JACC: CASE REPORTS VOL. 2, NO. 4, 2020


MINI-FOCUS ISSUE ON VALVULAR HEART DISEASE

BEGINNER

CASE REPORT: CLINICAL CASE

# Mechanical Mitral Valve Thrombosis in a Patient With Prior Nonbacterial Thrombotic Endocarditis

Kalyan R. Chitturi, DO, Miguel A. Castro, MD, Eric Salazar, MD, Michael Deavers, MD, Su Min Chang, MD, John J. Mahmarian, MD, Karla M. Kurrelmeyer, MD

## ABSTRACT

A 54-year-old woman with a mechanical mitral valve replacement presented with recurrent admissions for pneumonia and pulmonary edema. Multimodality imaging revealed mobile masses on the prosthesis and discrepant point of care and inpatient international normalized ratio levels owing to antiphospholipid antibody cross-reactivity on the outpatient assay. The prosthetic valve thromboses resolved with therapeutic anticoagulation. (**Level of Difficulty: Beginner.**)
(J Am Coll Cardiol Case Rep 2020;2:539-43) © 2020 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/).

A 54-year-old African American woman was directly admitted to the hospital after transesophageal echocardiography (TEE) revealed 2 highly mobile filamentous masses adherent to the annular ring of the mechanical mitral valve (MV) prosthesis (**Figure 1**, Video 1).

The TEE was performed 1 month after discharge from an outside hospital where she received treatment for pneumonia and acute pulmonary edema. Transthoracic echocardiography showed an elevated mean prosthetic MV gradient of 11.9 mm Hg in the setting of sinus tachycardia, concerning for possible valvular obstruction, though it did not detect any vegetations or mitral regurgitation.

On admission, she was afebrile and with normal heart rate and nontachycardic with an exam unremarkable for abnormal murmurs, signs of heart failure, or rashes. Notably, the international normalized ratio (INR) level was 1.7 on arrival, despite measuring 2.6 a few days earlier, and the patient maintained adherence with warfarin.

### LEARNING OBJECTIVES

- To make a differential diagnosis of prosthetic valvular masses with clinical assessment and multimodality imaging.
- To understand extra precautions necessary in monitoring anticoagulation on warfarin in patients with antiphospholipid syndrome and mechanical heart valves.

## PAST MEDICAL HISTORY

Her past medical history included cardioembolic stroke secondary to biopsy-proven nonbacterial thrombotic endocarditis of the native MV, for which she underwent surgical MV replacement with

From the Houston Methodist DeBakey Heart & Vascular Institute, Houston Methodist, Houston, Texas. Dr. Chang has received research grant support from Siemens. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, or patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

Manuscript received October 24, 2019; revised manuscript received January 7, 2020, accepted January 14, 2020.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2020.01.029

**ABBREVIATIONS AND ACRONYMS**

**APS** = antiphospholipid syndrome

**HIT** = heparin-induced thrombocytopenia

**INR** = international normalized ratio

**MHV** = mechanical heart valve

**MV** = mitral valve

**NBTE** = nonbacterial thrombotic endocarditis

**POC** = point of care

**PVT** = prosthetic valve thrombosis

**PT** = prothrombin time

**TEE** = transesophageal echocardiography

a St. Jude Medical Regent bileaflet mechanical prosthetic valve (St. Jude Medical, Minneapolis, Minnesota) and anticoagulation on warfarin 4 years before admission. Heparin-induced thrombocytopenia (HIT) complicated her postoperative course. Notably, she had 4 hospital admissions over the previous year for presumed pneumonia. She had no known history of malignancy, autoimmune disease, or other hypercoagulable disorders.

## DIFFERENTIAL DIAGNOSIS

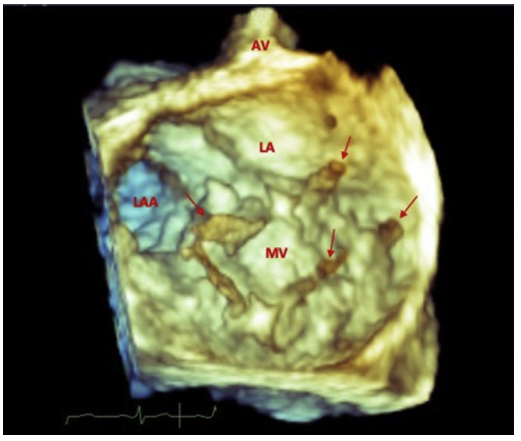
The differential diagnosis comprised the following conditions based on her clinical presentation and known medical history:

