Contents lists available at ScienceDirect



IJC Heart & Vasculature



journal homepage: http://www.journals.elsevier.com/ijc-heart-and-vasculature

Cardiac calcified amorphous tumor: A systematic review of the literature



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ARTICLE INFO

Article history: Received 29 September 2014 Accepted 20 January 2015 Available online 29 January 2015

Keywords: Calcified amorphous tumor Heart Nonneoplastic Mass Review

ABSTRACT

Background: Calcified amorphous tumor (CAT) of the heart is a rare non-neoplastic intracavitary cardiac mass. Several case reports have been published but large series are lacking. Objective: To determine clinical features, current management and outcomes of this rare disease. Design: A systematic review of all articles reporting cases of CAT in order to perform a pooled analysis of its clinical features, management and outcomes. Data sources: An electronic search of all English articles using PUBMED was performed. Further studies were identified by cross-referencing from relevant papers. Inclusion criteria: We restricted inclusion to articles reporting cases of CAT in the English language literature published up to July 2014. Data extraction: One author performed data extraction using predefined data fields. Results: A total of 27 articles, reporting 42 cases of CAT were found and included in this review. Conclusion: In this review, the most frequent presenting symptoms were dyspnea and embolic events. Mitral valve and annulus were the most frequent location of CAT. Surgery was most of the time required to confirm diagnosis, and was relatively safe. Overall outcome after surgical resection was good. © 2015 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Calcified amorphous tumor (CAT) of the heart is a rare nonneoplastic intracavitary cardiac mass, with microscopic features of calcification and amorphous fibrinous material. Since its first description in 1997 as a specific entity by Reynolds and colleagues [1], several case reports have been published. Still, large series are lacking and, to date, we have no clear overview of the scope of the disease. In this article, we aim to perform a systematic review of the literature and to build a registry of all published cases of CAT in order to determine its clinical features, current management and prognosis.

2. Methods

We performed a systematic search using PubMed, according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines, for articles reporting cases of CAT in the English language literature. Additional articles were identified by a manual search of references of relevant papers. Authors of articles were contacted, if needed, to obtain additional data that was of interest to

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our review. We included all articles published since the first report (May 1st, 1997) up to July 31st, 2014. The titles and abstract of the identified articles were screened to determine if they met inclusion criteria. Full text articles were then retrieved and reviewed. Reference lists of the retrieved articles were searched for relevant literature. Predetermined variables were first author, year of publication, title, journal, patient clinical informations (age, gender...), tumor size and location, presenting symptoms, associated conditions, treatment, follow-up and outcome.

3. Results

A total of 27 articles reporting 42 cases of CAT were found. Table A lists the clinical characteristics of the patients. Table B reports the pooled clinical data. The mean age at presentation was 54 years (range 16–85), with a female predominance (64%). CAT was detected in all cardiac chambers, but predominated on the mitral valve or annulus (36%), in the right atrium (21%) or the right ventricle (17%). Mean tumor size was 29×17 mm, ranging from 1.7 mm punctate lesion to very large masses (20 × 90mm) or even diffuse left ventricular (LV) infiltration.

The most frequent presenting symptom was dyspnea (45%) followed by syncope (21%). Pulmonary or systemic embolization was reported in 31% of the cases. CAT was discovered incidentally in 17% of the patients.

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Table A Clinical characteristics of published

Clinical characteristics of published cases of calcified amorphous tumor.

