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VALVULAR HEART DISEASE

CASE REPORT: CLINICAL CASE

Recurrent Annular Thrombosis and Embolism Following Mitral Valve Repair

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ABSTRACT

A patient without evident systemic thrombophilia developed recurrent ischemic stroke following surgical mitral valve repair. Thromboembolism proved resistant to anticoagulation; however, following explantation of the prosthesis, she became asymptomatic with normal valve function. We postulate that an unusual reaction to prosthetic material was the source of thromboembolism. (JACC Case Rep. 2024;29:102582) © 2024 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 63-year-old woman developed slurred speech 20 months after mitral valve repair surgery. She reported antecedent fatigue and malaise; however, she denied fever, chills, night sweats, weight loss, recent viral illness, vaccination, dental or surgical procedures, or travel.

Upon evaluation, she was afebrile with heart rate 71 beats/min, blood pressure 132/72 mm Hg, and arterial oxygen saturation 99% while breathing room air. There was no jugular venous distension, precordial murmur, or peripheral edema. The electrocardiogram showed sinus rhythm with ventricular ectopy. Computed tomography and magnetic resonance imaging of the brain found no infarction or hemorrhage (Supplemental Figure 1A). Computed tomography of chest and carotid duplex Doppler ultrasound studies were unremarkable. Transthoracic echocardiography (TTE) showed a mobile mass on the posterior aspect of the mitral annulus prolapsing into the left atrium (Video 1A). There was minimal mitral regurgitation, a mean trans-mitral diastolic gradient of 4 mm Hg at 84 beats/min, and left ventricular ejection fraction 50%. Using transesophageal echocardiography (TEE), the mass measured 1.8 × 0.5 cm; there was mild mitral stenosis and regurgitation (**Figure 1A**, Video 1B) and a 0.5 cm mobile mass on the lateral aspect of the tricuspid valve annulus (**Figure 2**, Video 2).

TAKE-HOME MESSAGES

- The potential for a rare thrombotic reaction to sutures or other artificial material used during surgical mitral valve repair exists even in the absence of systemic thrombophilia.
- Complete removal of prosthetic material during re-operation can resolve the source of thromboembolism while preserving physiologic valve function.

PAST MEDICAL HISTORY

The patient had a history of bileaflet mitral valve prolapse and regurgitation secondary to Barlow's

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ABBREVIATIONS AND ACRONYMS

INR = international normalized ratio

MTHFR = methylenetetrahydrofolate reductase

PTFE = polytetrafluoroethylene

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

deformity. She had undergone valve repair with a P2 quadrangular resection and sliding leaflet plasty, Gore-Tex neochordoplasty to P1, a 34-mm Cosgrove-Edwards annuloplasty band implantation, and tricuspid valve repair with a posterior deVega annuloplasty 20 months before the onset of neurologic symptoms. She had hyperlipidemia but no prior stroke. She did not use tobacco or intravenous drugs and reported no allergies. Her medications included aspirin and atorvastatin.

