Subvalvular Thrombosis of the Mitral Valve—A Rare Cause of Cardioembolic Stroke

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INTRODUCTION

Native mitral valve (MV) calcification of the leaflets and annulus is not an uncommon finding on echocardiography. Mitral annular calcification (MAC) has been shown to be associated with stroke in a number of studies.[1-3] This case report describes a patient who suffered an embolic stroke and was found to have a large thrombus in the mitral subvalvular apparatus.

CASE PRESENTATION

We present a 67-year-old man with a history of hyperlipidemia, coronary artery disease, and dilated cardiomyopathy secondary to prior myocardial infarction. The patient presented with new generalized weakness and was found to have a wide based gait and dysmetria on initial examination in the emergency room. They had tachycardia (heart rate 101 bpm) and an elevated blood pressure on presentation (blood pressure 185/119 mm Hg). A distinct grade II/VI coarse systolic murmur heard best at the apex was noted. The exam was otherwise normal. A noncontrast computed tomography of the head showed chronic microangiopathic changes and old basal ganglia lacunar infarcts. Magnetic resonance imaging of the head showed multiple bilateral punctate foci of restricted diffusion within multiple vascular territories, presumed embolic in nature, as well as moderate small-vessel ischemic disease. Magnetic resonance imaging angiography of the head and neck showed a nondominant, diminutive right vertebral artery with chronic severe stenosis. There were no other high-grade stenoses.

As part of stroke workup the patient underwent a transthoracic echocardiogram (TTE), which revealed normal left ventricular (LV) size with mild LV systolic dysfunction (ejection fraction of 48% using biplane modified Simpson's method). There was hypokinesis to akinesis of the basal to mid septum and inferior walls. Additionally, MAC was seen with focal calcification of the posterior MV annulus. A mobile echogenic mass measuring. 2.9 × 1.0 cm was found adjacent to the posterior MAC and attached to the subvalvular apparatus of the posterior MV (Figure 1; Video 1). The valve leaflets were not involved and appeared normal. There was mild mitral regurgitation and no mitral stenosis. The mean transmitral gradient was 3 mm Hg (heart rate 77 bpm), and estimated MV area by the continuity equation was 2.2 cm^2. Further workup was pursued including erythrocyte sedimentation rate and C-reactive protein, which were mildly elevated to 38 mm/hour (normal 0-32 mm/hour) and 1.86 mg/dL (normal <0.5 mg/dL), respectively. Rheumatoid factor was within normal limits. Blood cultures showed no growth. Notably, the patient had no episodes of atrial fibrillation seen on telemetry.

The patient was started on therapeutic anticoagulation with an intravenous heparin infusion, and given their presentation with stroke, the decision was made to pursue surgical removal of the mass. Coronary angiography was performed prior to surgery, which demonstrated no obstructive disease and patent prior right coronary artery stent. Intraoperatively, a transesophageal echocardiogram (TEE) was done that revealed findings similar to the TTE (Figure 2, Video 2). There was no atrial or left atrial appendage thrombus. Surgical exploration revealed extensive posterior MAC and thickening of the leaflets. The valve was competent and had no significant stenosis. Careful probing below the posterior leaflet of the MV demonstrated a 3.0-cm mass, which was connected to the subvalvular apparatus. Utilizing gentle mechanical dissection, the mass was removed from the subvalvular apparatus. The mass was sent to pathology for definitive histologic evaluation, which confirmed a thrombus with organization. Postoperative TEE as well as 2-month follow-up TTE did not reveal any residual thrombus. The patient was discharged on warfarin with an international normalized ratio goal of 2 to 3 with an anticipated duration of 3 months.

DISCUSSION

Intracardiac masses can have a range of differentials including tumor, thrombus, infection (vegetation), and, less commonly, caseous calcification and cysts. Our patient had negative blood cultures, no echocardiographic evidence of a significant regurgitant lesion or valvular pathology, and no other clinical signs of infection. Therefore, endocarditis was ruled out as a differential. The most common primary cardiac tumor is a myxoma.[4] Myxomas are generally found in the left atrium attached by a stalk to the fossa ovalis. Rarely, they can be found on the left atrial free wall, MV leaflets, or right atrium.[5] The location and morphology of the mass in this case was not consistent with a myxoma. Fibroelastomas can be present on the downstream or ventricular aspect of the MV. However, these are usually small and attached to the endocardial surface of the valve (as compared to the subvalvular apparatus of the MV in our patient).[6] While metastatic disease is more common than primary cardiac tumors, there was no evidence of any

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VIDEO HIGHLIGHTS

Video 1: Two-dimensional TTE, apical 3-chamber view, demonstrates calcification of the posterior MV annulus and a large echogenic mass (thrombus) present on the ventricular aspect of the MV adherent to the mitral annulus.