Report	Case no	Sex	Age	Tumor site	Presentation	Follow-up	Comorbidities/underlying disease	Size (mm)	Treatment
Reynolds et al. (1997) [1]	1	М	16	LA	Exercise intolerance, near-syncope	Residual calcifications in LA	Mediastinal RT and chemo for neuroblastoma at age 3 months	$\begin{array}{c} 45\times23\times\\ 3\end{array}$	Surgical excision
	2	М	30	LV	Near-syncope, chest pain, palpitations	Small residual calcified nodule in LV, 3 years 6 months	None	$\begin{array}{l} 30 \times 12 \times \\ 10 \end{array}$	Surgical excision
	3	F	33	RV	Shortness of breath	Lost to follow-up	Recurrent PE	20 imes 23	Surgical excision
	4	F	34	RV	Vertigo, orthopnea	Lost to follow-up	Systemic lupus-like illness	35 imes 25 imes 15	Surgical excision
	5	F	48	MV	CVA	NED 4 months	MR and TR, cleft mitral valve leaflet	30 × 2	Surgical excision
	6	F	60	LV, MV	CVA, retinal emboli	Alive, left jugular foramen tumor	MR and AR with enlarged LA	15	Surgical excision
	7	М	65	RV, TV	Shortness of breath	Died of non cardiac cause 30 days after diagnosis	CAD, recurrent PE	33 × 27 × 12	No surgery
	8	F	67	RA	Syncope	NED 18 years	CAD, CHF	65 imes 50 imes 50	Surgical excision
	9	М	67	LV	Syncope	NED 1 year 4 months	CAD, ESRD, tumoral calcinosis	$15\times3\times3$	Surgical excision
	10	F	73	RA, SVC	Dizziness, dyspnea on exertion	NED 1 year 5 months	Diverticulitis, partial resection, total parenteral nutrition	20 imes 90	Surgical excision
	11	F	75	LV	"Funny sensation" in chest	NED 6 years 11 months	Diabetes mellitus	$\begin{array}{c} 20\times20\times\\ 20\end{array}$	Surgical excision
Chaowalit et al. (2005) [15]	12	F	20	RV	PE, dyspnea	N/A	Chest trauma 3 years earlier	$\begin{array}{c} 40 \times 22 \times \\ 18 \end{array}$	Surgical excision
Lewin et al. (2006) [12]	13	F	60	RV	Syncope	Died 1 day after surgery	No prior cardiac history.	$\begin{array}{l} 40\times 30\times \\ 25\end{array}$	Surgical excision
Fealey et al. (2007) [14]	14	F	20	RV	PE, cough, shortness of breath, fatigue	Residual calcified RV nodule, recurrent PE 2 years after surgical resection, second resection	None	$\begin{array}{l} 40\times35\times\\ 25\end{array}$	Surgical excision
Khulbey et al. (2008) [16]	15	М	26	RA	Prolonged fever and constitutional symptoms		Atrial septal closure	$\begin{array}{c} 30 \times 20 \times \\ 20 \end{array}$	Surgical excision
Inamdar et al. (2008) [17]	16	F	85	MA	Chronic fatigue	N/A	MAC, ESRD, HTN, DM	23 imes 9	Surgical excision
Ho et al. (2008) [3]	17	Μ	44	LV and mitral chordal apparatus diffuse infiltration	Shortness of breath on exertion	N/A	Severe LV systolic dysfunction	Diffuse infiltration	Referred for heart transplantation
Gutierrez et al. (2008) [18]	18	М	35	RA	Septic shock	NED 2 months	ESRD (Alport syndrome), HTN	$\begin{array}{c} 20 \times 15 \times \\ 14 \end{array}$	Surgical excision
Flynn et al. (2009) [19]	19	М	Young	RV	Syncope, PE, severe tricuspid	N/A	N/A	$\begin{array}{c} 14 \times 12 \times \\ 5 \end{array}$	Surgical excision and pulmonary TEA
Habib et al. (2010) [5]	20	F	58	MA, MV, diffuse LV infiltration	regurgitation Ventricular tachycardia	Medical treatment, persistent VT	Ventricular tachycardia, SCD, mild mitral regurgitation	Diffuse infiltration	Medical treatment
Gupta et al. (2010) [20]	21	F	40	RA	Shortness of breath on exertion, cough, fatigue	NED 8 months	None	$\begin{array}{c} 30 \times 20 \times \\ 15 \end{array}$	Surgical excision
Vaideeswar et al. (2010) [13]	22	М	56	RA	Progressive shortness of breath, PE, blurring of vision	NED 2 years	N/A	N/A	Surgical excision and pulmonary TEA
	23	М	35	RA	Exertional dyspnea, dizziness on walking, PE	Died 7 days after surgery	N/A	$\begin{array}{c} 32\times23\times\\ 13\end{array}$	Surgical excision and pulmonary TEA
Kubota et al.	24	F	64	LV, MA	Incidental	NED 3 years	ESRD, DM	3×27	Surgical excision
(2010) [8] Creaney et al	25 26	M F	44 69	LV, PM LV, MV	Incidental Left-sided heart	NED 3 years	ESRD	6 × 28	Surgical excision
Greaney et al. (2011) [21]	20	I,	69	LV, IVI V	failure, stroke	NED 3 months	Severe COPD	20	Surgical excision
Ananthakrishna et al. (2011) [22]	27	F	45	LV	Breathlessness	NED 4 months	Rheumatic heart disease	$\begin{array}{l} 40\times35\times\\ 20\end{array}$	Surgical excision, mitral and aortic valve replacement
(22) Vlasseros et al. (2011) [2]	28	F	65	LV, MV	Visual loss (central retinal artery occlusion)	NED 8 months	DM, HTN	$\begin{array}{c} 26\times17\times\\ 5\end{array}$	Surgical excision and MVR
Lin et al. (2011) [23]	29	F	74	LA	Incidental	NED 6 months	None	14×27	Surgical excision
(2011) [23] De Sousa et al. (2011) [24]	30	М	17	TV	Cardiomegaly	NED 3 months	Ebstein anomaly	$\begin{array}{c} 15 \times 15 \times \\ 13 \end{array}$	Surgical excision and TV valvuloplasty

