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Case Report

Mobile thrombus originating from densely calcified mitral annulus with cerebral embolism



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ABSTRACT

Mitral annular calcification (MAC) has been considered a predisposition and an association of thrombo-embolic disease. Superimposed thrombus on MAC is under-appreciated as a potential cause of systemic thrombo-embolism. This report describes an elderly gentleman, who had recurrent cerebral embolism and in one of the episodes, a large mobile thrombus was detected on the ventricular surface of calcified mitral annulus. The thrombus disappeared after initiation of anti-coagulation.

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1. Introduction

Mitral annulus calcification (MAC) is a non-inflammatory chronic degenerative process of the fibrous support structure of the mitral valve, preferentially involving the posterior part of the mitral annulus and often associated with risk factors of athero-thrombosis.¹ It is observed in 10% of the elderly men and about 16% of the elderly women.² MAC may also occur in younger patients with advanced renal disease or other metabolic disorders that result in abnormal calcium metabolism. The putative sequelae of MAC include mitral stenosis, mitral regurgitation, infective endocarditis, atrial arrhythmias, heart block, congestive heart failure and stroke.³ The Framingham study revealed that stroke was twice more frequent in patients with MAC despite adjustment for conventional risk factors and independent of presence or absence of atrial fibrillation and/or heart failure.² A possible link between MAC and cerebral embolism was reported in a study that comprised 16 autopsies, but none of which showed

a thrombus on the mitral annulus.⁴ A recent study has shown spontaneous fistulization of the caseous calcification and extrusion of the cheesy material mixed with calcium as the mechanism of embolic stroke.⁵ The exact mechanism of stroke in MAC is speculative and possibly multi-factorial; however a total of about twenty cases have been reported so far in the literature with vanishing mobile masses on the calcified annulus consistent with thrombi.^{6–14} This report deals with an elderly person with recurrent cerebral embolism, who was detected to have a large mobile mass on the ventricular surface of the mitral annulus consistent with thrombus in one of the several echocardiographic examinations. The mass and neurological symptoms disappeared on anti-coagulation.

2. Case report

A 73-year-old man with long-standing diabetes mellitus, hypertension and previous coronary bypass surgery

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was admitted to this hospital with a several-day history of light-headedness, followed by a sudden onset of loss of speech and cognition. He was on long-term aspirin and statin therapy. CT scan and MRI of brain showed a fresh frontal lobe infarct with several old infarcts. A year prior to that, he had similar complaints with unsteady gait and frequent falls. Detailed neurological examination at that time revealed some small fresh cerebral infarcts but no significant carotid artery disease and 24-h Holter monitoring showed no atrial fibrillation. Six months prior to index hospitalization, he had almost similar complaints of giddiness, unsteady gait and forgetfulness. Detailed cardiac and neurological examination, at that time, revealed a fresh lacunar infarct, dense mitral annular calcification with no thrombus and normal left ventricular function on transthoracic echocardiogram (TTE) and first-degree atrio-ventricular block (PR interval 320 ms). He was implanted with a dual-chamber pacemaker with some relief of symptoms. In the latest hospitalization, his physical examination showed a pulse rate of 88 beats/min (atrial-sensed and ventricular paced rhythm on ECG) and a blood pressure of 132/72 mmHg; his other findings were some neurological deficit in right lower limb and memory loss which gradually recovered over next five days. Laboratory studies showed anemia (hemoglobin level of 11.1 g/dl), with the following levels: serum creatinine, 1.24 mg/dl; total protein, 5.7 g/dl; albumin, 2.9 g/dl; blood sugar, 158 mg/dl; plasma homocysteine level of 16 pg/mL, calcium, 8.1 mg/dl; sodium 129 meq/L and phosphate, 4.3 mg/dl. Other basic laboratory data were normal. Immediately, he received anticoagulation therapy with heparin in combination with

anti-platelet therapy of 150 mg/day oral aspirin and 75 mg/day clopidogrel. He was again referred for an echocardiogram to evaluate the underlying heart disease and a possible embolic source. TTE showed not only normal left ventricular function, moderate mitral regurgitation, normal sizes of cardiac chambers, but also the presence of a single mobile mass (16 mm × 8 mm) superimposed on the ventricular side of the calcified mitral annulus of the posterior leaflet (Figs. 1 and 2, Video 1). After comparing echocardiographic images with her last two studies (1 year and six months before admission), we were able to verify the newly developed mobile mass on the MAC.

