

CARDIAC TUMORS AND PSEUDOTUMORS

A WIDE DIFFERENTIAL AND WIDER CLINICAL IMPACT

Three Cases of Caseous Calcification of the Mitral Annulus Resulting in Spontaneous Fistulation



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INTRODUCTION

Caseous calcification of the mitral annulus (CCMA) is a rare form of mitral annular calcification (MAC) commonly seen in elderly patients with renal dysfunction. According to several studies, it affects only 0.067% of the population, making up only 0.63% of MAC cases.¹ CCMA is commonly misdiagnosed as an abscess, tumor, or infective vegetation on the mitral valve.²

The mechanism involved in liquefaction and caseation in CCMA is not well understood. As the prevalence of CCMA is higher in patients with end-stage renal disease, an altered calcium phosphate metabolism is implicated in its pathogenesis.³ On echocardiography, CCMA is typically located at the posterior annular region of the mitral valve and appears as a mass with a central area of echolucency resembling liquefaction, surrounded by a hyperechogenic structure representing calcification. This may create a so-called string-of-pearls appearance.² Rarely, CCMA is associated with the anterior mitral annulus.¹

Although a rare condition, CCMA can result in fistula formation, valve disease, and systemic embolization. The indications for surgical intervention include complications of mitral valvular dysfunction (stenosis or regurgitation), embolic manifestations, or when the possibility of a tumor cannot be ruled out.² It is reported that patients with CCMA may be at increased risk of embolic strokes.⁴ The high prevalence of cerebral embolization from CCMA is likely attributed to spontaneous fistula formation and embolization of caseous necrotic debris.

There is no consensus on the optimal management of asymptomatic CCMA patients. Elective surgical resection of a CCMA mass may be considered for patients considered at high risk for systemic embolization. This report discusses 3 CCMA cases.

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CASE PRESENTATION 1

A 61-year-old man with long-standing hypertension, diabetes mellitus, and end-stage renal disease on hemodialysis for 18 years had a routine transthoracic echocardiogram (TTE) performed that revealed an incidental finding of a mobile mass on the posterior mitral valve leaflet (Figure 1A and B, Videos 1 and 2).

The physical examination and electrocardiographic findings were normal. The TTE revealed an abnormal round mass in the posterior mitral periannular region. The TTE from the left ventricular long axis showed hyperintense echoes at the mass margins and hypointense echoes in the center, but from the left ventricular short axis, the mass was observed as a homogenous hyperintense mass. The mass measured 10 × 9 mm. Aside from the mass, a mobile string-like structure was observed attached from the mitral valve to the papillary muscle. A transesophageal echocardiogram (TEE) was performed to further evaluate the findings on TTE and confirmed a mobile, thickened, and calcified structure at the P2 region of the posterior mitral valve leaflet (Figure 1C and D, Videos 3 and 4). On the basis of these findings, it was considered that the patient was predisposed to having an embolism. Therefore, the patient was referred for cardiac surgery and the mass was surgically removed. A mitral valve repair was also performed (Figure 1E, Video 5). During surgery, the walls of the mass were hard. Upon opening, the encapsulated mass revealed a white, milky, “toothpaste-like” discharge, which is a characteristic feature of CCMA.

On pathological examination, the mass contained a central region of amorphous eosinophilic acellular material surrounded by macrophages and lymphocytes. Multiple calcifications and necrotic zones were noted at the periphery (Figure 1G). The mobile string-like structure seen on echocardiography was found to be a calcified structure entwined within, but separate from, the chordae tendineae seen attached to the papillary muscle (Figure 1F). Based on the pathologic findings, a fistulous communication between the CCMA mass and the left ventricle (LV) was suspected, resulting in the mobile calcified structure, which could be a potential source for embolization.

CASE PRESENTATION 2

An 83-year-old man underwent serial TTE due to a history of diabetes mellitus and end-stage renal disease on hemodialysis for 1 year. ATTE performed 2 years earlier had incidentally revealed a mass adjacent to posterior mitral valve leaflet exhibiting a string-of-pearls appearance, which suggested CCMA (Figure 2A, Video 6). One year earlier, another TTE confirmed that the size of the mass had increased from 11 to 18 mm (Figure 2B, Video 7). The TTE on this current

VIDEO HIGHLIGHTS

Video 1: Case 1: TTE parasternal long-axis view shows a mass in the posterior mitral annulus. The center of the mass appears echolucent and is encircled by an echogenic rim creating a string-of-pearls appearance. There is also increased thickening and calcification of a band extending from the mitral valve toward the papillary muscle.

