of the brain showed small subacute lacunar infarcts without evidence of embolic infarct (Fig. 2).

The possibility of NBTE or mitral valve thrombus was considered given the presence of vegetation in the absence of fever, negative blood cultures and history of APS. The patient was commenced on enoxaparin, prednisone 100 mg daily and hydroxychloroquine 200 mg twice a day. TEE performed 1 week later showed a significant reduction in the size of the mitral valve vegetation (0.6 × 0.7 cm) (Fig. 3). The patient was discharged with an 8-week course of steroid taper, hydroxychloroquine, and indefinite warfarin (INR goal 2.0–3.0). At a follow-up visit 6 months later, TEE showed resolution of the mitral valve vegetation with very small residual nodular focal calcific densities on the mitral valve leaflets with mild to moderate mitral regurgitation. She had age-appropriate cancer screening after discharge including a normal mammogram and a colonoscopy showing diverticulosis and tubular adenoma.

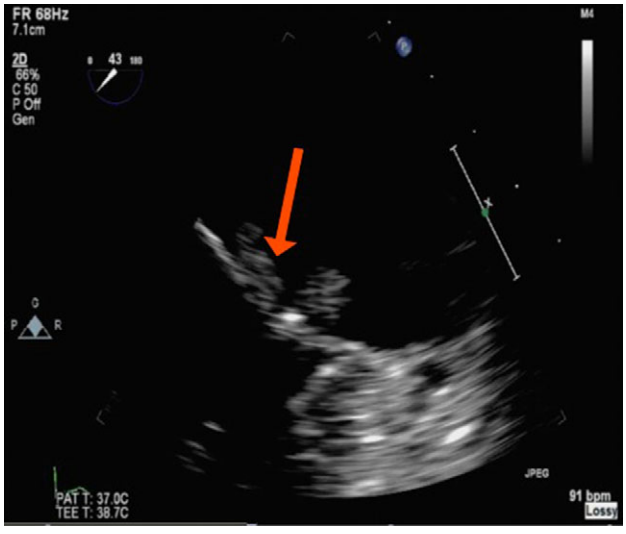

Figure 1: TEE revealing a broad based, irregular, mobile mitral mass (1.4 × 0.7 cm) on the atrial surface of the mitral leaflet, involving the co-optation points.

DISCUSSION

NBTE is a rare non-infectious cause of endocarditis in which there is a deposition of sterile platelet thrombi consisting of platelets, fibrin, immune complexes and mononuclear cells on heart valves, particularly the mitral and aortic valves [1]. The prevalence ranged between 0.3% and 9.3% [2]. Although NBTE is commonly related to malignancies, which account for 80% of the cases [1], it can occasionally be a clinical manifestation of autoimmune diseases [3]. Endothelial injury, immune complexes, hypoxia, hypercoagulability and carcinomatosis have been hypothesized to play a role in the pathogenesis [4]. Patients are often asymptomatic but could present with thromboembolism. Vegetations in NBTE are easily dislodged since there is little inflammatory reaction at the site of attachment [5, 6]. Diagnosis of NBTE requires the presence of vegetations on echocardiogram and exclusion of infective endocarditis. Multiple blood cultures should be taken to rule out any infectious causes. TEE has 90% sensitivity for the detection of NBTE [4].

The mitral valve lesion in our patient is most likely NBTE given her underlying disease of APS and no evidence of infection demonstrated by repeatedly negative blood cultures. There was no evidence of cancer on CT abdomen and pelvis, colonoscopy or mammogram. APS is an immune-mediated acquired thrombophilia defined by vascular thrombosis with persistent antiphospholipid antibodies on two or more occasions at least 12 weeks apart [7]. Heart valve disease (HVD) is the most frequent cardiac manifestation of APS, occurring in 14.3% of the patients [8]. HVD is defined by the presence of valve lesions and/or moderate to severe valve dysfunction in the absence of a history of rheumatic fever or IE [7]. The pathogenesis behind HVD and APS involves inflammation and thrombotic mechanisms [9–11].