The mass was on the ventricular surface of the postero-medial annulus at the top of a calcified ridge, highly mobile and echo-dense. There was no clinical or echocardiographic evidence of infective endocarditis. Multi-planar reconstruction of the 3D echocardiographic acquisition showed the mass to be of uniform density and not obstructing the mitral orifice (Fig. 3). Doppler duplex examination of the neck vessels showed small, calcified plaques in both internal carotid arteries. Thus, 2 mg/day oral warfarin was started and gradually increased to get INR in therapeutic range. Additional laboratory tests including 2 sets of tests for blood cultures, coagulation function (antithrombin-III, fibrin degradation products, protein C, and protein S), tumor markers (carcinoembryonic antigen, CA19-9), and autoimmune antibodies (anti-nuclear antigen, anti-DNA antigen, and anti-cardiolipin IgG) were negative. After two weeks of anticoagulation, TTE was repeated and the mobile mass was no longer present (Figs. 1 and 3). Real-time, three-dimensional trans-thoracic echocardiography was successfully used to visualize the mobile mass on the MAC (Fig. 3, Video 2).

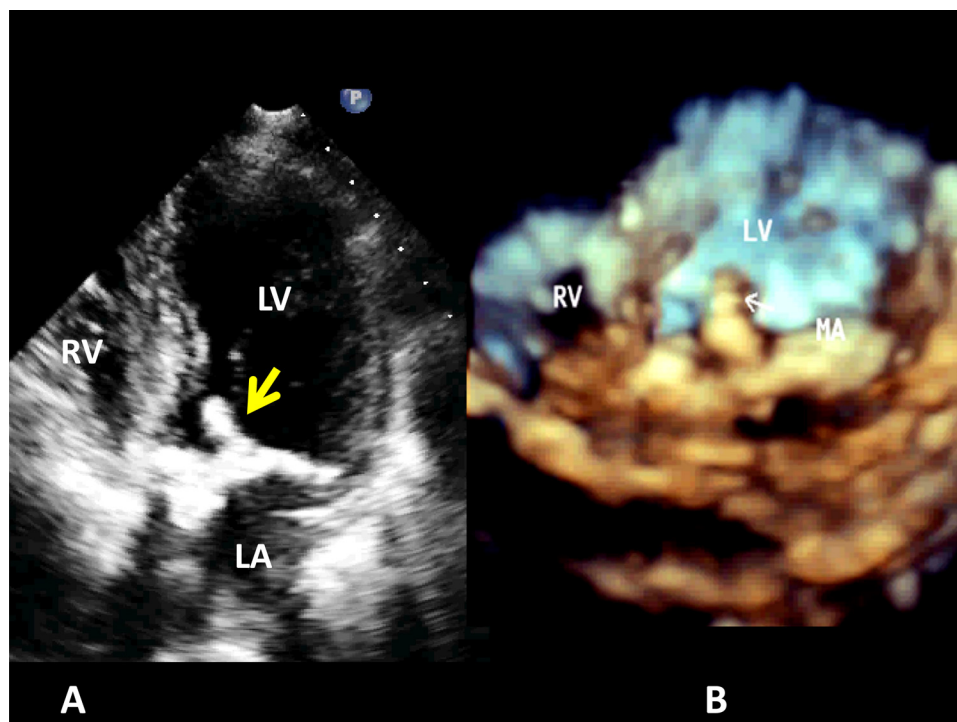


Fig. 1 – Modified 4-chamber view (A) showing an oblong echo-dense mass on MAC (yellow arrow). Real-time 3D echocardiographic image (B) showing the mass (white arrow).