Video 2: Case 1: TTE parasternal short-axis view at the level of the papillary muscles shows an echogenic mass near the posteromedial papillary muscle.

Video 3: Case 1: TEE midesophageal 4-chamber image focusing on the mitral valve shows a mass in the posterior mitral annulus. The mass has an echogenic rim creating a string-of-pearls appearance.

Video 4: Case 1: A lump in the P2 region of the mitral valve is seen on the three-dimensional short-axis image.

Video 5: Case 1: Video taken during cardiac surgery with the left atrium opened and the mitral valve exposed shows a white, milky, toothpaste-like discharge.

Video 6: Case 2: Initial apical 2-chamber view shows a mass within the posterior mitral annulus measuring 11 mm.

Video 7: Case 2: Apical 2-chamber view acquired 12 months after the initial presentation showed an increase in the size of the mass to 18 mm.

Video 8: Case 2: Apical 2-chamber view acquired 1 year later shows a further increase in the size of the mass to 20 mm along with an additional structure distal to the mass.

Video 9: Case 2: TEE midesophageal 2-chamber view focusing on the mitral valve shows a globular mass at the posterior mitral valve.

Video 10: Case 2: On the three-dimensional short-axis image, a mass in the P2 region of the mitral valve is seen.

Video 11: Case 2: TEE midesophageal 2-chamber view with color Doppler compare shows the perforation of the posterior mitral leaflet with associated mitral regurgitation.

Video 12: Case 3: TTE zoomed apical long-axis views show an echogenic mass in the region between the posterior aortic root and the anterior mitral leaflet. The mass measures 16 × 9 mm.

Video 13: Case 3: TTE zoomed apical long-axis views show an echogenic mass in the region between the posterior aortic root and the anterior mitral leaflet. The mass measures 29 × 14 mm.

Video 14: Case 3: TEE midesophageal 5-chamber view revealed a mass on the anterior mitral valve.

Video 15: Case 3: On the three-dimensional TEE short-axis image, a mass superior and anterior to the anterior mitral valve is seen.

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presentation demonstrated that the size of the mass had increased further to 20 mm, and a new mobile structure was observed adjacent to the mass (Figure 2C, Video 8). Spontaneous fistula formation of the CCMA to the LV was suspected.

On physical examination, a grade 2/6 systolic murmur was auscultated at the apex. A TEE revealed a mass in the P2 region of the mitral valve, a mobile structure attached to the mass, moderate mitral regurgitation, and a perforation of the posterior mitral valve (Figure 3, Videos 9-11). Color Doppler on TTE was limited due to CCMA, and the assessment of mitral regurgitation was suboptimal. A TEE was therefore performed, and color Doppler suggested moderate mitral regurgitation based on visual estimation. The patient underwent cardiac surgery, which confirmed that the mass was located in the mitral valve P2-P3 region, and also confirmed a partial perforation of the P1 region and mobile tissue, which extended from the CCMA mass. The CCMA mass was resected, and a mitral valve replacement was performed.

CASE PRESENTATION 3

The third case is a 73-year-old man with a history of hypertension, chronic atrial fibrillation, end-stage renal disease on hemodialysis for 32 years, hypertension, and dialysis amyloidosis. Furthermore, he had a bioprosthetic aortic valve replacement for severe aortic stenosis and coronary artery bypass grafting 4 years prior. During his regular checkup, his physical examination was unremarkable. Routine TTE was performed, which revealed a mass measuring 16 × 19 mm in the region between the posterior aortic root and the anterior mitral leaflet (Figure 4A, Video 12). Aside from its location, the mass exhibited findings characteristic of CCMA as previously described. Six months later, the size of the mass increased to 29 × 14 mm (Figure 4B, Video 13).