1. **Prosthetic valve thrombosis (PVT).** Inadequate anticoagulation or an acquired lupus anticoagulant may have led to mechanical MV thrombosis. The subtherapeutic INR level on admission, the echocardiographic appearance, and location of the masses on the atrial surface were consistent diagnostic features (1).
2. **Pannus.** Fibrous tissue ingrowth around the prosthetic valve can lead to pannus formation. The moderate echodensity of the masses and timing from the initial surgery are features consistent with a pannus, which may occur concurrently with PVT (2). Her recurrent hospitalizations also involved episodes of acute pulmonary edema, raising concern for valvular obstruction from pannus formation.
3. **Prosthetic valve infectious endocarditis.** Multiple hospitalizations for presumed pneumonia over the previous year raised the question as to whether she had culture-negative infective endocarditis all along.
4. **Recurrent nonbacterial thrombotic endocarditis (NBTE).** Owing to past biopsy-proven disease (**Figure 2**), recurrent NBTE remained in the differential, with possible etiologies including an occult malignancy, autoimmune disorder, or antiphospholipid syndrome (APS).

## INVESTIGATIONS

Although a subtherapeutic INR level and the majority of the echocardiographic features favored PVT, the moderate echodensity and subacute clinical presentation are consistent with prosthetic valve infective endocarditis and precluded initiation of empiric thrombolytic therapy without further investigation (3). PVT is more responsive to fibrinolysis, whereas other conditions may require a surgical evaluation, so she underwent multidetector computed tomography to aid diagnosis (4). The multidetector computed tomography detected the thin, highly mobile masses, though the study was limited in tissue characterization due to inherent temporal resolution and beam artifact from the prosthesis (**Figure 3**).

**FIGURE 1 Mitral Valve Masses on Echocardiography**




Surgeon's view of the mitral valve (MV) apparatus on 3-dimensional echocardiography showing a broad-based sheetlike mass accompanied by 3 filamentous masses **(arrows)** on the atrial surface of the MV. AV = aortic valve; LAA = left atrial appendage, LA = left atrium.

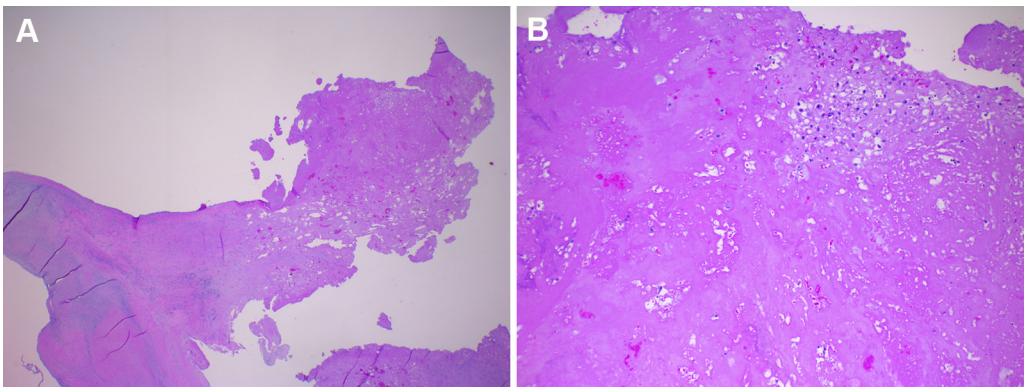
## MANAGEMENT

Upon admission, 3 sets of blood cultures were obtained, and the patient was started on broad-spectrum antibiotics and continuous bivalirudin infusion (in the setting of HIT) for empiric treatment of infectious endocarditis and PVT, respectively. A hematologist conducted a comprehensive investigation of thrombophilia disorders and APS. She clinically improved during her 2-week hospitalization despite an unrevealing initial infectious and hematologic work-up and was discharged with a fondaparinux bridge to warfarin and antibiotics.

However, she shortly decompensated with acute dyspnea, prompting readmission 6 days later. A chest radiograph revealed acute pulmonary edema, and TEE confirmed the same MV masses without significant interval change in size or hemodynamically significant valvular disease. All infectious work-up, including zoonotic organisms, remained negative. Laboratory studies returned consistent with triple-positive APS (**Table 1**).

Closer inspection of the clinic point-of-care (POC) INR assay by her cardiologist in consultation with a

**FIGURE 2** Mitral Valve Mass Histopathology




Histology of the previous mitral valve mass confirming nonbacterial thrombotic endocarditis. **(A)** The mass has an irregular surface and a bland eosinophilic appearance (hematoxylin and eosin, 20×). **(B)** It is composed of fibrin and platelets with focal macrophages and lymphocytes (hematoxylin and eosin, 100×).

hematopathologist determined that prothrombin time (PT) reagent cross-reactivity with lupus anticoagulant may have led to falsely elevated readings and unintentional subtherapeutic warfarin dosing, likely resulting in PVT, rather than in recurrent NBTE. Accordingly, her cardiologist increased the warfarin dose with plans for outpatient monitoring with an INR assay insensitive to lupus anticoagulant. Repeat TEE 1 month after discharge confirmed complete resolution of the masses.