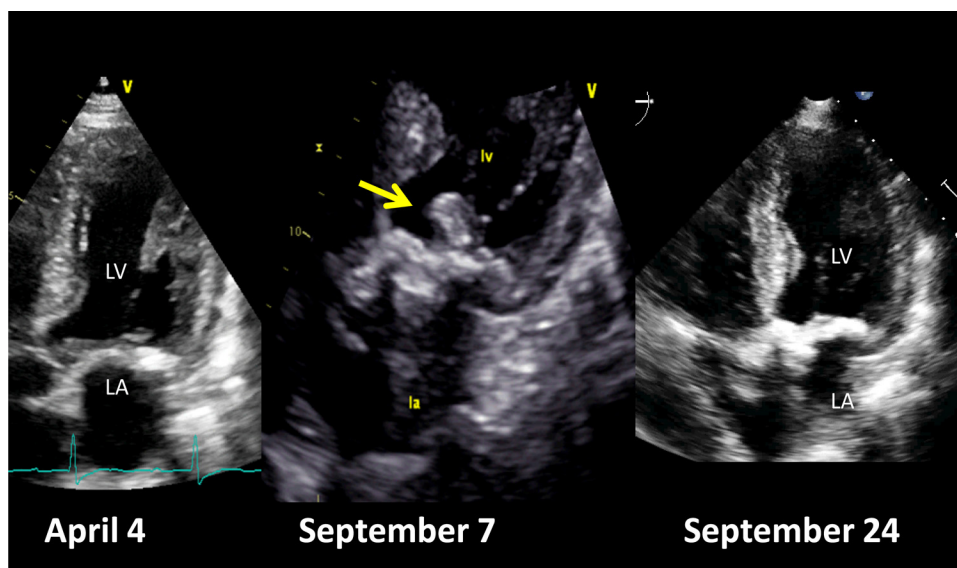


Fig. 2 – Modified 4-chamber views on three different occasions. The middle figure shows the mass on the MAC which subsequently disappeared on anti-coagulation (the right image).