A TEE revealed a mass between the posterior aortic root and the anterior mitral leaflet (Figure 4C and D, Videos 14 and 15). As CCMA rarely occurs in the anterior mitral valve,¹ gadolinium scintigraphy and contrast-enhanced computed tomography (CT) were performed to characterize the lesion further. There was no mass accumulation on scintigraphy, essentially excluding active cardiac sarcoidosis. Contrast-enhanced CT revealed that the mass extended from the aortic valve to the mitral-aortic intervalvular fibrosa (MAIF; Figure 5). Coronary angiography was performed to rule out a coronary artery aneurysm, and no aneurysm was detected.

Based on these findings, the likely diagnosis of this mass was CCMA within the MAIF. As the patient had previously had open-heart surgery, it was postulated that this surgery likely contributed to CCMA developing in this atypical location.

As the mass expanded rapidly, the patient was at high risk for spontaneous fistula formation. Therefore, he underwent cardiac surgery, which confirmed the location of the mass in the MAIF. Intraoperatively, the mass was already ruptured, so the CCMA contents leaked out. Observation through the aortic valve revealed a hole in the MAIF. The patient then received bioprosthetic aortic valve replacement and mitral valve replacement.

DISCUSSION

We have presented 3 cases of CCMA with surgically confirmed spontaneous fistula formation. The indications for surgical intervention include mitral valvular dysfunction, embolic manifestations, or when the possibility of a tumor cannot be ruled out.²

Patients with CCMA are reported to be at increased risk of embolic strokes, likely attributed to spontaneous fistula formation and embolization of caseous necrotic debris. In addition to fistula formation as an indication for surgery, advanced age >70 years old, female gender, and hypertension each confer a higher likelihood for cardioembolic