Table A (continued)

Report	Case no	Sex	Age	Tumor site	Presentation	Follow-up	Comorbidities/underlying disease	Size (mm)	Treatment
Fujiwara et al.	31	М	58	MA	Incidental	N/A	ESRD, MAC	N/A	Surgical excision
(2012) [7]	32	М	65	MA	Incidental	N/A	ESRD, MAC	7×2	Surgical excision
Nishigawa et al. (2012) [25]	33	F	78	LA	Incidental	N/A	MAC	1.7	Surgical excision
Nazli et al. (2013) [4]	34	F	54	LV	Central retinal artery occlusion	NED 1 year	Hypothyroidism	38 imes 25	Surgical excision
Yamamoto et al. (2013) [26]	35	F	82	MA	Progressive heart failure	N/A	N/A	37 imes 4	Surgical excision
Kawata et al. (2013) [9]	36	М	59	MA	Incidental	N/A	DM, ESRD, MAC	28 imes 6	Surgical excision
Rehman et al. (2014) [27]	37	F	62	RV	Severe exertional dyspnea, chronic pulmonary embolism	N/A	Atrial septal defect	30 imes 20	Surgical excision
Mohamedali et al. (2014) [10]	38	F	69	MA	Dyspnea, epigastric pain	N/A	ESRD, MAC	$7 \times 3 \times 3$	Surgical excision
Choi et al. (2014) [28]	39	F	57	RA	Dyspnea, fever, cough	NED 1 year	N/A	$\begin{array}{c} 19 \times 13 \times \\ 8 \end{array}$	Surgical excision
Hussain et al. (2014) [29]	40	F	80	LV	Near-syncope	N/A	HTN, dyslipidemia, CAD, lung adenocarcinoma	50	Surgical excision
	41	F	69	MV	Palpitations	N/A	HTN, DM, dyslipidemia	10 imes 10	Surgical excision and MV valvuloplasty
	42	F	60	RA	Dyspnea	N/A	Breast cancer 10 years earlier	16 imes 23	Surgical excision

