RESEARCH ARTICLE

Risk of Cerebral Embolization with Caseous Calcification of the Mitral Annulus: Review Article

Charles A. Dietl¹*, Christopher M. Hawthorn² and Veena Raizada³

¹Department of Surgery, Division of Cardiothoracic Surgery, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA
²School of Medicine Division of Cardiology, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA
³Department of Internal Medicine, Division of Cardiology, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA

Abstract:

Background:

Caseous calcification of the mitral annulus (CCMA) is believed to have a benign prognosis. Several authors have recommended conservative management in asymptomatic patients. However, the prevalence of cerebrovascular events (CVE) in patients with CCMA has never been evaluated before. The aims of this study are to investigate whether patients with CCMA are at increased risk of cerebral embolization, and to determine whether elective surgical resection of CCMA should be considered to prevent a cardioembolic stroke.

Methods:

A comprehensive literature search was obtained from MEDLINE via PubMed.gov, ScienceDirect.com, and Google Scholar using the following search queries: caseous calcification of the mitral annulus, intracardiac pseudotumor, mitral annular calcification, and cardioembolic stroke.

Results:

From our initial search that yielded 1,502 articles, we identified a total of 130 patients with CCMA reported in 86 publications. Literature review revealed that the prevalence of CVE associated with CCMA is 19.2% (25 of 130) which is significantly higher than the prevalence of CVE reported with mitral annular calcification (MAC), 11.8% (214 of 1818) (range 4.8% to 24.1%) ($P = 0.01796$) (odds ratio = 1.78; 0.95 confidence interval = 1.1278 – 2.8239). Only four of 25 (16.0%) patients with CCMA who suffered a CVE had history of atrial fibrillation (AF).

Conclusion:

Based on our review, it would be reasonable to consider elective surgical resection of CCMA in asymptomatic patients who are good surgical candidates, because patients with CCMA may be at increased risk of embolic strokes, which are unrelated to AF.

Keywords: Cardioembolic stroke, Caseous calcification, Caseous calcification of the mitral annulus, Cerebral embolism, Mitral annulus calcification, Stroke.

* Address correspondence to this author at the Division of Cardiothoracic Surgery, Department of Surgery, ACC-2, MSC 10 5610, University of New Mexico, Albuquerque, NM 87131-0001, USA; Tel: (+1) 505-272-6901; Fax: (+1) 505-272-6909; E-mails: cdietl@comcast.net, CDietl@salud.unm.edu
INTRODUCTION

Approximately one-fifth of all ischemic strokes are cardioembolic. Several cardiac conditions have been identified as potential sources of embolism. Atrial fibrillation (AF) is the most common cause of cardioembolic stroke. Other major potential sources are: mitral stenosis, prosthetic valves, infective endocarditis, marantic endocarditis, recent myocardial infarction, dilated cardiomyopathy, left ventricular aneurysm, and intracardiac tumors. Mitral annular calcification, caseous calcification of the mitral annulus, calcific aortic stenosis, patent foramen ovale, atrial or ventricular septal defects, and atrial septal aneurysm may also be associated with cardioembolism [1]. Mitral annular calcification (MAC) is a common echocardiographic finding, mainly in older patients. The association between MAC and atrial fibrillation, cerebral embolization, acquired mitral stenosis, hypertension, hyperlipidemia, diabetes, coronary artery disease, aortic atheroma, and diffuse atherosclerosis has been well documented. According to several clinical and clinicopathologic studies [2 - 9], the risk of cerebrovascular events (CVE) in patients with MAC ranges from 4.8% to 24.1% (Table 1).

Caseous calcification of the mitral annulus (CCMA) is a rare variant of MAC, seen as a tumor-like echo-dense mass containing central areas of echolucencies at the posterior periannular region of the mitral valve on echocardiography [10]. Several authors have suggested that conservative management is recommended if the diagnosis of CCMA can be made by echocardiography in asymptomatic patients because CCMA is usually a benign condition [10 - 13]. However, the prevalence of CVE in patients with CCMA has never been evaluated before. The aims of this study are to investigate whether patients with CCMA are at increased risk of cerebral embolization, and to determine whether elective surgical resection of CCMA should be considered to prevent a cardioembolic stroke.

Table 1. Prevalence of cerebrovascular events in patients with MAC.

| Author       | Year | Patients with MAC | CVE (%) |
|--------------|------|-------------------|---------|
| Fulkerson    | 1979 | 80                | 5 (6.2%)|
| Furlan       | 1984 | 63                | 3 (4.8%)|
| Lin          | 1987 | 142               | 16 (11.3%)|
| Nair         | 1989 | 99                | 10 (10.1%)|
| Benjamin     | 1992 | 160               | 22 (13.8%)|
| Aronow       | 1992 | 365               | 88 (24.1%)|
| Boon         | 1997 | 657               | 51 (7.8%)|
| Kizer        | 2005 | 252               | 19 (7.5%)|
| Total        |      | 1818              | 214 (11.8%)|

CVE = cerebrovascular event; MAC = mitral annulus calcification.

MATERIALS AND METHODOLOGY

A comprehensive literature search on all peer-reviewed studies published in English language was obtained from MEDLINE via PubMed.gov, ScienceDirect.com, and Google Scholar on landmark and related articles to investigate whether patients with CCMA are at increased risk of cerebral embolization. The search queries included: caseous calcification of the mitral annulus, intracardiac pseudotumor, mitral annular calcification, and cardioembolic stroke. To ensure that no potentially relevant articles were missed, the reference lists of all the articles included in the search were checked and cross-referenced.