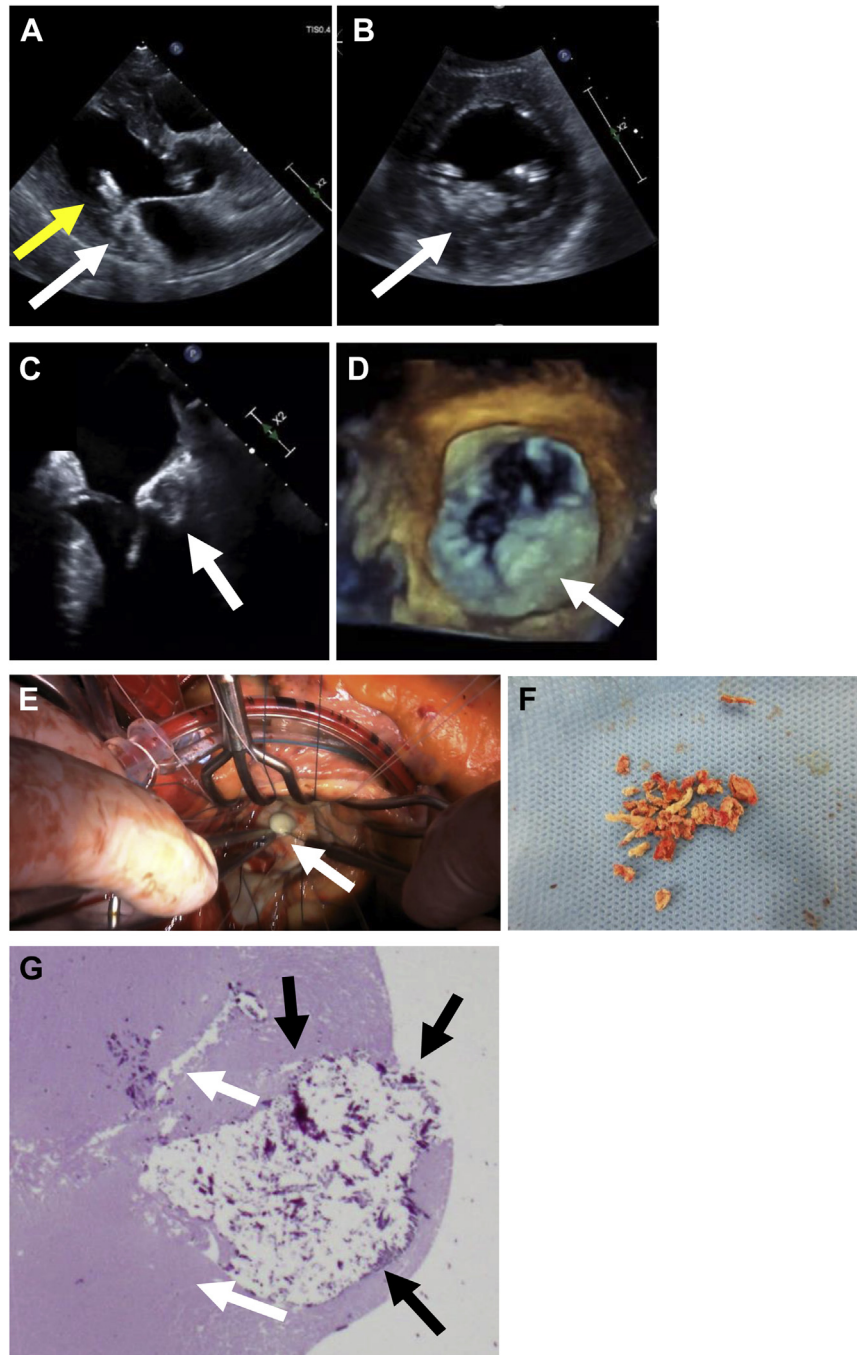


Figure 1 (A) TTE parasternal long-axis view shows a mass in the posterior mitral annulus (*white arrow*). The center of the mass appears echolucent and is encircled by an echogenic rim creating a string-of-pearls appearance. There is also increased thickening and calcification of a band extending from the mitral valve toward the papillary muscle (*yellow arrow*). (B) TTE parasternal short-axis view at the level of the papillary muscles shows an echogenic mass near the posteromedial papillary muscle (*arrow*). (C) TEE midesophageal 4-chamber image focusing on the mitral valve shows a mass in the posterior mitral annulus. The mass has an echogenic rim creating a string-of-pearls appearance. (D) On the three-dimensional TEE short-axis image, a lump in the P2 region of the mitral valve is seen (*arrow*). (E) Photo taken during cardiac surgery with the left atrium opened and the mitral valve exposed shows a white, milky, tooth-paste-like discharge. (F) Photo of the mobile string-like structure, which was a calcified structure entwined within, but separate from, the chordae tendineae attached to the papillary muscle. (G) Histology with hematoxylin and eosin staining demonstrates calcifications (*black arrow*), inflammation, and necrosis (*white arrow*).

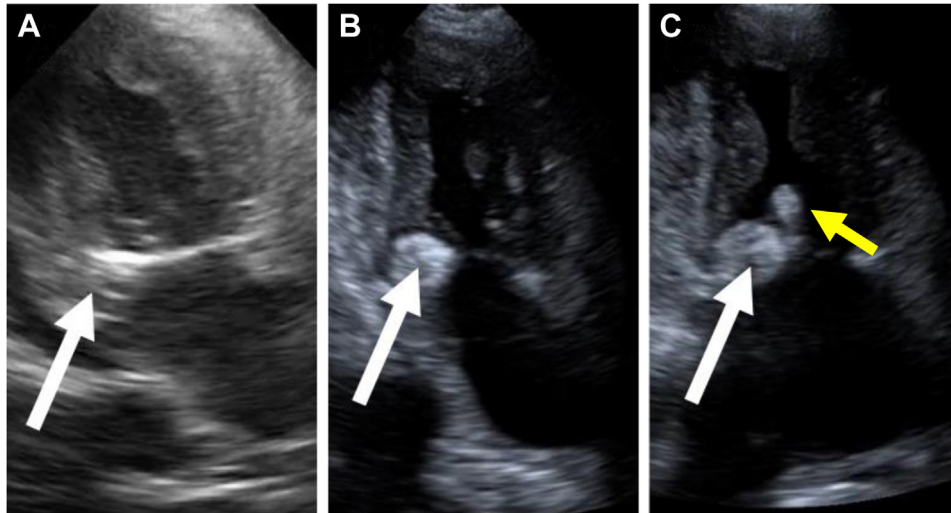


Figure 2 (A) Initial apical 2-chamber view shows a mass within the posterior mitral annulus measuring 11 mm (*arrow*). (B) Apical 2-chamber view acquired 12 months after the initial presentation showed an increase in the size of the mass to 18 mm (*arrow*). (C) Apical 2-chamber view acquired 1 year later shows a further increase in the size of the mass to 20 mm (*white arrow*) along with an additional structure distal to the mass (*yellow arrow*).