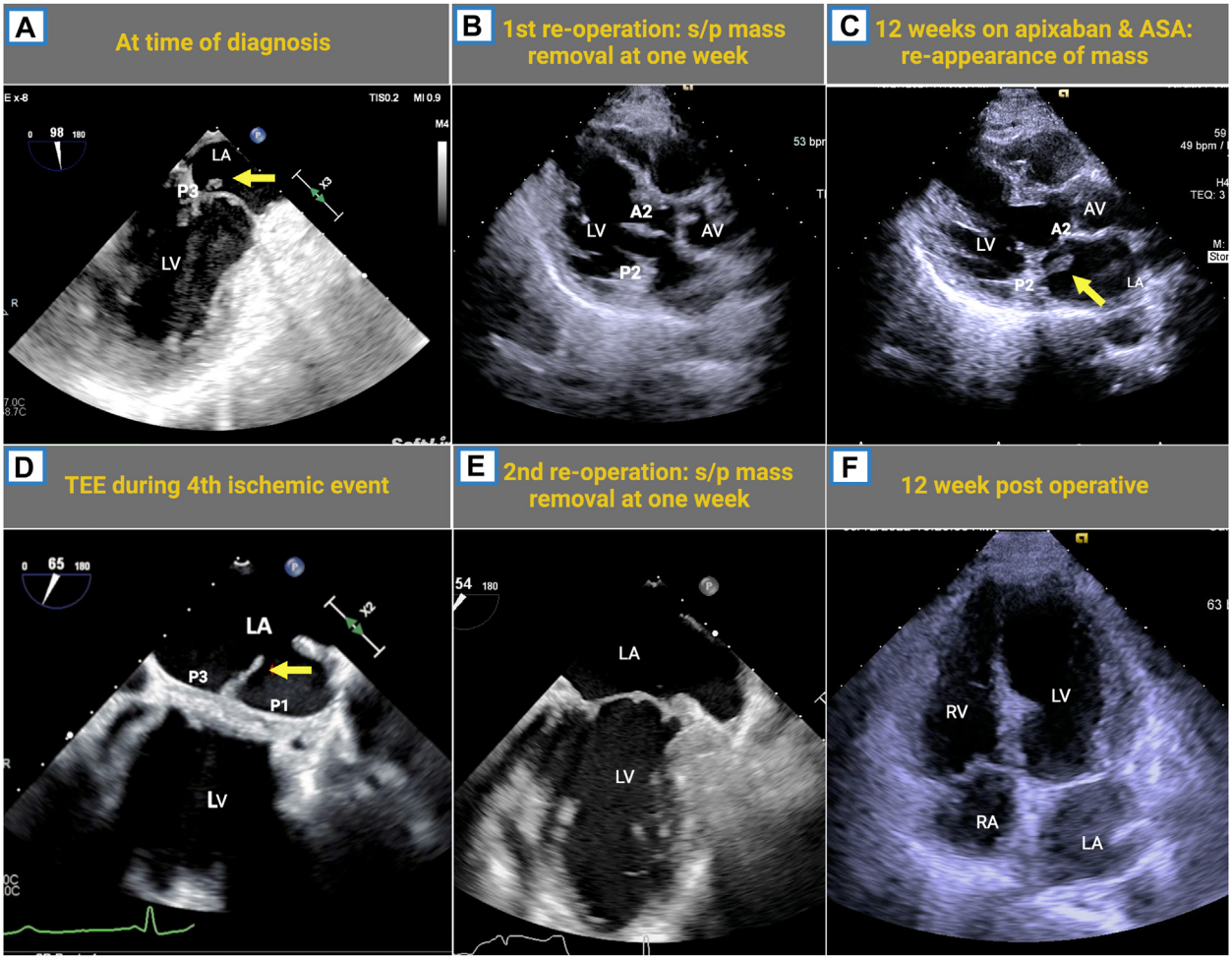
DIFFERENTIAL DIAGNOSIS

Causes of cardiac valve masses after valve repair or replacement include infectious vegetation, dehisced surgical material, avulsion of annular calcific or granulomatous substances, pannus, primary or metastatic tumor, and thrombus—all potentially sources of embolism.[1]

INVESTIGATIONS

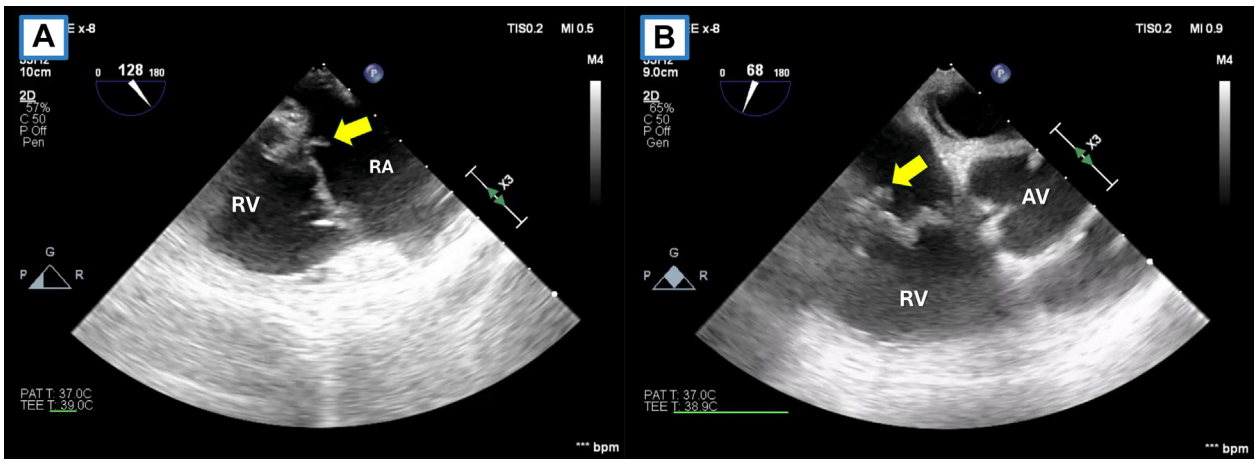
Initial laboratory data included erythrocyte sedimentation rate 26 mm/h, C-reactive protein 1 mg/dL,

