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Cardiac myxomas: A narrative review

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Abstract

Cardiac myxomas are common primary neoplasm of the heart. They are biologically benign but “functionally malignant” because of the potential for embolization. They arise most commonly from the left atrium, but no chambers of the heart are immune. They may be sporadic in the majority but also familial as a part of the Carney complex. Two morphological forms exist – polypoid and papillary. Polypoid myxomas often present with obstructive features, while the papillary forms are more prone to embolization. Histogenesis is still controversial; the current view centres around origin from the primitive pluripotent mesenchymal cells. They may be of giant proportion, be calcified or get infected. Clinical presentation typically involves the triad of intracardiac obstruction, embolic events, and constitutional symptoms. Precordial examination findings may simulate those of mitral or tricuspid stenosis. The presence of tumour plop and change of the physical conclusions with changing position may help differentiation between the two. Echocardiography is the investigation of choice. Echogenic polypoid or papillary mobile mass within the atrial cavity remaining attached to the interatrial septum through a stalk are the tell-tale echocardiographic features. Cardiac magnetic resonance and computed tomographic scanning may have incremental diagnostic value. Histopathological examination reveals abundant loose myxoid stroma with scattered round, polygonal or stellate cells with dense irregular nuclei. Genetic testing may detect mutations in the *PRKAR1A* gene in the familial form of cardiac myxoma, *i.e.*, the Carney complex. Surgical excision is the mainstay of

treatment with low operative mortality, excellent post-operative survival, and low recurrence rate. The current trend favours minimal-access surgery with or without robotic assistance. Physicians should have appropriate preparedness to make a timely diagnosis and enthusiastic treatment to avoid potentially fatal complications.

Key Words: Myxoma; Cardiac; Neoplasm; Carney Complex; Echocardiography; Embolism

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Core Tip: Cardiac myxomas are biologically benign but “functionally malignant”. They can cause life-threatening embolic events. Associated constitutional symptoms may mimic those of inflammatory or connective tissue disorders. Timely diagnosis is of utmost importance, because it offers scope for definitive treatment, *i.e.*, surgical excision. Cardiac myxomas are relatively rare diagnosis, so physicians should have appropriate preparedness to deal with this entity. This review article has sum up the available information, offers practical tips, and highlights the recent advances.

INTRODUCTION

Cardiac myxomas are common primary neoplasm of the heart. Despite a preference for the left atrium, it can involve any of the cardiac chambers. The unusual feature of cardiac myxoma is that it has the biological potential to embolise and grow at the site of embolization^[1], causing organ infarction. Timely diagnosis and treatment are essential for the prevention of sometimes life-threatening complications. Though a well-known entity, some aspects of cardiac myxoma are still evolving.

Epidemiology

Cardiac myxoma is a rare disease; however, the exact prevalence is unknown. The reported prevalence is 0.03% in the general population^[2]. Annual incidence of cardiac myxoma may be 0.5 to 1 case per million individuals^[3,4]. A recently-published Spanish study revealed higher incidence; age-adjusted incidence was 1.6 per million population adjusting to the world population as a reference, and 2.1 per million adjusting to the European population^[5]. Myxomas are the commonest primary cardiac tumour constituting 50% to 85% of benign ones^[6-8]. Middle-aged persons are commonly affected, but no age is immune. The tumour has got female preponderance with a female-to-male ratio of approximately 3:1^[3,4]. Two epidemiological forms of cardiac myxoma exist – sporadic and familial – the former is far more common than the latter, constituting about 95% of cases^[6].

Anatomy

Cardiac myxomas can affect any chamber of the heart, but the left atrium is most commonly affected. Sites affected include: left atrium about 75%, right atrium 15%-20%, left ventricle 3%-4%, and right ventricle 3%-4%^[9-12]. Regarding origin, myxoma has a predilection for limbus fossa ovalis of the interatrial septum. However, it can arise from the posterior atrial wall, anterior atrial wall, and atrial appendage (Figure 1). The sporadic myxomas are usually single and bear these characteristics. On the other hand, familial myxomas may be multiple, multicentric, arising from atypical sites^[13]. So, less

commonly, myxomas may be bi-atrial or multi-chamber; the latter may be part of the Carney complex^[14-18] (Figures 2 and 3). Only rarely, myxomas affect the heart valves^[7,19-21].