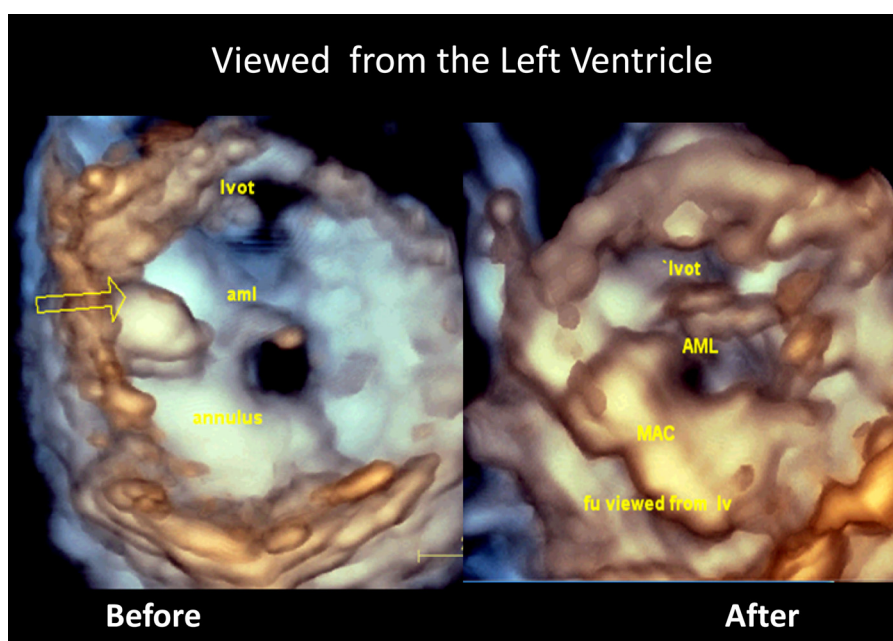


Fig. 3 – 3D trans-thoracic echocardiographic multi-planar reconstruction. Viewed from the left ventricular apex. The left panel shows the mass (yellow arrow) on the mitral annulus before anti-coagulation and the right panel shows disappearance of the mass. ivot – left ventricular outflow tract, AML – anterior mitral leaflet, MAC – mitral annulus calcification.

3. Discussion

Although several studies have demonstrated an association between MAC and stroke; a causal link has not been established.^{1,2} The causes of stroke in patients with MAC are uncertain, but most speculation has centered on an embolic pathogenesis. Autopsy reports have documented calcific emboli to the brain and other organs in a few patients with MAC.^{4,5} Some authors have also suggested that MAC serves as a nidus for thrombus formation.⁶⁻¹⁴ The present case supports this

hypothesis. In our case of recurrent cerebral infarction, one of the echocardiographic studies showed a newly developed mobile mass, which could directly cause cerebral embolism. In our case, the mass was located on the ventricular side of the MAC of the posterior leaflet and disappeared after 3 weeks of anticoagulation therapy. Although the precise mechanisms of the development of the mobile mass on the MAC are unknown, it is possible to postulate that the morphology and the size of the MAC affect the process of the mobile mass formation on the MAC. Liquefaction necrosis, caseous transformation and ulceration of the mitral valve endothelium, with exposure of

underlying calcium has been demonstrated in autopsy studies⁴ and may provide a nidus for thrombus formation. In this autopsy study, two-thirds of the stroke in the presence of MAC were considered embolic. Because one third of the strokes in the subjects with MAC were considered to be non-embolic (atherothrombotic or hemorrhagic), other mechanisms of the relation between MAC and stroke must be considered. Earlier reports linked MAC with advancing age, elevated systolic blood pressure, diabetes mellitus, atrial fibrillation, heart failure and atherosclerosis.^{1,2} All these factors can increase shear stress on the calcified mitral annulus during ventricular systole leading to roughened surface and nidus for thrombus formation. Consequently, MAC may be predictive of stroke because of the clustering of risk factors for stroke in subjects with MAC. For example, high blood pressure may predispose patients to MAC and to stroke; MAC may serve as a marker for severe chronic hypertension and a concomitant risk of stroke. Furthermore, MAC may be associated with an increased risk of stroke by serving as a surrogate for other unknown or unmeasured risk factors.

Echocardiographic detection of a mobile mass on the MAC is not frequently found on routine echocardiograms. Sia et al. reported only 3 such cases in 4000 echocardiographic studies¹³; however, the frequency might be underestimated. It is difficult to detect a small mass beside the massive MAC, especially with ultrasound artifacts and hence, the relationship between a mass on the MAC and systemic embolism is not well recognized. Careful observation of both ventricular and atrial sides of a MAC is needed to evaluate possible embolic sources by using trans-thoracic echocardiography. 80% of the patients with MAC and superimposed mobile mass are symptomatic with cerebral embolism.⁶⁻¹⁴ A majority of the masses were on the posterior part of the annulus and also on the ventricular surface.

In summary, super-imposed thrombus on MAC is under-appreciated as a potential cause of stroke. Clinicians need to consider this potential entity in patients with extensive MAC and a thrombo-embolic event as the diagnosis may significantly modify treatment. However, until large studies can confirm, it is difficult to propose routine anti-coagulation in patients with MAC, who develop stroke unless definite thrombi can be demonstrated.

Conflicts of interest

The authors have none to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.ihj.2016.02.014](https://doi.org/10.1016/j.ihj.2016.02.014).

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