AR: aortic regurgitation, CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease, CVA: cerebrovascular accident, DM: diabetes mellitus, ESRD: end-stage renal disease, F: female, HTN: hypertension, LA: left atrium, LV: left ventricle, M: male, MA: mitral annulus, MAC: mitral annular calcification, MR: mitral regurgitation, MV: mitral valve, N/A: not available, NED: no evidence of disease, PE: pulmonary embolism, PM: papillary muscle, RA: right atrium, RT: radiotherapy, RV: right ventricle, SCD: sudden cardiac death, TEA: thromboendarterectomy, TR: tricuspid regurgitation, TV: tricuspid valve, VT: ventricular tachycardia.

The most frequently associated conditions were valve disease (31%) concomitant with MAC (14%), end-stage renal disease (ESRD) (21%), diabetes (14%), and coronary artery disease (12%).

Surgery was performed in most of the reported cases (93%), with a vast majority of favorable outcomes. Nonetheless, two patients died postoperatively (5%). Medical treatment was favored in 2 cases presenting diffuse calcium infiltration of the LV. Recurrence occurred in 1 case and residual calcifications were observed in 14% on follow-up imaging studies. The mean follow-up without evidence of disease was 12 months.

4. Discussion

This review, encompassing all published cases of CAT allows giving a scope of this rare disease. However, there might have been some bias. Indeed, the condition is inherently underreported, since suspected but unoperated and thus unconfirmed cases were probably, were probably most of the time not reported.

Pathophysiologic hypotheses involving an organized thrombus origin favored by hypercoagulability [1] and/or phosphocalcic metabolism abnormalities [2] have been raised, but the pathogenesis of CAT remains poorly understood. Our review does not support the hypothesis of hypercoagulability.

Although endomyocardial biopsy was used for diagnosis in one case of diffuse LV infiltration [3], ruling out other cardiac masses or neoplasms requires surgery for histological confirmation in most of the cases, as clinical presentation of patients with cardiac masses tends to be similar. Current imaging cardiac techniques do not specifically differentiate cardiac CAT from other masses, but some features may contribute to establish the diagnosis [4]. On echocardiography, CAT usually appears as a calcified endocavitarian mass that may be located in any cardiac chamber, on any valves or on valvular annuli (Fig. 1). Size can vary from small punctate lesions to very large masses. Diffuse LV myocardial infiltrations have been reported [3,5] but these forms probably constitute a distinct type of disease.

Because of the calcifications, CAT can be mistaken for osteosarcoma, calcified myxoma or vegetations on imaging studies but the histopathologic appearance of the former is straightforward and entirely benign as it is composed of nodular calcium deposits surrounded by an amorphous hyalinized material [6] (Fig. 2). Clinical characteristics of the patient are also helpful, as patients frequently present concomitant conditions such as pre-existing valve disease (MAC for instance), endstage renal disease (ESRD), or other cardiovascular risk factors. MAC-

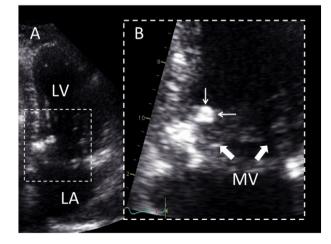


Fig. 1. 2D echocardiography of CAT (personal unpublished data). Echocardiographic four chamber view (Panel A) showing a mobile mass of 7×9 mm, attached on the ventricular side of the mitral annulus, close to the posterior commissure. Zoom view (Panel B) allows characterizing the relationship of the mass (small arrows) with the mitral leaflets (large arrows). LV, left ventricle; LA, left atrium.