Statistical Analysis

The Chi-squared test was used to determine whether there is a significant difference between the observed frequencies of cerebrovascular events in patients with CCMA compared to MAC. \( P \) values less than 0.05 were considered significant.

RESULTS

From our initial search that yielded 1,502 articles, we identified a total of 130 patients with CCMA that were reported in 86 English-language publications (see Appendix 1). These include 57 publications on caseous calcification of the mitral annulus, 14 articles on liquefaction necrosis of the mitral annulus, 7 articles on mitral annular calcification that included patients with CCMA, and 8 papers on intracardiac pseudotumors that were included because the patients
had CCMA. In addition, 435 articles were reviewed to evaluate the prevalence of stroke in patients with MAC.

The first manuscript describing “caseation” of the calcified mitral ring was published in 1970, consisting of 7 cases of CCMA identified in an autopsy study by Pomerance [14] among 258 cases of MAC. Most of the publications on CCMA (74/86, or 86.0%) were single case reports. The three largest published series consisted of 19, 14 and 6 patients, respectively [10 - 12]. A total of 137 patients with CCMA were identified in these 86 publications, 130 of which were clinical cases, in addition to 7 postmortem cases reported by Pomerance [14].

The mean age of patients with CCMA was 69.5 years (range 23 to 92 years-old). Female gender predominated (94/130, or 72.3%). The majority of the 130 patients reported in clinical studies (111/130, or 85.4%) diagnosed to have CCMA were being evaluated because they were symptomatic. Only 14 (10.8%) of the 130 patients with CCMA were completely asymptomatic, and the clinical history was unknown in 5 (3.9%). The most common symptom at presentation was dyspnea on exertion or at rest (49/130 patients, or 37.7%). Twenty-two (44.9%) of the 49 patients presenting with dyspnea had moderate or severe mitral regurgitation (MR), and five (10.2%) had moderate or severe mitral stenosis (MS). Other symptoms included: cerebrovascular events (CVE), syncope, palpitations, and chest pain.

The prevalence of CVE in patients with CCMA was significant. Twenty-three of 130 (17.7%) patients presented with a stroke [10, 15 - 32], and 2 additional patients being managed conservatively had a CVE during follow-up [11, 33] (Table 2). Thus, the total number of patients with a confirmed diagnosis of CCMA who had a CVE was 25 of 130 (19.2%). Atrial fibrillation (AF) was present in 21 (16.2%) of the 130 patients. However, only 4 of the 25 (16.0%) patients with a CVE had documented AF, whereas the majority (21/25, or 84.0%) of CCMA patients with a CVE did not have AF (Table 2). Harpaz and associates [10] reported AF in 2 of their 19 patients, and a CVE in 5 of their patients. It is not clear from their article whether the two patients with AF presented with CVE or not.

Associated risk factors included hypertension, present in 61.5% (80/130) patients, dyslipidemia in 23.8% (31/130), diabetes mellitus in 16.9% (22/130), and end-stage renal disease (ESRD) on chronic hemodialysis in 11.5% (15/130). However, the prevalence of these risk factors is likely to be higher, because the comorbidities were not mentioned in 24 patients.

The diagnosis of CCMA was made with transthoracic echocardiography (TTE) in approximately half the cases (64/130, or 49.2%), and by transesophageal echocardiography (TEE) in 9 additional patients. The typical appearance of CCMA on 2-dimensional echocardiography is a round, echodense mass mimicking an intracardiac tumor, containing central areas of echolucencies resembling liquefaction, located in the posterior aspect of the mitral annulus or periannular region [10]. The echodense mass was located in the posterior aspect of the mitral annulus in 124 patients (95.4%), and involvement of the base of the anterior leaflet was reported in 6 cases (4.6%). Additional diagnostic imaging studies, including cardiac computed tomography (CT) scan, and cardiac magnetic resonance imaging (CMRI) were necessary to establish the diagnosis of CCMA in 37 patients. In 18 (13.8%) patients the diagnosis of CCMA was not suspected from preoperative studies and was made intraoperatively.

Almost two-thirds of the patients (84/130, or 64.6%) reported in the literature were managed conservatively, including 9 patients who presented with a CVE. During follow-up, 3 medically treated patients had a CVE (2 of whom died), 2 had syncopal episodes and 4 patients died: 2 from a CVE, 1 had sudden death, and 1 from erosion of the CCMA mass into the circumflex artery.

Forty-two patients (32.3%) were referred to surgery, 5 of whom refused, thus only 37 of the 111 (33.3%) symptomatic patients underwent an operation. Only 10 (38.5%) of the 26 patients with a preoperative diagnosis of possible cardiac tumor established by TTE underwent resection. The most common indication for surgical treatment was the association of CCMA with severe mitral regurgitation in 22 patients and severe mitral stenosis in 5. The surgical procedure consisted of resecting the CCMA mass, combined with mitral valve replacement (MVR) in 24 patients and mitral annuloplasty in 6.