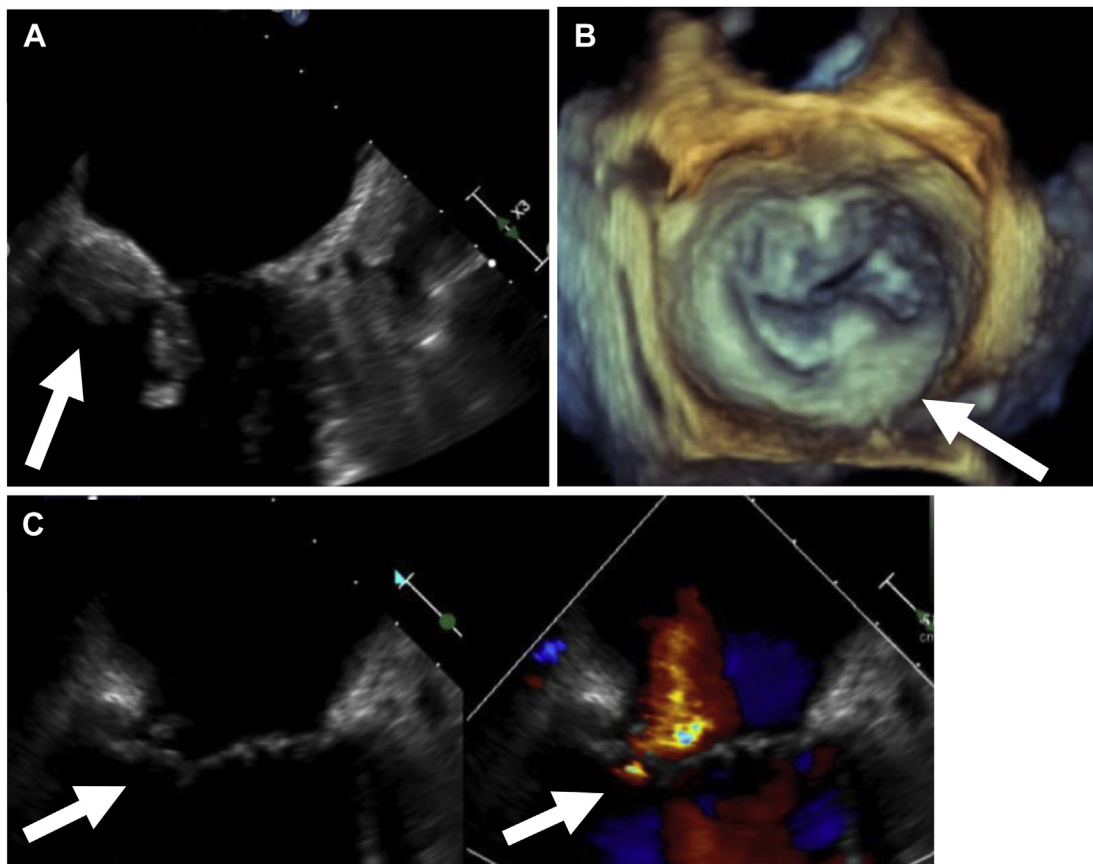


Figure 3 (A) TEE midesophageal 2-chamber view focusing on the mitral valve shows a globular mass at the posterior mitral valve (*arrow*). (B) On the three-dimensional TEE short-axis image, a mass in the P2 region of the mitral valve is seen (*arrow*). (C) TEE midesophageal 2-chamber view with color Doppler compare shows the perforation of the posterior mitral leaflet with associated mitral regurgitation (*arrows*).