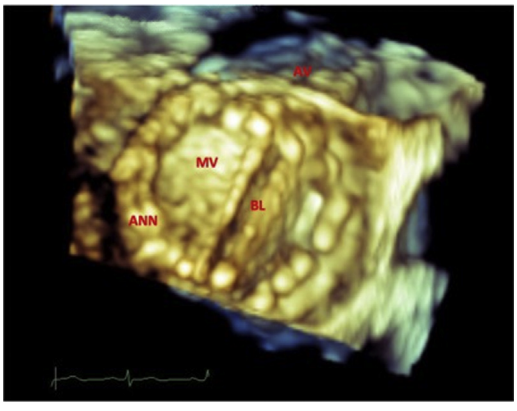
## DISCUSSION

Our patient with triple-positive APS and HIT was at a much higher risk of developing PVT than the average patient with a mechanical heart valve (MHV). A thorough evaluation of secondary etiologies of NBTE at her initial presentation 4 years before could have led to earlier diagnosis of APS and potentially prevented PVT from informed surgical planning and improved monitoring of anticoagulation on warfarin.

Because both conditions were undiagnosed at the time, her surgeon chose an MHV, given her age, owing to superior durability over bioprosthetic valves, which have a lower risk of thromboembolic complications (5). Patients with APS who undergo valve replacement surgery have increased late morbidity and mortality risk with a high frequency of thromboembolic events observed in patients receiving an MHV, and bioprosthetic valves are increasingly considered in these patients regardless of age (6).

Lack of awareness regarding her underlying APS contributed significantly to her subsequent development of PVT owing to unintentional subtherapeutic dosing of her warfarin based on an INR assay sensitive to lupus anticoagulant. Management of PVT invariably consists of anticoagulation, and vitamin K antagonists remain the preferred agent in patients with a previous thromboembolic event, mechanical aortic or MVs, and APS (7). Most reagents used in the measurement of PT and INR can be safely used to monitor patients on warfarin with

**FIGURE 3** Transesophageal Echocardiography Post-Optimal Anticoagulation




Transesophageal echocardiography showing complete resolution of the mechanical MV thrombi after 4 weeks of optimal anticoagulation. ANN = annulus; BL = bileaflet; other abbreviations as in Figure 1.

**TABLE 1 Laboratory Studies Revealed Triple-Positive APA (β2 Glycoprotein, Anticardiolipin, Lupus Anticoagulant)**

| Laboratory Test | Value | Reference Range |
|---|---|---|
| ANA screen | Negative | Negative |
| Anti-SSA Ab | Negative | Negative |
| Anti-SSB Ab | Negative | Negative |
| C3 complement level, mg/dl | 86 | 90–180 |
| C4 complement level, mg/dl | 12 | 10–40 |
| ANCA screen | Negative | Negative |
| β2 glycoprotein IgM titer, SMU | 19.4 | 0–20 |
| β2 glycoprotein IgG titer, SGU | 124.9 | 0–20 |
| Anticardiolipin IgM titer, MPL | 24 | 0–12 |
| Anticardiolipin IgG titer, GPL | 141 | 0–14 |
| Lupus-sensitive aPTT, s | 94.9 | 27.0–38.0 |
| STACLOT LA (hexagonal PL), s | 39.5 | 0–8.0 |
| Lupus anticoagulant (DRVVT), s | 125.0 | 29.0–46.0 |
| DRVVT/DRVVC ratio, s | 1.64 | 0–1.22 |
| Factor II activity assay, % | 9 | 70–120 |
| Factor VII activity assay, % | 27 | 70–150 |
| Factor VIII activity assay, % | 270 | 60–150 |
| Factor IX activity assay, % | 25 | 70–152 |
| Factor X activity assay, % | 7 | 70–120 |
| Factor XI activity assay, % | 138 | 60–145 |
| Heparin PF4 Ab OD reading | 0.218 | 0–0.399 |
| Heparin PF4 Ab, IgG | Negative | Negative |
| SRA, unfractionated heparin, % | 0 | 0–20 |
| SRA, unfractionated heparin interpretation | Negative | Negative |

Ab = antibody; ANCA = antineutrophil cytoplasmic antibodies; ANA = antinuclear antibody; APA = antiphospholipid antibody; aPTT = activated partial thromboplastin time; DRVVC = dilute Russell viper venom confirm; DRVVT = dilute Russell viper venom time; GPL = G phospholipids; MPL = M phospholipids; OD = optical density; SGU = standard G unit; SMU = standard M unit; SRA = serotonin release assay; SSA = anti-Sjögren's-syndrome-related antigen A; SSB = anti-Sjögren's-syndrome-related antigen B; STACLOT LA = hexagonal phospholipid neutralization assay.

antiphospholipid antibodies. Phospholipid concentrations in PT reagents are higher than those in the partial thromboplastin time reagents, which are typically lupus anticoagulant-sensitive (8).