Patients with NBTE should be anticoagulated given the high rates of systemic embolization [4]. Anticoagulants of choice for NBTE in APS are heparin (unfractionated or low-molecular-weight) followed by warfarin (target INR 2.0–3.0) indefinitely [12]. There has been no trial showing direct comparison between long-term heparin and warfarin in NBTE. Older studies showed that heparin was effective in preventing thromboembolism in NBTE [5, 13]. However, in malignancy-associated NBTE, little benefit has been observed with warfarin in preventing thromboembolism [13]. It is worth mentioning that most of the patients in these previous trials had malignancy-associated NBTE. There has been no trial comparing heparin versus warfarin in NBTE related to autoimmune/inflammatory conditions. Warfarin has been shown to be beneficial in preventing recurrent thrombotic events among patients with APS [14]. Anticoagulation should be continued indefinitely, since recurrent thromboembolism is frequent following its discontinuation [15].

Hydroxychloroquine can be considered in APS especially in patients with coexisting SLE to prevent thrombosis [16]. There is no strong evidence supporting the use of HCQ in APS without SLE. Longer use of HCQ has been shown to reduce thrombosis in SLE patients with positive aPL antibody [17]. HCQ was associated with lower risk of thrombosis in asymptomatic aPL-positive individuals [16]. The addition of HCQ to standard therapy was shown to significantly improve obstetrical outcomes in APS with pregnancy [18]. Rituximab has been used to treat complications of APS such as thrombocytopenia, skin and heart valve involvement as well as to treat catastrophic APS [19, 20]. There has been no trial showing the role of rituximab in NBTE.

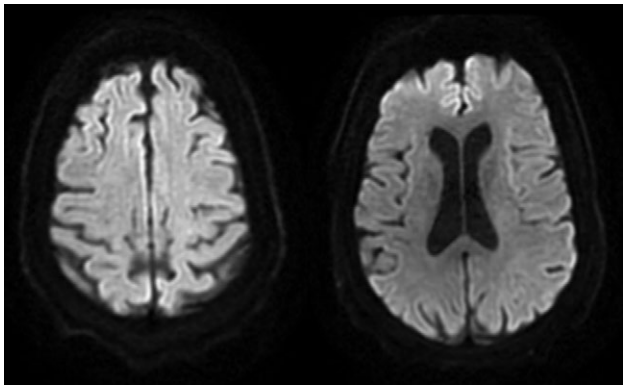

Figure 2: Diffusion weighted imaging of MRI showing no evidence of acute embolic stroke.

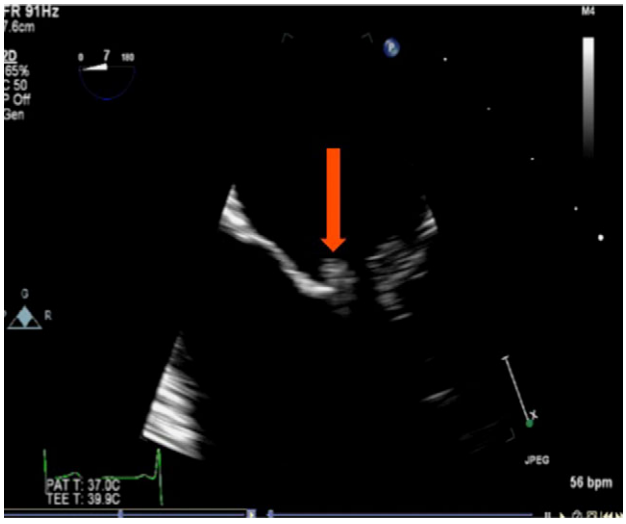

Figure 3: Repeat TEE revealed regression of the mitral valve vegetation (0.6 × 0.7 cm).

However, rituximab has recently been shown to prevent recurrent thrombotic complications in warfarin-resistant SLE-associated APS [21]. There was a disagreement whether corticosteroid therapy could be helpful for acute valve inflammation. Poor data regarding the efficacy of corticosteroids do not enable firm recommendations to be made [22, 23]. The indications for surgery are similar to IE and include heart failure, acute valve rupture, though reports suggested that prevention of recurrent embolization was the most common reason for surgery [4, 24].