Table 2. Prevalence of cerebrovascular events and atrial fibrillation in reported cases of CCMA.

| Author       | Year | Pts (n) | CVE         | Rhythm     | Treatment       |
|--------------|------|---------|-------------|------------|-----------------|
| Harpaz [10]  | 2001 | 19      | CVE 5       | AF 2 NSR 17| observation 16 + surgery 3 |
| DeLuca [11]  | 2008 | 14      | CVE 1 (at F/U)| AF 5 NSR 9 | observation 14 |
| Davidson [15] | 2006 | 1       | CVE (retinal embolus) | ? | surgery |
| Lubarsky [16] | 2007 | 1       | CVE         | ?          | observation     |
| Poh [17]     | 2007 | 1       | CVE         | ?          | surgery         |
According to our review, 43.2% (16 of 37) of the surgical patients were ≥70 years-old patients, and only 7 (28.0%) of the 25 CCMA patients with a CVE underwent surgery, 5 of whom were ≥70 years-old. The overall surgical mortality was 8.1% (3 of 37) for all published CCMA cases, including 2 of 16 patients aged ≥70 years-old (12.5% mortality).

In addition to the literature search, we report 3 patients who were diagnosed to have CCMA intraoperatively. One patient was referred to surgery with a suspected diagnosis of left atrial myxoma; another patient with diagnosis of severe MS and heavy MAC; and another patient, who presented with TIA’s, was referred for resection of a subaortic mass that was attached to the anterior mitral annulus and was causing subtotal LV outflow tract obstruction (Fig. 1). On sectioning, the encapsulated mass contained a white toothpaste-like caseous material in all 3 patients.

**DISCUSSION**

Caseous calcification of the mitral annulus (CCMA) is a rare variant of MAC, which is observed in 0.067% of all echocardiographic exams, and is present in 0.63% of all patients with MAC [10, 11]. The typical appearance of CCMA is an echo-dense mass containing central areas of echoluencies at the posterior periannular region of the mitral valve on echocardiography [10, 11]. Caseous calcification of the mitral annulus is frequently misdiagnosed as an intracardiac tumor [10]. Several authors have suggested that conservative management is recommended if the diagnosis of CCMA...
can be made by echocardiography in asymptomatic patients because CCMA is usually a benign condition [10 - 13].

However, the prevalence of CVE in patients with CCMA has never been evaluated before. Our comprehensive review of the literature revealed that the prevalence of cardioembolic events associated with CCMA is 19.2% (25 of 130) which is significantly higher than the prevalence of CVE reported with mitral annular calcification (MAC), 11.8% (214 of 1818) (range 4.8% to 24.1%) \( (P = 0.01796) \) (odds ratio = 1.78; 0.95 confidence interval = 1.1278 – 2.8239).

Furthermore, the prevalence of CVE in patients with CCMA may be underestimated, because the vast majority of articles on CCMA were single case reports with no follow-up data, or very brief periods of follow-up, and the longest follow-up recorded was 3.8 years [10], whereas articles on the risk of stroke in patients with MAC usually refer to an older population followed for longer periods, up to 8-years [6]. It is also quite possible that several cases reported in the literature as “MAC” during the 1980’s and 1990’s may have been CCMA, due to underdiagnosis of CCMA, as many cardiologists were not familiar with this condition [13]. In addition, improvements in echocardiography and widespread use of cardiac imaging modalities during the last decade have helped to uncover this rare variety of MAC, which has been greatly underappreciated, and even unrecognized in the past [10].

In several case reports, CCMA was directly linked to cerebral embolization [18 - 32]. Thorough review of all cases of CCMA presenting with a stroke excluded thrombus formation and other possible intracardiac source of embolism by TEE or during operation in all 25 cases. The possible mechanisms for cerebral embolization from CCMA lesions include: (1) spontaneous fistulization and embolization of caseous material that may leak directly into the left atrium or ventricle [18, 20]; (2) embolization of caseous necrotic debris from the CCMA lesion [25]; and (3) embolization of calcium and cholesterol particles [32].

Higashi and associates [18] suggested that there was a causal relationship between the CCMA lesion and the stroke, because there was no evidence of extracranial atherosclerosis, and because they were able to demonstrate in one patient that the central cavity within the CCMA communicated with the left atrium (Fig. 2). The authors believed that caseous material leaked from the CCMA lesion into the systemic circulation and embolized to the brain. In another case report, Chevalier and colleagues [20] were able to confirm during surgery a direct communication between the CCMA and the left ventricle in a patient who presented after two strokes, and suggested that spontaneous fistulization is a possible mechanism of embolization of caseous material. Another two articles addressing the issue of possible coexisting extracranial carotid disease suggested that embolization originated from the CCMA lesion, and not from the carotid arteries. Matsuyama and coworkers [25] reported a case where caseous necrotic debris from the CCMA lesion had embolized to the brain and heart in a postmortem exam, in a patient without coexisting extracranial carotid disease (Fig. 3). Sequeira and associates [32] found bilateral branch retinal artery occlusion secondary to calcium and cholesterol emboli in the retinal vessels of a young patient on hemodialysis complaining of visual disturbances, in which the carotid ultrasound did not reveal any plaques within the internal carotid arteries.