Video 2: Two-dimensional TEE, 4-chamber view (0°) with depth adjusted to visualize the MV, demonstrates calcification of the posterior MV annulus and a large echogenic mass (thrombus) present on the ventricular aspect of the MV adherent to the mitral annulus.

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systemic neoplastic process.[6] After careful consideration of the differential diagnoses, the mass was thought to be most consistent with an MV thrombus. We did note mildly elevated levels of inflammatory markers. However, these were thought to be secondary to ischemic stroke rather than an acute inflammatory process.[7]

Valvular thrombotic lesions can be seen in systemic lupus erythematosus, primary antiphospholipid syndrome, and nonbacterial thrombotic endocarditis. In these cases, the aortic valve and MV are generally involved and the pathology usually presents as a cluster of small echogenic masses.[8] Our patient had a negative rheumatologic workup and had a single large mass associated with the subvalvular apparatus rather than the MV leaflets. Calcification of the native MV leaflets and annulus can result in the formation of thrombi, the likelihood of which is increased by MV prolapse and existing valvular disease such as rheumatic MV disease.[9] Mitral annular calcification results from progressive calcification of the fibrous mitral annulus (particularly the posterior annulus). Mitral annular calcification has been found to be associated with stroke in a number of studies. In a study of 117 patients with MAC on echocardiography, it was found that compared to age- and gender-matched controls, patients with MAC have a significantly higher incidence of cerebrovascular events.[1] In another large study using patients from the Framingham cohort, the investigators found the MAC (as assessed by M-mode echocardiography) to be independently associated with increased risk of stroke (relative risk = 2.1). The authors postulate that the mechanism of stroke in these patients was likely cardioembolic as 67% of strokes were thought to be embolic in this study.[2] These findings are in line with an autopsy study of 1,342 patients, which revealed that 11% of patients with MAC had evidence of systemic calcareous embolization. Necrosis, caseous transformation, and ulceration may form the nidus for thrombosis.[3] Although prior literature has been suggestive of a thromboembolic phenomenon secondary to MAC-associated thrombosis, no clear causal link has been established. Therefore, although it is impossible to establish MAC as the definitive etiology of MV thrombus in this patient, this is the most likely etiology in the absence of other risk factors for thrombosis and the differential diagnosis as described above. Our case report provides further support for the hypothesis of thrombosis as a mechanism for MAC-related cardioembolic stroke.

Eicher and colleagues[10] in their study of 182 patients with arterial thromboembolic events report 3 patients with MAC associated with thrombosis. In contrast to our patient who had a mass on the ventricular side of the MV, the 3 patients in this report had a mass on the atrial aspect of the valve. Mohan *et al.*[11] describe a MAC-associated MV mass that was presumed to be thrombus on the ventricular aspect of the valve. This highlights the importance of a thorough evaluation of both the ventricular and atrial aspects of the MV in patients with significant MAC and thromboembolic phenomena. Of note, a highly