Myxomas may be “more solid” polypoid in approximately two-thirds of cases or ‘softer’ papillary in one-third cases^[22] (Figure 4). The polypoid myxomas are generally pedunculated, more compact, and have got less tendency to undergo fragmentation and consequent embolisation^[6]. On the other hand, papillary or villous myxomas are gelatinous, less compact, fragile, and have a high potential for spontaneous fragmentation and embolisation to the central nervous system, kidney, spleen, extremities, and coronary vessels (Figure 5).

Myxomas are considered biologically benign but “functionally malignant” tumours. They usually remain localised to the site of origin. They have got a well-documented potential for fragmentation and embolisation. Besides this, metastasis to different locations, including the brain, sternum, spine, and pelvis, has been described^[23-29].

Myxomas may be enormous, occupying significant parts of the concerned cavity, sometimes termed “giant myxoma” (Figure 6). Rarely, they undergo calcification or osseous metaplasia^[30-32] (Figure 7). Occasionally, they get infected^[33-35] (Figure 8).

Histology

Histologically cardiac myxomas are mainly composed of stellated fusiform, and polygonal cells immersed in an amorphous myxoid stroma^[36] (Figure 9). Multi-nucleated cells are also observed. The cells are shaped and structured in chained rings or nests around the capillaries^[37]. The surface of the tumour is often layered by flattened endothelium, while the tumour mass is infused liberally by thin-walled vessels lacking pericytes.

Immunohistochemically, a wide array of biological molecules has been found to be related to the cardiac myxomas, including CD31, CD34, CD56, FVIIIa, S-100 protein, calretinin, vimentin, desmin, smooth muscle myosin, α 1 antitrypsin, and Alpha 1-antichymotrypsin^[38].

The histogenesis of myxoma is poorly understood; however, the current opinion favours origin from primitive pluripotent mesenchymal cells. Genes encoding heart precursor markers may get reactivated and expressed in cardiac myxoma cells leading to differentiation along endothelial/endocardial lines^[39]. Previously, myxomas were thought to arise from Prichard structures, the microscopic endocardial/endothelial structures lined by plump endothelial cells, located in the fossa ovalis^[40,41]. Origin from neuroendocrine tissue was also proposed.

Clinical presentation

The clinical presentation of cardiac myxoma depends on their location, size, and mobility and is typified by the triad of intracardiac obstruction, embolisation, and constitutional symptoms^[6]. In a French series of 112 cases of cardiac myxoma, intracardiac obstruction in the form of mitral valve obstruction was the commonest manifestation (67%), followed by embolisation (29%) and constitutional symptoms (34%)^[22].

Intracardiac obstruction: Intracardiac obstruction is common in polypoid myxoma. Because of preferential location, mitral valve pseudo-obstruction is the typical presentation^[42-48]. Pulmonary hypertension may be present^[43,47]. Valvular obstruction may even lead to syncope^[46,49].

Right atrial myxomas may obstruct the tricuspid valve, the manifestation of which may be heart failure^[50,51] or even collapse^[52].

Embolisation: Embolisation is typically a feature of papillary-type myxomas because of their loose consistency and fragility. Overall, embolism occurs in 30% to 40% of patients with myxomas^[6]. Site of embolisation depends on the location of the tumours. Left atrial myxomas commonly embolise to the brain, causing ischaemic stroke and occasionally visual loss. Coronary, renal, and limb arteries may also be affected. In a retrospective study of 162 patients with cardiac myxomas surgically treated between

1998 and 2014 in China, the embolic event was observed in 33 patients (20.4%) – brain 15.43%, limb 3.70%, pulmonary 0.62%, and coronary 0.62%^[53]. Tumour location (atypical), macroscopic appearance (irregular surface), mean platelet volume, and high platelet count were strong risk factors for embolic events in patients with cardiac myxomas in this study. Cerebral embolisation is relatively common, leading to ischaemic stroke^[54,55] and cerebral aneurysm formation^[56]. Retinal artery occlusion and consequent visual loss have also been reported^[57-60]. Coronary embolisation is a rare but well-documented and potentially fatal complication of cardiac myxomas^[61-64]. Systemic embolisation may affect multiple sites, *e.g.*, coronaries, viscera, and limbs^[65-67]. Right-sided myxomas are less prone to embolisation. However, right atrial myxoma, when present, may cause a pulmonary embolism^[68-73].