Fig. (2). Apical three-chamber view on transthoracic echocardiography after an embolic stroke. There is a partial deficit (arrow) on the rim of the caseous calcification of the mitral annulus. Ao = aorta; LA = left atrium; LV = left ventricle. (Reprinted from Journal of Cardiology Cases, Volume 2, Issue 3, 2010, e141-e143). Haruhiko Higashi, Takahiro Ohara, Satoshi Nakatani, Shuji Hashimoto, Takako Torii, et al. A case of caseous calcification of the mitral annulus: A potential source of embolic stroke [18]. (Reprinted with permission from Elsevier).
In addition to these studies, Poh and co-workers [17] observed a sudden decrease in size of the left atrial mass on repeat echocardiograms in a patient who presented with an embolic stroke. This finding suggests that the CCMA lesion leaked caseous material into the systemic circulation, causing an embolic stroke. Deluca and associates [11] hypothesize that the reduction in size of the CCMA mass observed in 3 patients could be secondary to central liquefaction and gradual filtration of caseous material through microscopic leaks of the external wall.

One may argue that AF, which was present in 21 (16.2%) of 130 patients with CCMA could be a contributing factor for the increased prevalence of CVE in these patients. However, only 4 of 25 patients (16.0%) with CCMA who suffered a CVE had documented history of AF (Table 2). Thus, the available data shows that there is no correlation between AF and CVE in patients with CCMA, suggesting that the high prevalence of CVE was likely secondary to the CCMA, and not to the associated AF. In other words, patients with CCMA may be at increased risk of cerebral embolization which is not related to atrial fibrillation.

In summary, our study shows that 1 out of 5 patients with CCMA suffered embolic strokes. Patients with advanced age ≥70 years-old, female gender, and hypertension are even more likely to have cardioembolic strokes. Anticoagulation and antiplatelet therapy are ineffective to prevent a cardioembolic stroke in patients with CCMA, because the mechanism of embolization from CCMA lesions is unlikely to be related to thrombi. As an alternative, surgical treatment has been recommended by several investigators in patients who suffered a CVE.

Fig. (3). Microscopic appearance of left middle cerebral artery. The lumen is occluded by amorphous caseous debris material (arrow). Masson trichrome stain. (Reprinted from Pathology International, Volume 62, Issue 7, 2012, 496-499). Taka-aki Matsuyama, Hatsue Ishibashi-Ueda, Yoshihiko Ikeda, Kazuyuki Nagatsuka, Kotaro Miyashita, et al. Critical multi-organ emboli originating from collapsed, vulnerable caseous mitral annular calcification [25]. (Reprinted with permission from John Wiley and sons).

THERAPEUTIC IMPLICATIONS

Many investigators have suggested that conservative management is justified if the diagnosis of CCMA can be made by echocardiography in asymptomatic patients [10 - 13]. However, there is no consensus on the optimal management for CCMA, as stated by Elgendi and Conti [13] in a recent review article. The authors suggest that, in most cases, conservative management for this lesion is sufficient, and that anticoagulation should be considered only in patients with CCMA who present with embolic manifestations [18, 22, 28]. In contrast, several authors recommend surgical intervention for associated mitral valvular dysfunction (either stenosis or regurgitation), embolic manifestations, or when it is impossible to rule out the possibility of a tumor.

The diagnosis of CCMA should be a major reason for concern because of the high prevalence of embolic stroke, which is likely attributed to embolization of caseous necrotic debris. Although anticoagulant therapy has been considered for some of these patients, anticoagulation is ineffective to prevent a cardioembolic stroke in these patients. As suggested by Corre and colleagues [28], further studies are needed to resolve the optimal treatment to decrease the
Risk of Cerebral Embolization with Caseous Calcification

The Open Cardiovascular Medicine Journal, 2016, Volume 10

227

risk of embolization in patients with CCMA. Thus, it is important to differentiate CCMA from MAC. Although MAC can be a nidus for thrombus formation, and has been described as a possible mechanism of stroke, the mechanism of embolization from CCMA lesions is unlikely to be related to thrombi, because review of all cases of CCMA presenting with a stroke revealed no thrombus formation and no other intracardiac source of embolism.

This may be an argument in favor of elective surgical resection of the CCMA lesion in asymptomatic patients who are good surgical candidates, because anticoagulation and antiplatelet therapy are probably ineffective to prevent a cardioembolic stroke in patients with CCMA. This suggestion is also based on the fact that the reported surgical mortality was quite acceptable (8.1%), especially considering that 43.2% (16 of 37) of the surgical patients were ≥70 years-old.

CONCLUSION

Despite the fact that several reports suggest that CCMA is a benign condition, patients with CCMA may be at increased risk of embolic strokes, which are unrelated to atrial fibrillation. The high prevalence of cerebral embolization from CCMA is likely attributed to spontaneous fistulization and embolization of caseous necrotic debris. Most authors agree that surgical treatment is indicated in symptomatic patients with CCMA associated with severe mitral regurgitation or stenosis, and in patients who present with an embolic stroke. However, there is no consensus on the optimal management of asymptomatic patients with CCMA. Based on our review, it would be reasonable to consider elective surgical resection of CCMA masses in asymptomatic patients who are good surgical candidates, and also in selected elderly patients, because anticoagulation and antiplatelet therapy are ineffective to prevent a cardioembolic stroke in patients with CCMA.