FIGURE 1 Transesophageal Echocardiography and Transthoracic Echocardiography of Cardiac Mass on the Mitral Valve



Mobile echogenic density (yellow arrow) in the left atrium (LA) seen along the posterior mitral valve annulus during the first ischemic event (A) which is completely removed during the first re-operation (B). After switching from warfarin to apixaban and aspirin, a recurrent mobile mass is seen at the posterior mitral annulus (C). Transesophageal echocardiogram (TEE) showing a recurrent mobile mass during patient's fourth ischemic event (D) followed by complete removal of prosthetic material and the mobile mass (E). Twelve weeks postoperative follow-up showed no evidence of recurrent mass. A = anterior leaflets of mitral valve; ASA = aspirin; LV = left ventricle; RA = right atrium; RV = right ventricle; p = posterior leaflets of mitral valve; s/p = status post.

FIGURE 2 **TEE of Cardiac Mass on the Tricuspid Valve**



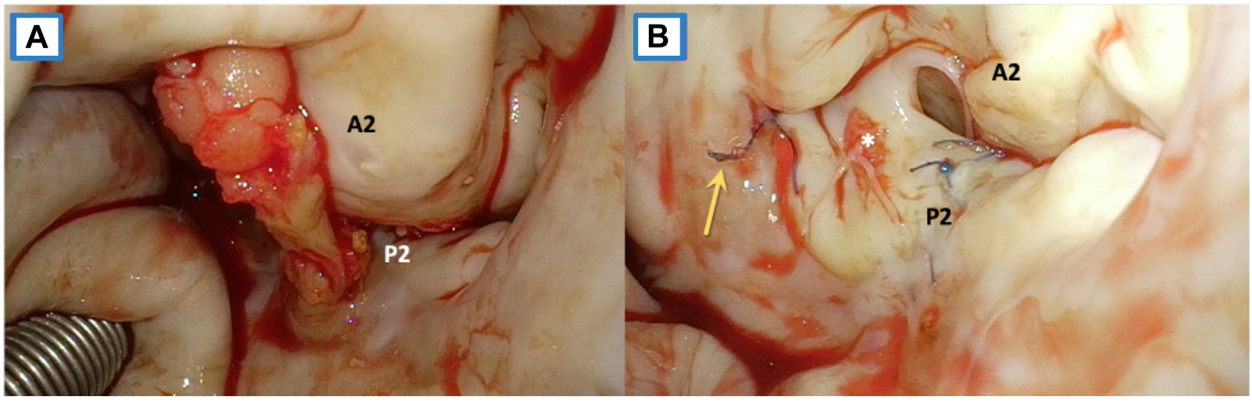
(A,B) Mobile echogenic density (yellow arrow) in the RA seen attached to the tricuspid annulus. Abbreviations as in Figure 1.

leukocyte count 11.1 × 10^3/mm^3, and international normalized ratio (INR): 1.2. Serum creatinine and electrolytes were normal. Blood cultures proved sterile. At re-operation, there was a 1.5 × 0.7-cm fibrinous mass behind the posterior segment of the mitral annuloplasty prosthesis (Figure 3A) and a similar but smaller mass adjacent to the lateral tricuspid annulus (Figure 4). Histopathologic examination confirmed inflammatory cells and fibrous material, suggesting a sterile reactive process.