Our patient developed NBTE while being on Rivaroxaban. Warfarin is the standard anticoagulation of choice for long-term secondary prevention of venous thromboembolism in APS. Based on a systematic review [25], 16% of APS patients treated with direct oral anticoagulants developed recurrent thrombosis. This rate is relatively higher than that of APS patients treated with moderate intensity warfarin (goal INR 2–3) in previous trials (3.4–5.5%) [26, 27]. A prospective trial comparing rivaroxaban and warfarin in APS patients also demonstrated higher endogenous thrombin potential in the rivaroxaban group, suggesting a higher thrombotic risk [28]. It was unclear why the patient was on Rivaroxaban rather than aspirin or warfarin as she had been treated at an outside institution. This could point towards suboptimal anticoagulation as a possible reason for this patient developing NBTE.

There was a concern that treating this patient with anticoagulant alone might not be sufficient because she developed NBTE while being on rivaroxaban (though not the anticoagulation of choice in APS as discussed above). Although HCQ has little evidence for its use in APS without SLE, it has been shown to be beneficial in aPL-positive individuals [16, 17]. In addition, HCQ is a relatively safe drug with very low rates of serious adverse reactions [29]. The fact that she had dramatic improvement of the mitral valve vegetation after receiving prednisone and hydroxychloroquine in addition to enoxaparin suggested that inflammatory process might play a role in the pathogenesis. Moreover, heparin also has anti-inflammatory effects in addition to antithrombotic property and has been shown to affect various inflammatory mediators [30]. Enoxaparin, which is a derivative of heparin, has been shown to decrease cytokine release in asthmatic patients [31]. The anti-inflammatory property of heparin may well be another reason for its role in the treatment of NBTE. The size of the vegetation decreased by half at 1 week and completely resolved at 6 months. Previous reports showed that the time to complete resolution ranged from 1 month to 1 year [32–34]. Further studies are needed to confirm the efficacy of hydroxychloroquine and corticosteroids in these patients.

In summary, we present a case of asymptomatic NBTE in the setting of APS while on anticoagulation. The patient had dramatic improvement of NBTE after initiation of hydroxychloroquine and corticosteroid in addition to low-molecular weight heparin. This suggested inflammatory nature of the lesion. Though controversial, the use of corticosteroids and immunosuppressive therapy can be considered in NBTE secondary to APS. Further studies are needed to determine their efficacy. Surgery is indicated for severe valvular dysfunction and recurrent embolism despite anticoagulation. Multidisciplinary approach to management is of paramount importance.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST STATEMENT

There is no conflict of interest.

FUNDING

There is no funding for this case report.

ETHICAL APPROVAL

No ethical approval is required.

CONSENT

Informed consent was obtained from the patient.

GUARANTOR

Natee Sirinvaravong is the guarantor of this case report.