STUDY LIMITATIONS

One possible source of bias is that patients who present with adverse events (like a stroke) are more likely to be published as case reports, and the exact denominator of patients with CCMA (without a stroke) is not known. Also, the precise prevalence of AF in the published CCMA cases is unknown, because the articles reviewed on patients with CCMA presenting with a stroke did not indicate whether continuous electrocardiographic monitoring or Holter were used to enhance detection of AF, except for one paper [28]. Unfortunately, the only way to determine the incidence of stroke in patients with CCMA would be to follow for several years a cohort of patients with and without CCMA who were stroke-free at baseline, and determine whether those with CCMA have a higher risk of subsequent strokes, independent of other risk factors. However, this type of study would be impractical because of the small number of patients with CCMA.

ETHICS REVIEW

The institutional Human Research Review Committee has reviewed and approved this research study on January 16, 2014. A copy of the New Study Approval is available for review by the Editor-in-Chief of this journal on request.

APPENDIX

All cases of CCMA reported in the English-language literature, listed in chronological order of publication.

Appendix 1. Prevalence of cerebrovascular events and atrial fibrillation in reported cases of CCMA.

| Author            | Year | Pts (n) | Age | Sex | Symptoms | Risk factors | TTE findings | Treatment | F/U |
|-------------------|------|---------|-----|-----|----------|--------------|--------------|-----------|-----|
| Pomerance [14]    | 1970 | 7       | 50-90 | 6F  | ?        | ?            | -----        | -----     | -----|
|                   |      |         |      | 1M  | ?        | ?            | -----        | -----     | -----|
| Kronzon           | 1983 | 3       | 73  | F   | syncope  | HT           | calcified mass | observation | sudden death |
|                   |      |         |     |     |          |              |              |           |      |
|                   |      |         | 23  | 1F  | CHF      | ?            | calcified mass | pericardiectomy | ----- |
|                   |      |         |     |     |          |              |              |           |      |
|                   |      |         | 61  | 1M  | CHF      | CAD + AF     | calcified mass + severe MR | resection + MVR | ----- |
| Teja              | 1987 | 1       | 57  | F   | DOE      | HT           | cardiac tumor | resection of tumor | ----- |
| Namura [33]       | 1992 | 1       | 60  | F   | asymptomatic | ESRD + HT | calcified mass | observation | death (CVE) |
| Gilbert           | 1997 | 1       | 65  | F   | DOE      | ?            | MV abscess + severe MR | resection + MVR | ----- |
| Isotalo           | 1999 | 1       | 42  | M   | empyema  | ESRD+HT+CAD  | -----        | observation | death |