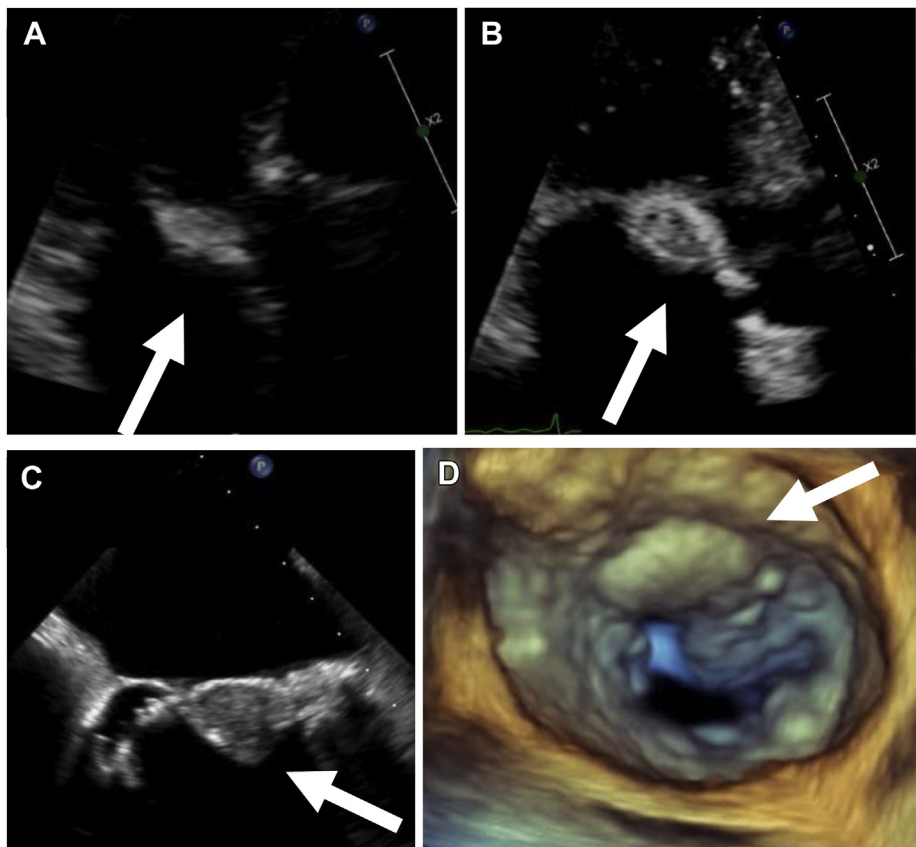


Figure 4 (A) TTE zoomed apical long-axis views show an echogenic mass in the region between the posterior aortic root and the anterior mitral leaflet (*arrow*). The mass measures 16×9 mm. (B) TTE zoomed apical long-axis views show an echogenic mass in the region between the posterior aortic root and the anterior mitral leaflet (*arrow*). The mass measures 29×14 mm. (C) TEE midesophageal 5-chamber view revealed a mass on the anterior mitral valve. (D) On the three-dimensional TEE short-axis image, a mass superior and anterior to the anterior mitral valve is seen (*arrow*).

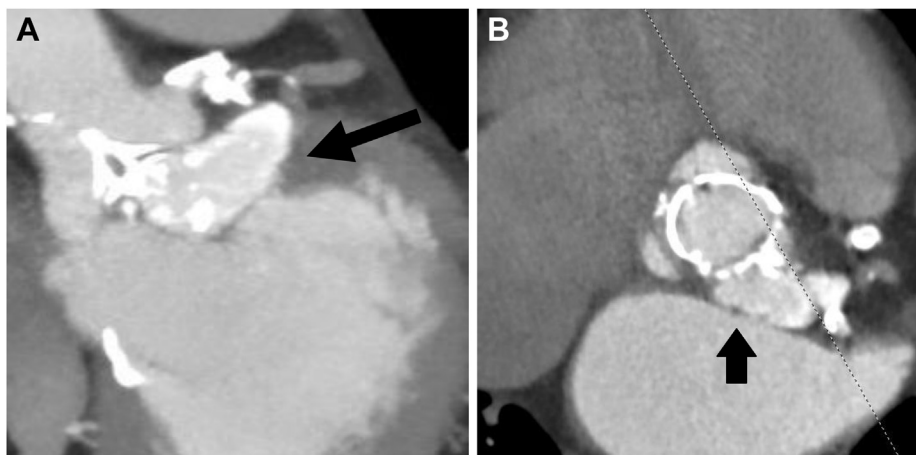


Figure 5 Contrast-enhanced CT in the coronal (A) and axial (B) planes revealed that the mass was located outside the aortic valve (*arrows*).

strokes, and individuals with these features may also be candidates for surgical resection.⁴ It is thought that the patients with CCMA who have a risk of cardioembolic strokes may be indicated for surgical resection.