Cardiac myxomas may even embolise per-operatively, leading to complications. Right atrial myxoma was reported to embolise during surgical excision, causing pulmonary embolism and cardiogenic shock, and subsequent recovery after removal of the tumour embolus from the pulmonary artery^[74].

Constitutional symptoms: Cardiac myxomas are commonly associated with constitutional symptoms mimicking inflammatory or connective tissue disorders^[75-77]. These symptoms are more common in women than in men, in right-sided myxomas than in left-sided ones, and also in large and multicentric myxomas^[78]. Malaise, anorexia, fever, arthralgia, and weight loss are common. The underlying pathophysiology may be releasing cytokines from the tumour, especially the interleukin-6 (IL-6)^[79]. In fact, IL-6 may be a more sensitive biomarker than C-reactive protein (CRP) in predicting the inflammatory status of patients with cardiac myxomas. Sessile, irregular, and voluminous tumours tend to be associated with higher circulating IL-6 levels^[80]. Myxomas occasionally present with pyrexia of unknown origin^[79,81]. They may mimic bronchial asthma^[82] or pulmonary tuberculosis^[14]. Rarely, myxomas are associated with pleural effusion^[14,83,84].

Infected myxoma: Occasionally, myxomas get infected, presenting with high fever and multiple embolic events^[85-88] (Figure 8).

Cardiac myxoma in pregnancy: Occasionally, cardiac myxomas are diagnosed for the first time in pregnancy, mostly by echocardiography. Favourable maternal and foeto-neonatal outcomes with surgical management of cardiac myxoma in the pregnant patients have been reported in a recent review of 44 articles with 51 patients^[89].

PHYSICAL EXAMINATION

Cardiac myxomas are typified by the triad of intracardiac obstruction, embolic manifestations, and constitutional symptoms. However, because of heterogeneity in location, size, morphology, and histopathology, they may remain entirely asymptomatic, present with classical manifestations, or produce life-threatening emergency of systemic embolisation or even sudden cardiac death^[90]. As little as 10% to as high as 50% of the myxomas may be diagnosed incidentally during clinical evaluation^[91,92]. General examination may reveal cachexia, fever, cyanosis, clubbing, or rash. Neck veins may be engorged, and there may be a prominent A wave in the jugular venous pulse. Precordial findings may mimic mitral stenosis. The first heart sound (S1) may be loud and widely split because of the delay in the closure of the mitral valve due to the prolapse of the tumour into the mitral valve orifice. The pulmonary component of second heart sound (P2) may be normal, or loud depending on the presence of pulmonary hypertension. The characteristic “tumour plop” is a low-pitched early diastolic sound just after the S2. It may be confused with the opening snap of rheumatic mitral stenosis; however, the latter is high-pitched. It may be followed by a low-pitched diastolic murmur. The tumour plop is produced by the impact of the myxoma against the endocardial wall or when its excursion is halted. Also, a third heart sound (S3), fourth heart sound (S4), or a diastolic murmur of functional mitral or tricuspid stenosis may be audible. Occasionally, a systolic murmur of mitral or tricuspid regurgitation

may be present. The auscultatory findings of cardiac myxomas characteristically change with changes in the position of the patient.

INVESTIGATIONS

Echocardiography is the critical investigation for the diagnosis of cardiac myxomas. Other imaging modalities like computed tomographic (CT) scanning and magnetic resonance imaging (MRI) play an ancillary role. Chest x-ray and electrocardiography (ECG) are of limited value. Haematological investigations are also routinely done. Histopathology confirms the diagnosis. Genetic testing plays a vital role in familial cases of myxomas.

Echocardiography

Transthoracic echocardiography (TTE) is the most practical investigation and often yields adequate information necessary for surgical resection. It makes the diagnosis, and determines the location, size and shape of the tumour and its connections. Transesophageal echocardiography (TEE) has got higher sensitivity and specificity, can detect small tumours, tumours located at atypical locations, and possible multi-chamber myxomas^[93-97].

Three-dimensional (3-D) TTE and TEE have also been used^[98]. In a European study, TEE was superior to TTE for myxoma detection (100% vs 95%) and attachment point identification (95.2% vs 64.5%)^[99].