28
| Author  | Year | Pts (n) | Age | Sex | Symptoms | Risk factors | TTE findings | Treatment | F/U |
|---------|------|---------|-----|-----|----------|--------------|--------------|-----------|-----|
| Koito   | 1999 | 1       | 58  | F   | asymptomatic | ESRD         | EM/CL        | observation | regression |
| Harpaz  | 2001 | 19      | 54-76 | F   | CVE 5 + sync 2 | HT 9 + DM 4 | EM/CL 19  | observation | 16 | 3 deaths |
| Morgan  | 2003 | 1       | 83  | F   | ?         | ?            | EM/CL        | observation | ----- |
| Novaro  | 2004 | 1       | 74  | F   | lethargy  | ?            | EM/CL        | observation | ----- |
| Alkadhi | 2005 | 1       | 70  | F   | DOE + syncope | HT         | EM/CL + severe MR | resection + annuloplasty | ----- |
| De Conti| 2005 | 2       | 64  | F   | DOE      | HT          | calcified mass | observation | ----- |
| Gramenzi| 2005 | 1       | 74  | F   | asymptomatic | ESRD + HT | EM/CL | observation | resolution |
| Morgan  | 2003 | 1       | 83  | F   | ?         | ?            | EM/CL        | observation | ----- |
| Novaro  | 2004 | 1       | 74  | F   | lethargy  | ?            | EM/CL        | observation | ----- |
| Alkadhi | 2005 | 1       | 70  | F   | DOE + syncope | HT         | EM/CL + severe MR | resection + annuloplasty | ----- |
| De Conti| 2005 | 2       | 64  | F   | DOE      | HT          | calcified mass | observation | ----- |
|Gramenzi| 2005 | 1       | 60  | F   | asymptomatic | ESRD + HT | EM/CL | observation | resolution |
| Davidson [15] | 2006 | 1 | 79  | F   | CVE (retina) | HT          | calcified mass + severe MR | resection + MVR | ----- |
| de Vrey | 2006 | 1       | 61  | M   | DOE      | HT + DM + DLP | calcified mass in LV | resection + annuloplasty | ----- |
| Di Bella| 2006 | 1       | 84  | F   | DOE      | HT + AF      | calcified mass + moderate MR | observation | ----- |
| Izgi    | 2006 | 1       | 62  | F   | angina   | HT + DLP    | EM/CL        | observation | ----- |
| Kato    | 2006 | 1       | 56  | F   | DOE      | ESRD + AF   | cardiac tumor + severe MS | resection + MVR | ----- |
| Marcu   | 2006 | 1       | 70  | M   | asymptomatic | CAD (CAB) | calcified mass | observation | ----- |
| Vanovermeire | 2006 | 1 | 79  | F   | DOE      | HT + DLP    | myxoma + severe MR | resection + MVR | death |
| Fernandes [12] | 2007 | 6 | 69  | F   | DOE + palpitations | HT + AF | EM/CL + moderate MR | observation | ----- |
| Johanssen| 2007 | 1 | 58  | M   | possible IE | ESRD + HT | possible vegetation | observation | ----- |
| Lubarsky [16] | 2007 | 1 | 70  | F   | CVE      | HT + DM (NSR) | MAC | observation | ----- |
| Poh [17] | 2007 | 1 | 74  | F   | CVE      | HOCM        | cardiac tumor | resection of tumor | ----- |
| Yokoyama| 2007 | 1       | 54  | M   | asymptomatic | ESRD + AVR | EM/CL | observation | progression |
| Zeina   | 2007 | 1       | 55  | M   | DOE      | HT + DLP    | calcified mass | observation | regression |
| Arora   | 2008 | 1       | 71  | M   | syncope  | ?           | EM/CL        | observation | ----- |
| Deluca  | 2008 | 14      | 59-79 | 10F | syncope 2 + MI 1 | ESRD 2 + AF 5 | EM/CL 14 + moderate MR | observation | CVE 1 + sync 2 |
| Di Bella| 2008 | 1       | 68  | M   | angina   | ?           | calcified mass | resection + MVR+CAB | ----- |
| Minardi | 2008 | 1       | 69  | F   | CHF      | DLP + PAF   | EM/CL + severe MR | resection + annuloplasty | ----- |
| Monti   | 2008 | 2       | 87  | F   | asymptomatic | ?            | cardiac tumor | observation | ----- |
| Biteker | 2009 | 1       | 73  | F   | DOE + palpitations | HT | calcified mass | observation | ----- |
| Blankstein| 2009 | 1 | 66  | M   | ?        | ?           | calcified mass | observation | progression |
| Correale| 2009 | 1       | 76  | F   | asymptomatic | HT           | MV tumor     | observation | resolution |
| Durão   | 2009 | 1       | 73  | F   | MI (embolus) | ?           | EM/CL        | resection + MVR | ----- |
| Fernández| 2009 | 1       | 75  | F   | asymptomatic | HT + PAF    | MV tumor     | observation | ----- |
| Marci   | 2009 | 2       | 82  | F   | palpitations | HT + PAF    | EM/CL        | observation | ----- |
|         |      | 71  | F   | MI | ? | EM/CL | observation | ----- |
| Author    | Year | Pts (n) | Age | Sex | Symptoms       | Risk factors            | TTE findings       | Treatment                | F/U |
|-----------|------|---------|-----|-----|----------------|-------------------------|--------------------|--------------------------|-----|
| Salisbury | 2009 | 1       | 62  | M   | DOE            | AF                      | EM/CL + severe MR  | refused surgery          | -----|
| Vizzardi  | 2009 | 1       | 65  | F   | DOE            | HT + DLP + LDP          | EM/CL              | observation              | -----|
| Warsame   | 2009 | 1       | 60  | M   | angina         | HT + DLP + CAD          | EM/CL              | observation              | -----|
| Assudani  | 2010 | 1       | 77  | F   | syncope        | HT + HOCM               | EM/CL + severe MR  | MVR + myectomy           | -----|
| Higashi [18] | 2010 | 1       | 76  | F   | CVE            | ESRD + HT (NSR)         | EM/CL              | anticoagulation          | -----|
| Jiménez   | 2010 | 1       | 63  | M   | DOE            |                        |                    | calcified mass           | observation              | -----|
| Rojas     | 2010 | 1       | 67  | F   | angina + VTach |                        |                    | tumor + moderate MR      | ?                          | ?    |
| Shrink    | 2010 | 3       | 63  | M   | asymptomatic   | (colon cancer)          |                    | EM/CL + severe MR        | observation              | -----|
| Spina     | 2010 | 1       | 81  | M   | DOE            | ?                       |                    | calcified mass + severe MR | resection + MVR        | -----|
| Stamou [19] | 2010 | 1       | 84  | M   | CVE (retina)   | ?                       |                    | tumor + severe MR + AS   | MVR + AVR                | -----|
| Chahal    | 2011 | 1       | 73  | F   | angina         | ?                       | EM/CL + dyn LVOTO    | observation              | -----|
| Chevalier [20] | 2011 | 1       | 72  | F   | CVE            | HT                      | calcified cyst      | resection + annuloplasty | -----|
| Collins   | 2011 | -       | -   | -   | -              | -                      | -                  | -                        | -   |
| Dubrey    | 2011 | 2       | 78  | F   | DOE            | HT + AF                 | cardiac tumor + AS  | observation              | -----|
| Garcia-L  | 2011 | 3       | 66  | F   | CHF            | HT + AF                 | tumor + moderate MR | observation              | -----|
| Garcia-L  | 2011 | 3       | 66  | F   | angina         | HT + DLP                | MV tumor            | resection + CAB          | -----|
| Akpinar   | 2012 | 1       | 68  | F   | syncope        | HT + CHB                | calcified tumor     | pacemaker                | -----|
| Akram [23] | 2012 | 1       | 59  | F   | CVE            | ESRD + HT               | EM/CL              | observation              | -----|
| Chen [24] | 2012 | 1       | 76  | F   | CVE + angina   | HT + DLP                | EM/CL + severe AS   | refused surgery          | -----|
| Fujiwara  | 2012 | 1       | 73  | F   | syncope        | CHB                     | cardiac tumor + moderate MS | resection + MVR     | -----|
| Lee       | 2012 | 1       | 60  | M   | angina         | HT + DM                 | cardiac tumor       | resection + CAB          | -----|
| Martinez  | 2012 | 1       | 76  | F   | palpitations   | AF + DLP                | EM/CL              | observation              | -----|
| Matsuyama [25] | 2012 | 1       | 92  | F   | CVE + CHF      | HT + DM + DLP           | MAC                | observation              | death (CVE) |
| McKernan [26] | 2012 | 1       | 84  | F   | CVE + MI       | ?                       | myxoma + moderate MR | resection + annuloplasty | death (reop) |
| Motwani [27] | 2012 | 1       | 64  | M   | CVE            | ?                       | MAC                | observation              | regression |
| Ribeiro   | 2012 | 1       | 84  | F   | CHF            | HT + DLP                | calcified mass + severe MR | refused surgery      | -----|
| Srivatsa  | 2012 | 1       | 75  | M   | asymptomatic   | HT + DLP + CAD          | calcified mass     | observation              | -----|
| Ueyama    | 2012 | 1       | 76  | F   | ?              | ?                       | cardiac tumor       | resection + MVR          | -----|
| Alizade   | 2013 | 1       | 79  | F   | CHF            | ?                       | cardiac tumor + severe MR | surgery (?)            | ?    |
| Alzuhairi | 2013 | 1       | 67  | F   | fatigue        | HT + DM + DLP           | possible myxoma     | observation              | -----|
| Corre [28] | 2013 | 1       | 83  | F   | CVE            | (NSR)                  | tumor + moderate MR | anticoagulation          | -----|
| Elgendy [13] | 2013 | 1       | 41  | F   | DOE + IE       | ESRD + DM               | EM/CL + severe MS   | resection + MVR          | -----|
| Franca    | 2013 | 1       | 83  | F   | DOE            | HT + DLP                | EM/CL              | observation              | -----|
| Kalayci [29] | 2013 | 1       | 59  | F   | CVE            | HT (NSR)                | calcified mass + severe MR | resection + MVR    | -----|
| Kawasaki  | 2013 | 1       | 69  | M   | angina         | HT + DM + DLP           | ----- | CAB only                | -----|
| Author      | Year | Pts | Age | Sex | Symptoms     | Risk factors | TTE findings               | Treatment                        | F/U |
|------------|------|-----|-----|-----|--------------|--------------|----------------------------|----------------------------------|-----|
| Kydd       | 2013 | 1   | 77  | M   | syncope      | ?            | cardiac tumor               | ?                                | ?   |
| Mallat     | 2013 | 1   | 82  | F   | asymptomatic | HT + DLP     | calcified mass              | observation                      | -----|
| Plank      | 2013 | 1   | 61  | F   | asymptomatic | HT           | calcified mass + LVOTO     | observation                      | -----|
| Pomeroy    | 2013 | 1   | 90  | M   | angina       | DM + CAD     | LA tumor vs MAC             | observation                      | -----|
| Pugliatti  | 2013 | 1   | 78  | F   | CVE          | DM (NSR)     | LA thrombus + moderate MR   | observation                      | -----|
| Demirkol   | 2014 | 1   | 78  | F   | DOE          | HT+DM+DLP    | calcified mass              | observation                      | -----|
| Mallisho   | 2014 | 1   | 78  | F   | CVE          | (NSR)        | EM/CL                      | refused surgery                  | -----|
| Możeńska   | 2014 | 1   | 76  | F   | asymptomatic | HT+DM+DLP    | possible myxoma             | observation                      | -----|
| Sequeira   | 2014 | 1   | 39  | F   | CVE + CHF    | ESRD + HT    | MAC + severe MS             | resection + MVR                   | -----|
| Shah       | 2014 | 1   | 77  | F   | DOE          | ?            | LA tumor + moderate MR      | observation                      | -----|