In cases 1 and 2, the CCMA seemed to have fistula formation and mobile structures seen on echocardiography. Case 3 demonstrated that the CCMA was rapidly expanding, leading to an increased risk for fistula formation. Case 3 was a patient over 70 years old who had long-standing hypertension, increasing the risk for cardioembolic strokes. These masses were surgically confirmed to have undergone spontaneous fistula formation.

Despite being at such a high risk, none of these patients had symptoms of systemic embolization or stroke, and we believe that frequent monitoring with echocardiography and performing open-heart surgery when the size of the mass was found to rapidly increase contributed to this favorable outcome.

In our opinion, it may be important to follow the CCMA course regularly to comprehensively assess the morphologic changes of the mass and to consider risk of cardioembolic strokes and indication of surgical treatment.

In case 1, TTE findings showed a 10 mm lesion with an associated mobile, calcified structure distal to the mitral valve. In case 2, the size of the mass increased from 11 to 18 mm within a year, with an additional mobile structure and perforation of the posterior mitral leaflet observed in a later year. In case 3, the mass developed rapidly (from 16 to 29 mm) within 6 months, and it had ruptured and leaked, resulting in perforation of the MAIF.

Four case reports of CCMA with spontaneous fistula formation have been published. The diameters of the masses in these cases were 36 × 19, 20 × 15, 6 × 5, and 40 × 30 mm, respectively.⁵⁻⁸ Considering our 3 cases, the mean and minimum diameters of CCMA, resulting in suspected spontaneous fistula formation, were 23 and 6 mm at the major axis, respectively.

Few studies have been reported about CCMA fistula formation. It is not clear whether there is any relevance between the size of the CCMA and the possibility of fistula formation, so more case reports are needed.

In cases 2 and 3, CCMA development also caused perforation of the mitral and aortic valves. There have been a few case reports of CCMA fistula formation causing mitral valve dysfunction and acute heart failure.⁹ Timely follow-up is recommended to detect valve damage caused by CCMA.

The mechanism involved in liquefaction and caseation in CCMA is not well understood, and the development of CCMA occurs in the same way. CCMA has a strong relation to the history of hypertension and chronic renal failure or hemodialysis. Altered calcium phosphate metabolism was likely involved in its pathogenesis.³ Usuku *et al*¹⁰ reported a CCMA case of developing mass after initiation of hemodialysis therapy. Hemodialysis therapy was initiated only 1 year ago in the patient in case 2. Meanwhile, the other 2 patients had a long history of hemodialysis.

CCMA is frequently misdiagnosed as other intracardiac masses; common differential diagnoses include tumors, thrombi, abscesses, and vegetations on mitral valve. Often first noted on TTE, the typical appearance is hyperechogenic around the tumor with a partially hypoechogenic or isoechogenic component within the tumor. CCMA can also often be misdiagnosed as other intracardiac masses.

A myocardial vegetation appears as an oscillating mass attached to valve tissue, and a paravalvular abscess appears as an echolucent cavity within the valvular annulus. Although they are commonly associated with valve dysfunction, their appearance can closely resemble CCMA.¹¹

The mobile structures attached to the mitral valve in cases 1 and 2 have an oscillating appearance, which is very similar to a vegetation. A vegetation is usually on the left atrial side of the mitral valve, whereas those structures seen in our patients were on the left ventricular side of the mitral valve. Importantly, infective endocarditis is a clinical diagnosis that uses the modified Duke criteria and persistently positive blood cultures, which helps to differentiate this from CCMA.

An additional differential diagnosis to consider is a calcified amorphous tumor, which also presents as an intracardiac mass and is commonly seen in elderly patients with renal dysfunction. These may also cause systemic embolization; the findings are similar to CCMA, and there is no clear way to differentiate them from each other without histology.¹²

CONCLUSION

The mechanism and natural course of CCMA is not well known. CCMA can result in fistula formation, valve disease, and systemic embolization. Follow-up with TTE is recommended for patients with CCMA to detect those complications and consider indications for surgical treatment.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.case.2022.04.004>.

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