MANAGEMENT

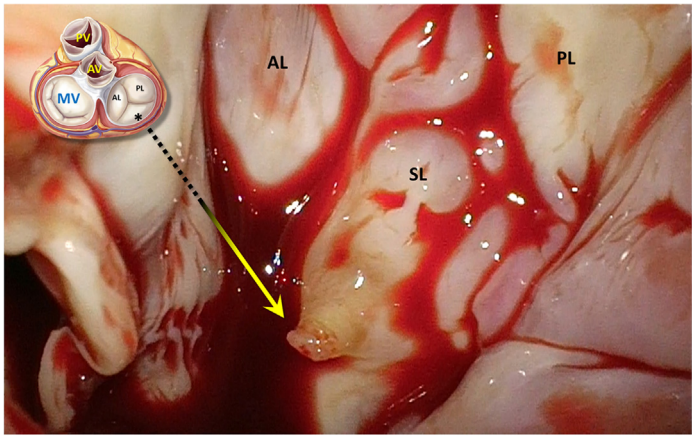
After removal of the mass, postoperative TTE confirmed no residual mass and preserved valvular and ventricular function (Figure 1B, Video 1A). The patient recovered promptly and was discharged on warfarin (target INR: 2.0-3.0). Hematologic evaluation identified low anticardiolipin β2 glycoprotein immunoglobulin M (IgM) antibodies; retesting a few weeks later again identified low anticardiolipin β2

FIGURE 3 **Intraoperative Photographs of the Cardiac Mass on the Mitral Valve**



(A) An elongated mobile fibrinous mass emerging just posteriorly to the mid-segment of the epithelialized mitral annuloplasty ring seen during the first re-exploration. (B) A small fibrinous collection organized at the insertion of the expanded polytetrafluoroethylene neo-chord knot (white asterisk) and smaller collections affixed on the 5-0 prolene surgical suture knot (yellow arrow), seen during the second re-exploration. Abbreviations as in Figure 1.

FIGURE 4 Intraoperative Photographs of the Cardiac Mass on Tricuspid Valve



Intraoperative image (surgeon's view) recorded during the first reoperation (2021), 2 years following the index mitral and tricuspid valve repair surgery. The roof of the right atrium is dissected and deflected medially (on the left of the photo) and laterally (on the right lower corner of the photo). The anterior (AL), septal (SL), and posterior (PL) tricuspid leaflets are shown in closed position. A schematic insert (upper left) shows the anatomic position and orientation of the tricuspid valve relative to the mitral (MV), aortic (AV), and pulmonary (PV) valve planes, and the location of the tricuspid annulus (white ring in the perimeter of the tricuspid valve). The yellow arrow indicates the base of the mobile fibrinous mass noted adjacent to the lateral annulus (also black asterisk in insert), after it was sharply excised. The original deVega tricuspid annuloplasty is not visible.

glycoprotein and antiphosphatidylserine IgM antibodies but was negative for IgG/IgA or rheumatologic markers (**Figure 5**). Subsequent testing found no antiphospholipid antibodies, and the patient insisted on substituting apixaban. After treatment with apixaban plus aspirin for 12 weeks, TTE identified a recurrent oval density at the site of previous thrombus formation, and she resumed warfarin while continuing aspirin (**Figures 1C and 6**). One month later, she developed slurred speech and left hemiparesis; imaging identified infarction in the distribution of the right middle cerebral artery (Supplemental Figure 1B). Despite increasing anticoagulation intensity to target INR >3, she experienced recurrent neurological deficits that resolved (Supplemental Figures 1C and 1D). After 3 episodes, TTE showed mitral annular thrombus without significant valve dysfunction (**Figure 1D**, Videos 3A and 3B). No extracardiac (ie, venous) thrombosis occurred. Extensive investigation for thrombophilia found no abnormalities except for a homozygous 5,10 methyltetrahydrofolate reductase (MTHFR) mutation with normal plasma homocysteine level (**Figure 5**). Body imaging found no evidence of malignancy.

Because of recurrent thromboembolism resistant to dual pathway inhibitory antithrombotic therapy and absence of extracardiac thrombosis, she underwent a third operation with explantation of the mitral annuloplasty ring and expanded polytetrafluoroethylene (ePTFE) neochord without re-implanting an annuloplasty prosthesis (**Figures 1E and 3B**). Intraoperative TEE confirmed normal mitral and tricuspid valve function without stenosis or regurgitation (Video 3A). Postoperatively, she resumed warfarin and aspirin.