The classical features of an atrial myxoma in echocardiography include polypoid or papillary mass attached to the interatrial septum through a stalk and moving to and fro into the cavity, sometimes protruding into the corresponding ventricular cavity across the atrioventricular valve (Figure 10). Sometimes, the tumour mass may get areas of liquefaction or calcification. Doppler echocardiography shows the hemodynamic consequences of atrial myxoma.

During echocardiography, differentiation between myxoma and thrombus is of crucial importance. Myxomas typically have a stalk, a preference for limbus fossa ovalis

of the atrial septum for stalk attachment, and characteristic mobility. On the other hand, the thrombus is usually situated in the posterior portion of the atrium, has a preference for the atrial appendage, has a layered appearance, and is most commonly seen in the presence of valvular mitral stenosis, atrial fibrillation and spontaneous echo contrast.

Contrast echocardiography can aid in the differential diagnosis of intracardiac masses based on ¹perfusion of the mass. Malignant tumours are frequently highly vascular and present greater contrast enhancement than the adjacent myocardium, whereas myxomas demonstrate partial perfusion lesser contrast enhancement than the adjoining myocardium, whereas thrombi, being avascular, show a complete absence of perfusion^[100-102].

Despite the invaluable role of echocardiography and other imaging modalities, histopathological examination is the gold standard test for confirmation of the diagnosis of cardiac myxomas. A recently-published study from Korea shows, out of ¹265 cases with an echocardiographic diagnosis of cardiac myxomas, 174 (65.7%) were surgically confirmed as myxomas. Compared with cardiac myxomas, other tumours were smaller and more frequently found in non-atrial sites^[103].

ECG

ECG findings are nonspecific. Atrial enlargement or ventricular hypertrophy may be present. In contrast to the findings in mitral valve disease, atrial fibrillation is uncommon^[6].

Other imaging modalities

Chest skiagram has got a limited role. Occasionally, it can present features of mitral stenosis, *e.g.*, straightening of the left cardiac border and double contour of the right cardiac border, and only rarely, tumour calcification. Signs of pulmonary hypertension may be present.

MRI provides helpful information about myxoma's size, shape, surface characteristics, and even its mobility on cine MR gradient echo (GRE). The ³most

frequent presentation is a mass isointense at T1-weighted and hyperintense at T2-weighted imaging with foci of hypointensity at one or two of these sequences^[104]. Also, tissue characteristics can be used to differentiate a tumour from a thrombus.

Computed tomography (CT) scanning, generally, is not useful for the diagnosis of cardiac myxomas because it cannot reliably differentiate between myxomas and thrombi^[105]. Typically, myxomas appear homogenous and isodense or slightly hypodense mass on non-contrast CT scanning, which does not show enhancement after iodinated contrast injection^[106]. However, CT is the preferred technique to detect calcification, which is encountered in 10%–30% of cases^[106,107].

Fluorodeoxyglucose positron emission tomography (FDG-PET) scanning is not typically indicated in the evaluation for myxoma^[108].

Angiocardiography

Now seldom used for diagnosis of cardiac myxomas because of availability of non-invasive investigation modalities especially echocardiography. Also, manipulation of a catheter during angiocardiography carries a high risk of embolisation of tumour fragments^[109,110]. In angiocardiography, cardiac myxomas typically appear as filling defects. In cases of left atrial myxoma, the levophase of a pulmonary angiogram may outline a radiolucent mass within the left atrium.

Genetic testing

Genetic testing for mutations in the PRKAR1A gene is increasingly used for diagnostic certainty of Carney complex.

Haematological tests

Erythrocyte sedimentation rate (ESR) and CRP are generally elevated. Anaemia may be present. IL-6 rises especially when constitutional symptoms dominate.

TREATMENT

Cardiac myxoma needs surgical excision often on an emergency basis. This is to reduce the risk of embolisation of the tumour. Surgery is otherwise simple; the root of the stalk and the full thickness of the adjacent interatrial septum is excised, and the consequent atrial septal defect is closed accordingly. Data published over the past decades show excellent overall outcomes in operative mortality, short- and long-term survival, and tumour recurrence^[4,101-118]. Surgical excision of 23 myxomas in Turkey between 2010 and 2017 showed excellent outcomes with no early or late mortality^[112]. A 16-year single-centre study from China reported no need for secondary surgery in $97.4\% \pm 2.5\%$ of cases after ten years. Overall, the actuarial survival was $98.4 \pm 1.6\%$ at five years and $96.0\% \pm 2.8\%$ at ten years^[113].