However, some PT reagents may remain sensitive to lupus anticoagulants (9). Falsely elevated INR levels are common with the majority of POC INR measurement systems in patients with APS (10). This likely explains the discrepancy between the INR values measured with a POC device in the outpatient clinic relative to the INR values obtained in the hospital core laboratory.

Awareness of the sensitivity of the particular reagents used in the INR measurement is critical for proper vitamin K antagonist dosing in APS patients with MHVs. Therefore, patients in our clinic with known antiphospholipid antibodies are monitored by a non-POC relatively lupus anticoagulant-insensitive INR assay. Additionally, a non-POC method independently verifies unexpectedly high POC INR values.

## FOLLOW-UP

The patient has had no hospital admissions over the previous year since up-titration of her warfarin dose, and therapeutic monitoring of warfarin with a lupus anticoagulant-insensitive INR assay. Repeat TEE and laboratory studies after hospitalization confirmed resolution of the echodensities, with normalization of the prosthetic MV gradient and the diagnosis of APS.

## CONCLUSIONS

Patients with APS and a MHV are at marked risk of PVT, a potentially life-threatening condition that may occur in the setting of subtherapeutic anticoagulation on warfarin. An evaluation for APS should take place before surgical or transcatheter valve replacement in stable patients with biopsy-proven or clinically suspected NBTE to inform decision making regarding choice of valve prosthesis and to ensure accurate monitoring of anticoagulation on warfarin. POC INR assays should be carefully interpreted in patients with APS, as lupus anticoagulant interaction may lead to unintentional underdosing of warfarin.

**ADDRESS FOR CORRESPONDENCE:** Dr. Miguel A. Castro, Houston Methodist DeBakey Heart & Vascular Institute, 6550 Fannin Street, Suite 1901, Houston, Texas 77030. E-mail: macastro@houstonmethodist.org. Twitter: @drmac85197141.

## REFERENCES

**1.** Lin SS, Tiong IY, Asher CR, Murphy MT, Thomas JD, Griffin BP. Prediction of thrombus-related mechanical prosthetic valve dysfunction using transesophageal echocardiography. J Am Coll Cardiol 2000;86:1097–101.

**2.** Dangas GD, Weitz JI, Giustino G, Makkar R, Mehran R. Prosthetic heart valve thrombosis. J Am Coll Cardiol 2016;68:2670–89.

**3.** Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound. J Am Soc Echocardiogr 2009;22:975–1014.

**4.** Gunduz S, Ozkan M, Kalcik M, et al. Sixty-four-section cardiac computed tomography in mechanical prosthetic heart valve dysfunction: thrombus or pannus. Circ Cardiovasc Imaging 2015;8:e003246.

**5.** Roudaut R, Serri K, Lafitte S. Thrombosis of prosthetic heart valves: diagnosis and therapeutic considerations. Heart 2007;93:137–42.

**6.** Colli A, Mestres CA, Espinosa G, et al. Heart valve surgery in patients with the antiphospholipid

syndrome: analysis of a series of nine cases. Eur J Cardiothorac Surg 2010;37:154–8.

**7.** Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg 2014;148:e1–132.

**8.** Tripodi A, de Laat B, Wahl D, et al. Monitoring patients with the lupus anticoagulant while treated with vitamin K antagonists: communication from the SSC of the ISTH. J Thromb Haemost 2016;14:2304–7.

**9.** Crowl A, Schullo-Feulner A, Moon JY. Warfarin monitoring in antiphospholipid syndrome and lupus anticoagulant. Ann Pharmacother 2014;48:1479–83.

**10.** Roche Diagnostics. CoaguChek ® XS PT test [package insert]. Available at: http://apsfa.org/docs/XS%20Strip%20Package%20Insert.pdf. Accessed February 22, 2019.

**KEY WORDS** antiphospholipid syndrome, antithrombotic therapies, mitral valve disease, nonbacterial thrombotic endocarditis, prosthetic valve thrombosis

**APPENDIX** For a supplemental video, please see the online version of this paper.