OUTCOME AND FOLLOW-UP

The patient recovered from surgery with little residual neurologic deficit and resumed unrestricted physical activity. Two years after explantation of the mitral annuloplasty ring and ePTFE neochord, she remains asymptomatic with echocardiographically normal valve function and neither thrombosis nor bleeding (Videos 4A and 4B).

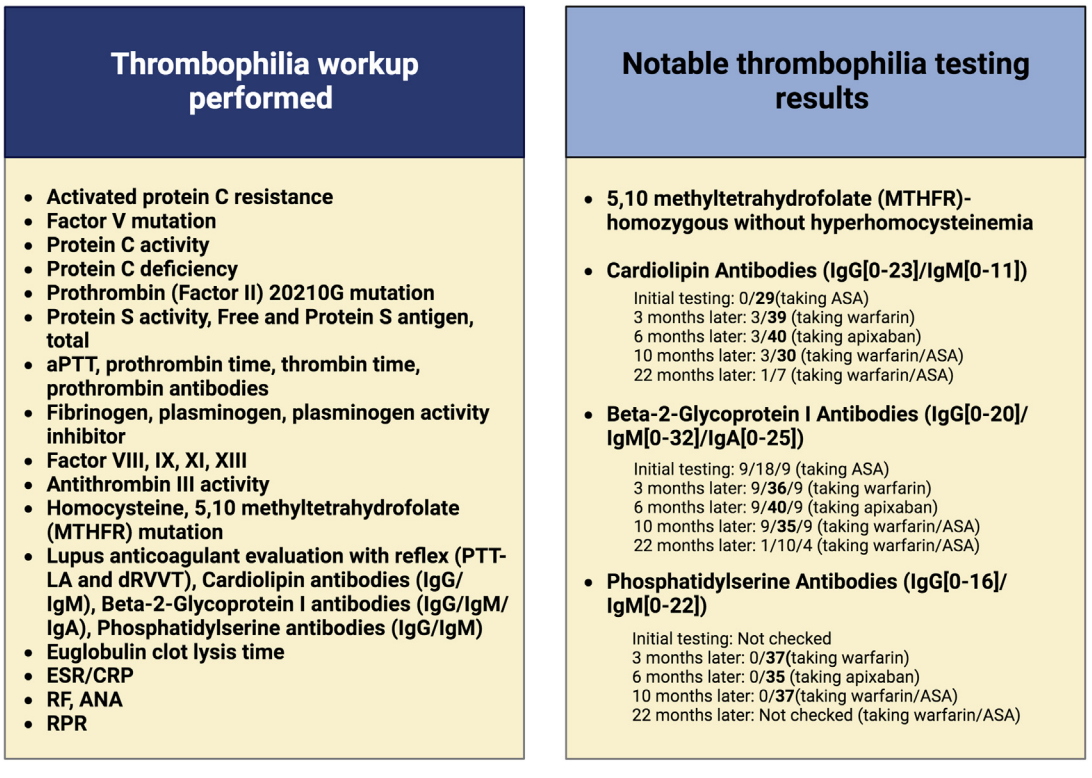
DISCUSSION

Thrombosis of mechanical prosthetic heart valves occurs frequently in the absence of systemic anticoagulation, and management is challenging with options ranging from thrombolytic therapy to surgical explantation. Bioprosthetic valves deployed surgically or by transcatheter techniques are considerably less prone to overt thrombus formation, but prosthetic leaflet thrombosis may cause thickening and reduced leaflet motion, the clinical consequences of which are variable and uncertain. Native valve thrombosis is extremely rare after surgical mitral repair. The patient we describe developed recurrent, resistant thrombosis involving the prosthetic material, resulting in repeated episodes of cardioembolic cerebral ischemia.