AF = atrial fibrillation; AS = aortic stenosis; AVR = aortic valve replacement; BFB = bifascicular block; CAB = coronary artery bypass; CAD = coronary artery disease; CCMA = caseous calcification of the mitral annulus; CHB = complete heart block; CHF = congestive heart failure; CVE = cerebrovascular event; DLP = dyslipidemia; DM = diabetes mellitus; DOE = dyspnea on exertion; dyn = dynamic; EM/CL = echogenic mass with central luencies; ESRD = end-stage renal disease; F = female; F/U = follow-up; HOCM = hypertrophic obstructive cardiomyopathy; HT = hypertension; IE = infective endocarditis; LA = left atrium; LVOTO = left ventricular outflow tract obstruction; M = male; MAC = mitral annulus calcification; MI = myocardial infarction; MR = mitral regurgitation; MS = mitral stenosis; MV = mitral valve; MVR = mitral valve replacement; NSR = normal sinus rhythm; PAF = paroxysmal atrial fibrillation; palpit = palpitations; reop = reoperation; sync = syncope; TEE = transesophageal echo; TTE = transthoracic echo; VTach = ventricular tachycardia.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

The authors are very grateful to Michael G Lopez, CCT (Cardiology PACS Administrator) for his technical assistance with echocardiography imaging.