REFERENCES

1. Eiken PW, Edwards WD, Tazelaar HD, Mcbane RD, Zehr KJ. Surgical pathology of nonbacterial thrombotic endocarditis

in 30 patients, 1985–2000. *Mayo Clin Proc* 2001;**76**:1204–12. 10.4065/76.12.1204.
2. Glass JP. The diagnosis and treatment of stroke in a patient with cancer: nonbacterial thrombotic endocarditis (NBTE): a case report and review. *Clin Neurol Neurosurg* 1993;**95**:315–8. 10.1016/0303-8467(93)90108-S.
3. Turiel M, Sarzi-Puttini P, Peretti R, Bonizzato S, Muzzupappa S, Atzeni F, *et al*. Five-year follow-up by transesophageal echocardiographic studies in primary antiphospholipid syndrome. *Am J Cardiol* 2005;**96**:574–9. 10.1016/j.amjcard.2005.04.022.
4. Asopa S, Patel A, Khan OA, Sharma R, Ohri SK. Nonbacterial thrombotic endocarditis. *Eur J Cardiothorac Surg* 2007;**32**:696–701. 10.1016/j.ejcts.2007.07.029.
5. Lopez JA, Ross RS, Fishbein MC, Siegel RJ. Nonbacterial thrombotic endocarditis: a review. *Am Heart J* 1987;**113**:773–84. 10.1016/0002-8703(87)90719-8.
6. Roldan CA, Sibbitt WL, Qualls CR, Jung RE, Greene ER, Gasparovic CM, *et al*. Libman-Sacks endocarditis and embolic cerebrovascular disease. *JACC Cardiovasc Imaging* 2013;**6**:973–83. 10.1016/j.jcmg.2013.04.012.
7. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, *et al*. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;**4**:295–306. 10.1111/jth.2006.4.issue-2.
8. Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, *et al*. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum* 2002;**46**:1019–27. 10.1002/art.10187.
9. Hojnik M, George J, Ziporen L, Shoenfeld Y. Heart valve involvement (Libman-Sacks endocarditis) in the antiphospholipid syndrome. *Circulation* 1996;**93**:1579–87. 10.1161/01.CIR.93.8.1579.
10. Ziporen L, Goldberg I, Arad M, Hojnik M, Ordi-Ros J, Afek A, *et al*. Libman-Sacks endocarditis in the antiphospholipid syndrome: immunopathologic findings in deformed heart valves. *Lupus* 1996;**5**:196–205. 10.1177/096120339600500306.
11. Zuily S, Regnault V, Selton-Suty C, Eschwege V, Bruntz JF, Bode-Dotto E, *et al*. Increased risk for heart valve disease associated with antiphospholipid antibodies in patients with systemic lupus erythematosus: meta-analysis of echocardiographic studies. *Circulation* 2011;**124**:215–24. 10.1161/CIRCULATIONAHA.111.028522.
12. Lockshin M, Tenedios F, Petri M, Mccarty G, Forastiero R, Krilis S, *et al*. Cardiac disease in the antiphospholipid syndrome: recommendations for treatment. Committee consensus report. *Lupus* 2003;**12**:518–23. 10.1191/0961203303lu391oa.
13. Sack GH Jr., Levin J, Bell WR. Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: clinical, pathophysiologic, and therapeutic features. *Medicine (Baltimore)* 1977;**56**:1–37. 10.1097/00005792-197756010-00001.
14. Pengo V, Ruffatti A, Legnani C, Gresele P, Barcellona D, Erba N, *et al*. Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. *J Thromb Haemost* 2010;**8**:237–42. 10.1111/jth.2010.8.issue-2.
15. Rogers LR, Cho E, Kempin S, Posner JB. Cerebral infarction from non-bacterial thrombotic endocarditis. Clinical and pathological study including the effects of anticoagulation. *Am J Med* 1987;**83**:746–56. 10.1016/0002-9343(87)90908-9.
16. Erkan D, Yazici Y, Peterson MG, Sammaritano L, Lockshin MD. A cross-sectional study of clinical thrombotic risk factors and preventive treatments in antiphospholipid syndrome. *Rheumatology (Oxford)* 2002;**41**:924–9. 10.1093/rheumatology/41.8.924.
17. Tektonidou MG, Laskari K, Panagiotakos DB, Moutsopoulos HM. Risk factors for thrombosis and primary thrombosis prevention in patients with systemic lupus erythematosus with or without antiphospholipid antibodies. *Arthritis Rheum* 2009;**61**:29–36. 10.1002/art.24232.
18. Mekinian A, Lazzaroni MG, Kuzenko A, Alijotas-Reig J, Ruffatti A, Levy P, *et al*. The efficacy of hydroxychloroquine for obstetrical outcome in anti-phospholipid syndrome: data from a European multicenter retrospective study. *Autoimmun Rev* 2015;**14**:498–502. 10.1016/j.autrev.2015.01.012.
19. Pons I, Espinosa G, Cervera R. Eficacia y seguridad de rituximab en el tratamiento del síndrome antifosfolipídico primario: análisis de 24 casos a partir de la revisión de la bibliografía. *Med Clín* 2015;**144**:97–104. 10.1016/j.medcli.2014.01.034.
20. Shiber S, Yair M. Catastrophic antiphospholipid syndrome: a case series. *Isr Med Assoc J* 2013;**15**:481–4.
21. Wang CR, Liu MF. Rituximab usage in systemic lupus erythematosus-associated antiphospholipid syndrome: a single-center experience. *Semin Arthritis Rheum* 2016;**46**:102–8. 10.1016/j.semarthrit.2016.02.002.
22. Krause I, Lev S, Fraser A, Blank M, Lorber M, Stojanovich L, *et al*. Close association between valvar heart disease and central nervous system manifestations in the antiphospholipid syndrome. *Ann Rheum Dis* 2005;**64**:1490–3. 10.1136/ard.2004.032813.
23. Petri MA. Classification criteria for antiphospholipid syndrome: the case for cardiac valvular disease. *J Rheumatol* 2004;**31**:2329–30.
24. Rabinstein AA, Giovanelli C, Romano JG, Koch S, Forteza AM, Ricci M, *et al*. Surgical treatment of nonbacterial thrombotic endocarditis presenting with stroke. *J Neurol* 2005;**252**:352–5. 10.1007/s00415-005-0660-z.
25. Dufrost V, Risse J, Zuily S, Wahl D. Direct oral anticoagulants use in antiphospholipid syndrome: are these drugs an effective and safe alternative to warfarin? A systematic review of the literature. *Curr Rheumatol Rep* 2016;**18**:74. 10.1007/s11926-016-0623-7.
26. Crowther MA, Ginsberg JS, Julian J, Denburg J, Hirsh J, Douketis J, *et al*. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. *N Engl J Med* 2003;**349**:1133–8. 10.1056/NEJMoa035241.
27. Finazzi G, Marchioli R, Brancaccio V, Schinco P, Wisloff F, Musial J, *et al*. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). *J Thromb Haemost* 2005;**3**:848–53. 10.1111/jth.2005.3.issue-5.
28. Cohen H, Hunt BJ, Efthymiou M, Arachchillage DR, Mackie IJ, Clawson S, *et al*. Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial. *Lancet Haematol* 2016;**3**:e426–36. 10.1016/S2352-3026(16)30079-5.