The first cerebral ischemic symptoms arose 20 months after initially uneventful repair, and the nature of the mass identified echocardiographically was not immediately clear (**Figure 6**). The differential diagnosis of cardiac masses is broad, but temporal proximity to surgery narrowed the possible etiologies to infectious vegetation, dehisced surgical material, avulsion of annular calcific or granulomatous substances, or thrombus. Mobile or large (>0.8 cm^2) masses associated with hemodynamic compromise due to valvular stenosis or regurgitation or systemic embolism generally require surgical intervention.[2]

Histopathologically, the mass contained inflammatory cells and fibrous tissue, suggesting a reactive pathophysiology. Inflammatory valve masses occur in patients with rheumatologic conditions, especially

FIGURE 5 Thrombophilia Workup Performed and Notable Test Results



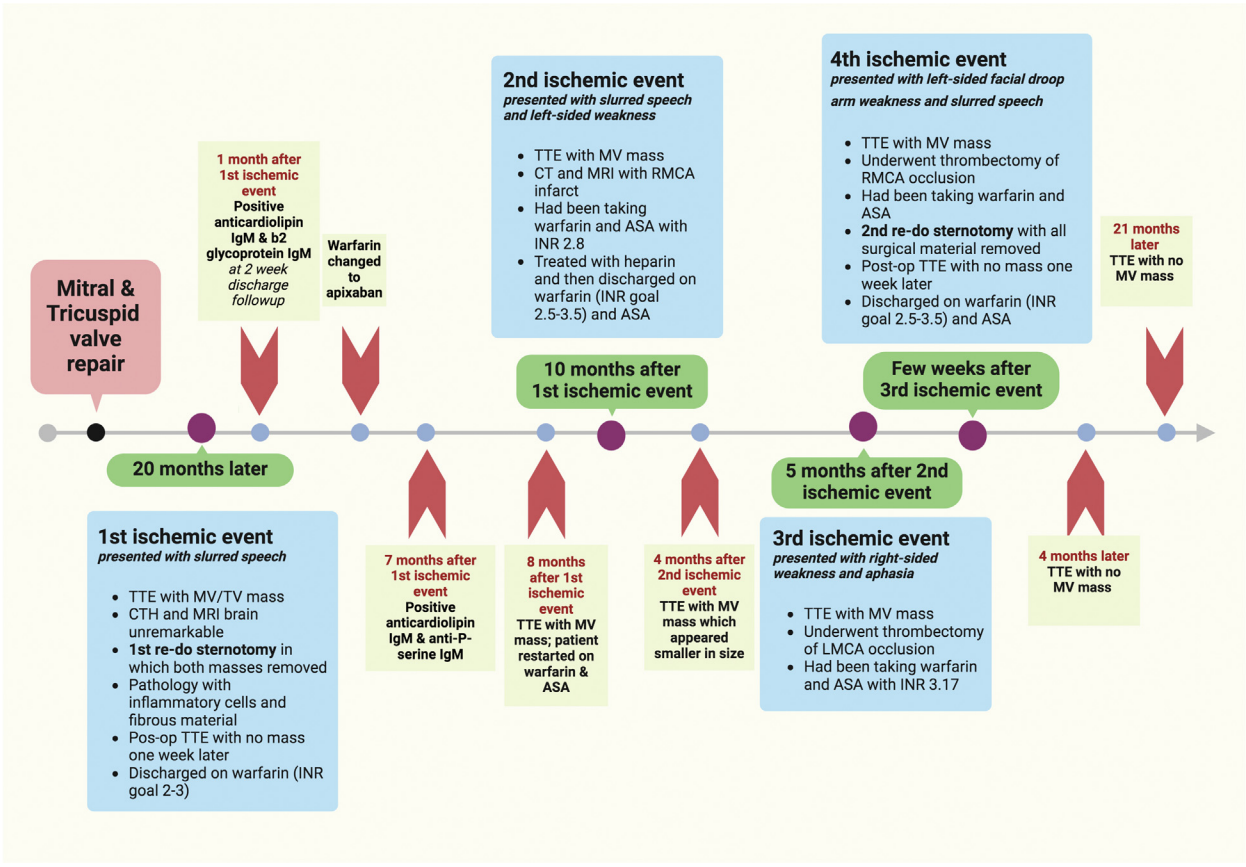
(Left panel) List of thrombophilia performed. (Right panel) Notable abnormal findings during the patient's treatment course. These include MTHFR mutation, cardiolipin, beta-2-glycoprotein, and phosphatidylserine antibodies. Additionally, specific IgG/IgM/IgA titers are also included with normal values at different time points in relation to various antithrombotic regimen. ANA = antinuclear antibody; aPTT = activated partial thromboplastin time; CRP = C-reactive protein; dRVVT = diluted russell viper venom time; ESR = erythrocyte sedimentation rate; Ig = immunoglobulin; PTT-LA = partial thromboplastin time-lupus anticoagulant; RF = rheumatoid factor; RPR = rapid plasma reagin.