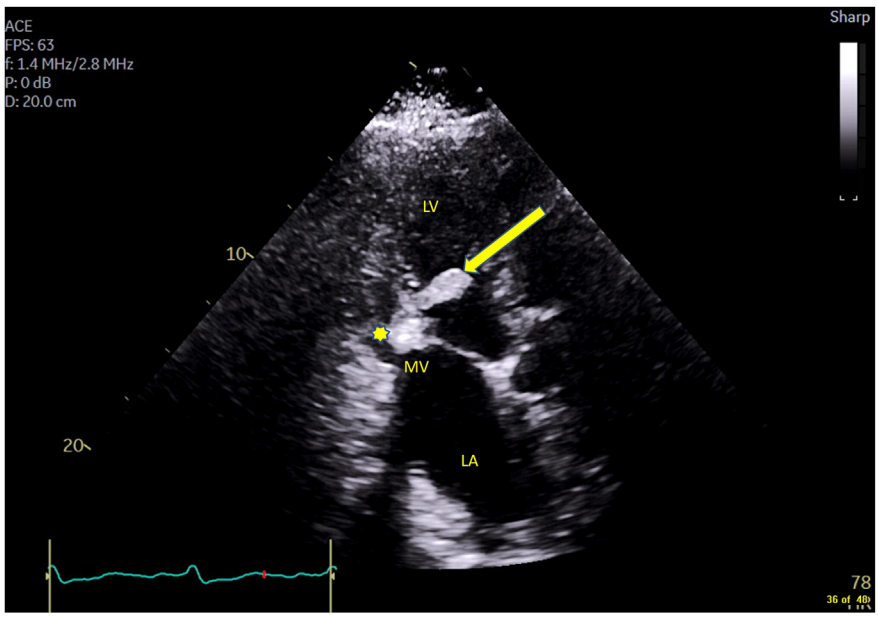

Figure 1 Two-dimensional TTE, apical 3-chamber view, systolic phase, demonstrates calcification of the posterior MV annulus (*) and a large echogenic mass (thrombus) present on the ventricular aspect of the MV adherent to the mitral annulus (*arrow*). Image quality was reduced due to overgaining. *LA*, Left atrium.

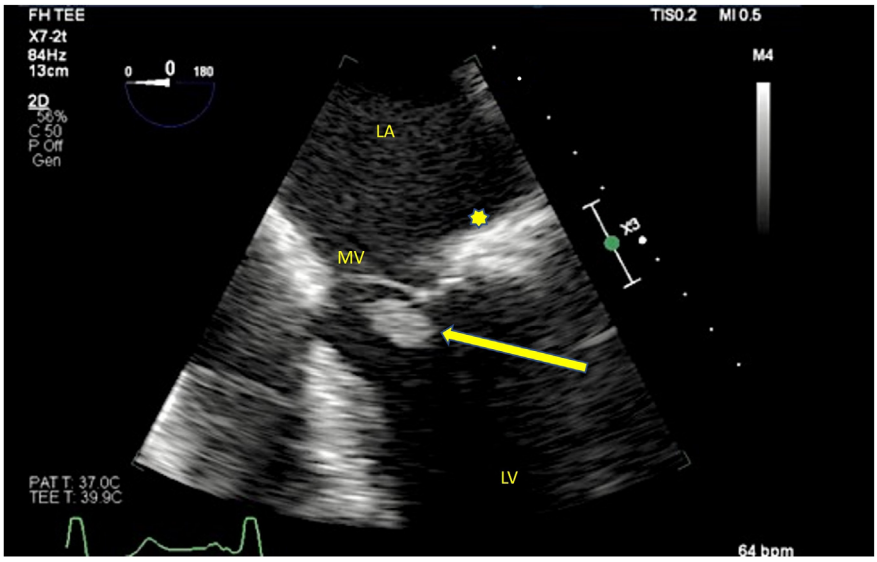

Figure 2 Two-dimensional TEE, 4-chamber view (0°) with depth adjusted to visualize the MV, systolic phase, demonstrates calcification of the posterior MV annulus (*) and a large echogenic mass (thrombus) present on the ventricular aspect of the MV adherent to the mitral annulus (*arrow*). Image quality was reduced due to overgaining to better visualize the echogenic mass. This figure demonstrates attenuation on the far-field (ventricular) aspect of the MV secondary to the highly reflective MAC. Therefore, while the mass is visible by overgaining, its attachment to the mitral annulus (seen on TTE) is incompletely visualized on TEE.

reflective surface such as MAC can lead to loss of ultrasound energy or "attenuation." This makes the area distal to such a surface hypoechoic or anechoic (shadowed), preventing adequate evaluation. The patterns of attenuation are different for TTE and TEE. For example, the ventricular aspect of the MV may have attenuation (far field) using TEE but not using TTE. Therefore, both modalities are complementary in evaluation for an MV thrombus and should be utilized when the clinical suspicion is high to avoid missing smaller thrombi. Another distinguishing feature of our report is that our patient was treated with surgical intervention rather than anticoagulation given the extent of cerebral infarction and size of the thrombus. This allowed us to have histopathological confirmation of thrombosis.

Although the American College of Cardiology/American Heart Association guidelines provide direction for management of prosthetic valve thrombosis, native valvular thrombosis is not addressed. In patients with nonbacterial thrombotic endocarditis, surgical intervention has been described in the presence of severe valvular dysfunction.[12] For patients with LV thrombus, the standard of care in general is anticoagulation for 3 to 6 months. Mobile and protuberant thrombi are the highest risk for embolization.[13] The guidelines recommend that a surgical approach for LV thrombi should only be considered if there is inability to tolerate anticoagulation or a high perceived risk for cardioembolic stroke or embolization.[14] However, our patient does not fit any of these clinical scenarios. In a recently published case series, caseous mitral valvular calcification was described as presenting a high risk for fistulization and embolization. The authors observe that patients with caseous MAC who have a higher risk for cardioembolic stroke may require surgery.[15] Our case was different from this series in that our patient's MAC was associated with a thrombus and the patient had already presented with a multivessel stroke.[15] Therefore we discussed this case at our multidisciplinary conference. Based on the high risk for embolization and low overall surgical risk, the patient and medical team made an informed decision to pursue a surgical approach.