A similar encouraging outcome was observed in Italy; surgical excision of 98 cardiac myxomas between 1990 and 2007 showed 3% operative mortality. Actuarial survival was 98%, 98%, and 89% at 5, 10, and 15 years, respectively. There was only one recurrence 68 mo after the first surgery^[115].

In a smaller series of 18 patients treated surgically over five years in the United Kingdom, no death occurred within 30 d post-procedure^[116]. Follow-up of surgical treatment of cardiac myxomas in Germany showed no in-hospital deaths. Out of 57 patients, 52 were alive at a median follow-up of 7.5 years^[117]. Between 2002 and 2008, 34 cardiac myxomas were operated on in a single centre in Pakistan; 32 patients survived the surgery, two patients died over a median follow-up of 34 mo, and 1 had recurrence at 27th month^[118]. 24 years of experience in 49 patients from Austria revealed relatively low early mortality of 2.0% and late mortality of 6.1%. The long-term prognosis was excellent, with an actuarial survival rate of 0.74. The rate of reoperations was low, with 2.0% after 24 years^[4]. In a recently published small study from Bangladesh, all 20 patients with cardiac myxoma survived the surgery, and one patient presented with recurrence 28 mo after the surgery^[111]. In recent years, cardiac myxomas have been excised successfully by minimally invasive surgery with or without robotic assistance^[119-122]. Robotic surgery has been associated with early restoration of normal quality of life and early return to employment^[121].

Utmost caution is warranted during surgical excision of cardiac myxomas because of their potential for embolisation per-operatively^[74].

FAMILIAL CARDIAC MYXOMAS

Familial cardiac myxoma is rare and tend to form a syndrome, *e.g.*, Carney complex. They can usually be distinguished from the sporadic forms by the presentation at a younger age, the unusual location and multicentricity of the lesions, and the presence of rare pathological conditions. In addition, a higher rate of recurrent lesions is usually associated with the familial forms of this disease. Carney complex is a rare multiple neoplasia syndrome, characterised by pigmented lesions of the skin and mucosa, cardiac and extra-cardiac myxomatous tumours, and multiple endocrine and non-endocrine neoplasms (Figure 3)^[123,124]. It is inherited as an autosomal-dominant disorder in 3/4th of the cases, while in resting 1/3rd, it occurs sporadically as a result of a *de novo* genetic mutation^[125]. The disease is caused by inactivating mutations or large deletions of the *PRKAR1A* gene located at 17q22–24 coding for the regulatory subunit type I alpha of protein kinase A (PKA) gene^[126]. Myxomatous tumour also occurs in the skin and breast. Lentigines, blue nevus, and cutaneous myxoma are the common skin manifestations (Figure 3). Primary pigmented nodular adrenocortical disease (PPNAD), and thyroid nodules are examples of endocrinopathies^[127,128].

The Carney complex is diagnosed by the diagnostic criteria defined by Stratakis *et al*^[124] (Table 1). Making the diagnosis, required either: (1) Two of the 12 manifestations of the disease listed; or (2) one of these 12 manifestations and one of the supplemental criteria. Genetic testing for mutations in the *PRKAR1A* gene confirms the diagnosis. For management, cardiac myxoma needs surgical excision. PPNAD and pituitary adenomas are managed surgically, or the latter, with somatostatin analogues^[129,130]. Prognosis is good at present; however, lifelong follow up is indicated^[126].

CONCLUSION

Cardiac myxomas are the commonest neoplasm of the heart. They are primarily sporadic but may be familial as Carney complex. Though histologically benign, myxomas are prone to cause intracardiac obstruction and embolisation. Associated constitutional features may mimic inflammatory and connective tissue disorders creating diagnostic dilemmas. Echocardiography is a versatile tool for making the diagnosis and choosing the optimum management strategy. Surgery is the mainstay of treatment with an excellent prognosis. Long-term follow-up is often needed to look for recurrence. Physicians should have appropriate preparedness to diagnose this uncommon entity. Only timely diagnosis and prompt surgery can reduce the morbidity and mortality of cardiac myxoma patients.

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