29. Felson DT, Anderson JJ, Meenan RF. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. Results of two metaanalyses. *Arthritis Rheum* 1990;**33**:1449–61. 10.1002/(ISSN)1529-0131.
30. Nouri M, Ahmadi A, Etezadi F, Barzegar E, Mojtahedzadeh M. Comparison of the effects of subcutaneous versus continuous infusion of heparin on key inflammatory parameters following sepsis. *Anesth Pain Med* 2016;**6**:33780. 10.5812/aapm.33780.
31. Shastri MD, Stewart N, Eapen M, Peterson GM, Zaidi STR, Gueven N, *et al*. Opposing effects of low molecular weight heparins on the release of inflammatory cytokines from peripheral blood mononuclear cells of asthmatics. *PLoS One* 2015;**10**:e0118798. 10.1371/journal.pone.0118798.
32. Choi JH, Park JE, Kim JY, Kang T. Non-bacterial thrombotic endocarditis in a patient with rheumatoid arthritis. *Korean Circ J* 2016;**46**:425–8.
33. Contractor T, Bell A, Khasnis A, Silverberg BJ, Martinez MW. Antiphospholipid antibody-associated non-infective mitral valve endocarditis successfully treated with medical therapy. *J Heart Valve Dis* 2013;**22**:36–8.
34. Mitma AA, Varghese JG, Witt D, Zarich SW. Stroke and a valvular lesion in a patient with stage IV non-small cell lung cancer. *BMJ Case Rep* 2016;**2016**:bcr2016215317. 10.1136/bcr-2016-215317.