CONCLUSION

We present a patient with new stroke and subvalvular thrombus associated with MAC who was treated with surgical intervention. This is a unique cause of thromboembolic stroke without valve pathology, which provides additional association and insight into MAC-related stroke. It also reflects the importance of a thorough cardiovascular investigation in patients where cardioembolic stroke is suspected.

ETHICS STATEMENT

The authors declare that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

CONSENT STATEMENT

The authors declare that since this was a noninterventional, retrospective, observational study utilizing deidentified data, informed consent was not required from the patient under an IRB exemption status.

FUNDING STATEMENT

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DISCLOSURE STATEMENT

The authors report no conflict of interest.

SUPPLEMENTARY DATA

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REFERENCES

1. Nair C, Thomson W, Ryschon K, Cook C, Hee TT, Sketch MH. Long-term follow-up of patients with echocardiographically detected mitral anular calcium and comparison with age- and sex-matched control subjects. Am J Cardiol 1989;63:465-70.
2. Benjamin EJ, Plehn JF, D'Agostino RB, Belanger AJ, Comai K, Fuller DL, et al. Mitral annular calcification and the risk of stroke in an elderly cohort. N Engl J Med 1992;327:374-9.
3. Lin C, Schwartz S, Chapman I. Calcification of the mitral annulus fibrosus with systemic embolization. A clinicopathologic study of 16 cases. Arch Pathol Lab Med 1987;111:411-4.
4. Habertheuer A, Laufer G, Wiedemann D, Andreas M, Ehrlich M, Rath C, et al. Primary cardiac tumors on the verge of oblivion: A European experience over 15 years. J Cardiothorac Surg 2015;10:56.
5. Altbach MI, Squire SW, Kudithipudi V, Castellano L, Sorrell VL. Cardiac MRI is complementary to echocardiography in the assessment of cardiac masses. Echocardiography 2007;24:286-300.
6. Tyebally S, Chen D, Bhattacharyya S, Mughrabi A, Hussain Z, Manisty C, et al. Cardiac tumors: JACC CardioOncology State of the Art Review. JACC CardioOncol 2020;2:293-311.
7. Di Napoli M, Papa F, Bocola V. C-reactive protein in ischemic stroke. Stroke 2001;32:917-24.
8. Joffe II, Jacobs LE, Owen AN, Ioli A, Kotler MN. Noninfective valvular masses: review of the literature with emphasis on imaging techniques and management. Am Heart J 1996;131:1175-83.
9. Kanjanauthai S, Nasir K, Katz R, Rivera J, Takasu J, Blumenthal R. Relationships of mitral annular calcification to cardiovascular risk factors: the multiethic study of atherosclerosis (MESA). Atherosclerosis 2010;213:558-62.
10. Eicher JC, Soto FX, DeNadai L, Ressencourt O, Falcon-Eicher S, Giroud M, et al. Possible association of thrombotic, nonbacterial vegetations of the mitral ring—mitral annular calcium and stroke. Am J Cardiol 1997;79:1712-5.
11. Mohan JC, Shukla M, Mohan V, Sethi A. Mobile thrombus originating from densely calcified mitral annulus with cerebral embolism. Indian Heart J 2016;68:S131-4.
12. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP III, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. Circulation 2021;143:e72-227.
13. Levine GN, McEvoy JW, Fang JC, Ibeh C, McCarthy CP, Misra A, et al. Management of patients at risk for and with left ventricular thrombus: a scientific statement from the American Heart Association. Circulation 2022;146:e205-23.
14. Abouelela Y, Gukop P, Livesey S. Surgical management of Libman-Sacks mitral valve endocarditis. Int J Surg Case Rep 2021;79:428-30.
15. Fujiwara M, Hatani Y, Fujimoto W, Yamashita S, Imanishi J, Iwasaki M, et al. Three cases of caseous calcification of the mitral annulus resulting in spontaneous fistulation. CASE 2022;6:355-60.