Fig. 2. CAT microscopic image (personal unpublished data). Microscopic findings showing heterogeneous calcium deposits with surrounding amorphous eosinophilic and fibrinous material (hematoxilin and eosin, original ×100).

related CAT seems to constitute a subgroup of CAT, and is usually associated with ESRD [7–10]. Kubota and colleagues proposed the descriptive term of "swinging calcified amorphous tumor" for mobile lesions arising from a MAC [8]. This subgroup of CAT seems to carry a high embolic risk, and rapid growth characteristics. Because of its mobile characteristics, one might postulate that CAT may causally contribute to the occurrence of stroke. However, the presence of MAC in itself is associated with an increased risk of stroke, independently of traditional risk factors [11]. In the current registry, CAT was associated with ESRD in 21% and with MAC in 14% of the patients.

The discovery of CAT may be incidental, but most of the time symptoms are related to embolization or obstruction, depending on its size

Table B

Demographic and clinical data of the population. (n = 42).

Variables	Values
Male gender	15 (36)
Age, years	54 ± 18
CAT localization	
Mitral valve or annulus	15 (36)
Right atrium	9 (21)
Right ventricle	7 (17)
Left ventricle	6 (14)
Left atrium	3 (7)
Tricuspid valve or annulus	2 (5)
Tumor size, mm	$29\pm16\times17\pm11$
Clinical presentation (multiple symptoms possible)	
Dyspnea	19 (45)
Syncope	9 (21)
Pulmonary embolism	8 (19)
Incidental	7 (17)
Systemic embolism	5 (12)
Chest pain	2 (5)
Other	9 (21)
Follow-up	
No evidence of disease, months	12 [2-216]
Residual disease	3 (14)
Recurrence	1 (5)
No data available (lost to follow-up or unavailable data)	21 (50)
Outcome	
Death (CAT or surgery related)	2 (5)
Associated conditions	
Valve disease	13 (31)
End stage renal disease	9 (21)
Mitral annulus calcification	6 (14)
Diabetes mellitus	6 (14)
Coronary artery disease	5 (12)
Hypertension	4 (10)
Congestive heart failure	2 (5)
Treatment	
Surgical excision	39 (93)
Other	3 (7)

Values are given as mean \pm SD, no. (%), or median [range].

and location. The most common presenting symptoms in this registry were dyspnea, embolic event and syncope. An embolic event is a frequent presenting condition and mobile lesions definitely indicate a higher embolic risk [8]. However, traditional cardiovascular risk factors are highly prevalent, which may contribute to the high prevalence of cerebrovascular events at presentation. Less frequently, atypical chest pain or ventricular arrhythmia may occur but the etiological role of the CAT is unclear [5]. The growth rate of CAT is largely unknown, but may be relatively fast, especially in MAC-related CAT. Indeed, tumors growing very rapidly in a time span of 6 weeks to 1 year have been reported [8,9].

Surgical resection remains the diagnostic and therapeutic standard for pedunculated lesions, although it carries some procedural risk: 2 patients (5%) died during the perioperative period [12,13]. Recurrence after surgery seems infrequent as only 1 patient presented recurrent disease 2 years after surgical resection [14].

5. Conclusions

Our systematic review, encompassing all published cases of CAT provides more insights into the clinical characteristics of this poorly known disease. Patients with CAT can present a large variety of symptoms, most of the time related to embolization or obstruction depending on the size and the location of the mass, but may also be discovered incidentally. CAT can arise from any cardiac chamber or valve, but in this review mitral valve and annulus appear to be its most frequent location and its size can vary from small punctate lesions to large pedunculated masses. Surgery is most of the time required to confirm diagnosis, and appears relatively safe. MAC-related CATs seem to constitute a subtype of this benign tumor, exhibiting specific characteristics including a rapid growth and a high embolic risk.

However, the natural history of the disease, its embolic potential as well as its best management strategy remain largely unknown. Therefore, there is a need for collecting the clinical data and building up a registry of all the patients presenting with echocardiographic features suggestive of CAT, in order better characterize the natural history of the disease, its outcome and the best therapeutic approach.

Competing interests

All authors declare that they have no conflicts of interest relevant to this manuscript.

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