Libman-Sacks endocarditis associated with systemic lupus erythematosus.[3] A previous report describes a noninfective mass exhibiting chronic inflammatory infiltrate 7 years after mitral valve repair in a 73-year-old man without rheumatological disease.[4]

Serologic markers of autoimmune disease were not detected in our patient, and the significance of raised serum IgM with normal IgG/IgA levels remains uncertain.[5] Our patient additionally had low titers of IgM (<40 GPL and/or MPL) which have an unclear association with thrombotic events.[6] Hematologic investigation did not identify diagnostic criteria for overt antiphospholipid syndrome, and there was no history of venous thrombosis or complications of pregnancy; however, her response to immunotherapy was not evaluated. Extensive evaluation for thrombophilia found a homozygous MTHFR mutation, which can be associated with hyperhomocysteinemia and subsequent overexpression of adhesion molecules and cytokines, platelet hyper-reactivity, and inhibited fibrinolysis,[7] but hyperhomocysteinemia was not present. Although viral syndromes have been shown to cause transient antiphospholipid antibodies, specifically coexisting IgG and IgM cardiolipin antibodies,[8] with thromboembolic phenomena, our patient had no recent or chronic viral illness or vaccinations which might precipitate a transient hypercoagulable state or explain the low titers of persistent IgM antibodies. The pathology of the mass and recurrence on the same valve further challenged the diagnosis of systemic thrombophilia.

Intensive therapy with both anticoagulant and platelet inhibitor medications did not prevent

FIGURE 6 Timeline of Significant Events



Timeline showing the ischemic events (blue boxes), starting with initial valve repair in 2019. Other notable events (yellow boxes) are described in the text.

recurrent thrombosis until the surgical material was removed. After explantation of all prosthetic material and the fibrinous mass, the patient experienced no further ischemic symptoms over 2 years, suggesting that the prosthetic material was ultimately causal. Padang et al[9] described 4 patients with thromboembolic complications related to either mitral or tricuspid annuloplasty rings with an identifiable mass attached to the annuloplasty material. Although ischemic stroke occasionally occurs early after mitral valve surgery,[10] these patients presented months after repair. One developed middle cerebral artery stroke 36 months after initial mitral valve repair. Although her thrombophilia screen was positive for heterozygous factor V mutation, she eventually underwent annuloplasty removal due to marked foreign-body reaction to the ring without further thrombus formation. Another presented with stroke 24 months after mitral valve repair. Given recurrent ischemic events and incomplete mass resolution with warfarin, the patient underwent re-operation with mitral valve replacement. In these 2 cases, the annuloplasty ring was deemed associated with an infrequent complication. No such events have been described with mitral annuloplasty bands or deVega annuloplasty.

We were unable to determine the factors mediating the subacute reaction prompting thrombus formation in the patient we describe. After explantation of all prosthetic material 2 years after initial repair, normal valve function was preserved as annular remodeling remained intact and durable during extended follow-up (Videos 4A and 4B). One might have considered biologic valve replacement at the time of either re-exploration, but inability to explain the unique underlying clinical condition made it prudent to avoid an irreversible commitment to prosthetic valve replacement.

CONCLUSIONS

This case highlights the rare potential for thrombus formation on material used for surgical mitral valve repair and the associated risk of cardiogenic embolism in a patient without intrinsic systemic thrombophilia. Thromboembolism proved resistant to antithrombotic therapy until the prosthetic material was removed. This became a viable option once enough time had elapsed for healing of the reconstructed valve with annular fibrosis, so valve function was maintained without artificial structural support.

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KEY WORDS cardioembolic stroke, mitral annular thrombus, mitral valve apparatus, mitral valve prolapse, neo-cord material

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