REFERENCES

[1] Arboix A, Alió J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. Curr Cardiol Rev 2010; 6(3): 150-61. [http://dx.doi.org/10.2174/157340310791658730] [PMID: 21804774]

[2] Fulkerson PK, Beaver BM, Auseon JC, Graber HL. Calcification of the mitral annulus: etiology, clinical associations, complications and therapy. Am J Med 1979; 66(6): 967-77. [http://dx.doi.org/10.1016/0002-9343(79)90452-2] [PMID: 156499]

[3] Furlan AJ, Craciun AR, Salcedo EE, Mellino M. Risk of stroke in patients with mitral annulus calcification. Stroke 1984; 15(5): 801-3. [http://dx.doi.org/10.1161/01.STR.15.5.801] [PMID: 6474529]

[4] Lin CS, Schwartz IS, Chapman I. Calcification of the mitral annulus fibrosus with systemic embolization. A clinicopathologic study of 16 cases. Arch Pathol Lab Med 1987; 111(5): 411-4. [PMID: 3566471]

[5] Nair CK, 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(7): 465-70. [http://dx.doi.org/10.1016/0002-9149(89)90321-4] [PMID: 2916432]

[6] Benjamin EJ, Plehn JF, D’Agostino RB, et al. Mitral annular calcification and the risk of stroke in an elderly cohort. N Engl J Med 1992; 327(6): 374-9. [http://dx.doi.org/10.1056/NEJM199208063270602] [PMID: 1625711]

[7] Aronow WS, Schoenfeld MR, Gustin H. Frequency of thromboembolic stroke in persons ≥ 60 years of age with extracranial carotid arterial disease and or mitral anular calcium. Am J Cardiol 1992; 70: 123-4. [http://dx.doi.org/10.1016/0002-9149(92)91408-V] [PMID: 1615858]

[8] Boon A, Lodder J, Cheriex E, Kessels F. Mitral annular calcification is not an independent risk factor for stroke: a cohort study of 657 patients. J Neurol 1997; 244(9): 535-41. [http://dx.doi.org/10.1007/s004150050140] [PMID: 9352449]

[9] Kizer JR, Wiebers DO, Whisnant JP, et al. Mitral annular calcification, aortic valve sclerosis, and incident stroke in adults free of clinical cardiovascular disease: the Strong Heart Study. Stroke 2005; 36(12): 2533-7. [http://dx.doi.org/10.1161/01.STR.0000190005.09442.ad] [PMID: 16254219]
Matsuyama TA, Ishibashi-Ueda H, Ikeda Y, Lubarsky L, Jelnin V, Marino N, Hecht HS. Images in cardiovascular medicine. Caseous calcification of the mitral annulus by 64-detector-computed tomography. J Am Soc Echocardiogr 2008; 21(7): 828-33.
[http://dx.doi.org/10.1016/j.echo.2007.12.004] [PMID: 1822637]

Fernandes RM, Branco LM, Galrinho A, McKernan NP, Culp WC Jr, Knight WL, Johnston WE, Sniecinski RM, Lazar HL. CASE 2--2012 intraoperative diagnosis and management of caseous mitral annular calcification with critical organ embolization. J Thorac Cardiovasc Surg 2009; 138(1): 174-9.
[http://dx.doi.org/10.1016/j.jtcvs.2008.09.047] [PMID: 19406335]

Harpaz D, Auerbach I, Vered Z, Motro M, Tobar A, Rosenblatt S. Caseous calcification of the mitral annulus: a neglected, unrecognized cause of embolic stroke. J Am Soc Echocardiogr 2011; 24(4): 365-73.
[http://dx.doi.org/10.1016/j.echo.2010.11.004] [PMID: 21265626]

Gulati A, Chan C, Duncan A, Raza S, Kilner PJ, Pepper J. Multimodality cardiac imaging in the evaluation of mitral annular caseous calcification. J Cardiovasc Magn Reson 2012; 14: 182.
[http://dx.doi.org/10.1186/1532-429X-14-182] [PMID: 22875831]

Corre J, Leroux L, Coste P. Caseous necrosis of mitral annulus: a rare cause of stroke. Case Rep Cardiol 2013; 2013: 841307.
[http://dx.doi.org/10.1155/2013/841307] [PMID: 2384241]

Kalayci A, Karabay CY, Sismanoglu M, et al. Caseous calcification of mitral annulus. Perfusio 2014; 29(3): 279-80.
[http://dx.doi.org/10.1177/0267659113505639] [PMID: 24045035]

Pugliatti P, Piccione MC, Ascenti G, et al. Images in cardiovascular medicine: caseous calcification of the mitral annulus. Echocardiography 2013; 30(2): E30-2.
[http://dx.doi.org/10.10111/echo.12033] [PMID: 23167713]
[31] Mallisho M, Hwang I, Alsafwah SF. Liquefaction necrosis of mitral annulus calcification. J Clin Ultrasound 2014; 42(6): 382-3. [http://dx.doi.org/10.1002/jcu.22115] [PMID: 24420234]

[32] Sequeira A, Morris L, Patel B, et al. Calcific mitral stenosis in the hemodialysis patient. Hemodial Int 2014; 18(1): 212-4. [http://dx.doi.org/10.1111/hdi.12094] [PMID: 24015751]

[33] Namura M, Kanaya H, Ohka T. Spherical liquefaction necrosis of mitral annular calcification in a chronic dialysis patient--liquefaction necrosis of mitral annular calcification. Jpn Circ J 1992; 56(8): 866-70. [http://dx.doi.org/10.1253/jcj.56.866] [PMID: 1527899]