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Cardiac myxoma: a comprehensive review

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Abstract

Heart tumours are a diverse group of tumours that may present with symptoms or be discovered incidentally when a patient is being evaluated for a physical or seemingly unrelated ailment. Cardiac myxoma, although rare, is the second most common benign primary cardiac tumours after papillary fibroelastoma. It occurs in sporadic form and familial form, as seen in Carney complex disorder. Cardiac myxoma can affect all age groups, but the majority manifests in their third to sixth decade of life, with a mean age of 50 years at diagnosis. There is a slight preponderance in females in a ratio of 2:1. Conversely, they are incredibly uncommon in fetuses and newborns but commonly diagnosed in children around a mean age of 9–10 years. About 90% originate in the atrium as a solitary or pedunculated mass. Within the atrial chamber, 75% occur on the left atrium close to the fossa ovalis, while others occur in the right atrium, ventricles, and valves. Serious complications often arise even in the absence of symptoms, and such complications include intracardiac obstruction, systemic and pulmonary emboli, as well as constitutional symptoms that mimic connective tissue and inflammatory diseases. There is no pathognomonic clinical presentation. Complete surgical excision of the tumour, including the use of robotic surgery, is the key component of a successful course of treatment. To monitor for tumour recurrence, long-term follow-up is frequently carried out with interval echocardiography. This review will focus on providing information on the various forms of cardiac myxoma, aetiology, molecular genetics, clinical presentation, histopathologic findings, differential diagnosis, treatment, and complications.

Keywords Cardiac tumours, Malignant, Benign, Metastatic, Vegetations, Immunohistochemistry

Introduction

Cardiac masses are a broad set of lesions, which may generally be categorized as tumour-like lesions or non-neoplastic lesions such as; vegetations, clots, calcifications, or other uncommon lesions, while the neoplastic lesions include; benign or malignant tumours (primary or metastatic tumours) as well as intracardial or pericardial neoplasms [1]. Cardiac masses are important because their malignant behavior disrupts hemodynamic functions as a result of obstruction to blood flow, embolisms, or electrical or mechanical dysfunctions [2].

Primary cardiac tumours although rare, the reported incidence ranges from 0.0017 to 0.3% and prevalence from 0.001 to 0.03% according to postmortem studies [3, 4]. In 2015, World Health Organization (WHO) updated the classifications of heart neoplasms into benign tumours and tumour-like lesions, tumours of uncertain biologic behavior, germ cell tumours, malignant tumours, and tumours of the pericardium [5]. Primary benign cardiac tumours are much more common than their malignant counterpart, accounting for about 75–90%[5–7]. Among the benign heart neoplasms, the WHO in 2021 recognized papillary fibroelastoma (PFE) as the most

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common cardiac neoplasm, different from what was previously known [5, 8].

Cardiac myxoma (CM), whose name is derived from the predominantly myxoid stroma, is composed of an extracellular matrix rich in glycoproteins and proteoglycans with polygonal cells scattered throughout. This tumour is thought to originate from the primitive mesenchymal cells that are capable of endothelial differentiation [4, 9–11]. It can occur in all ages but more frequently in women than in men [12]. CM are usually solitary and pedunculated, frequently connected to the atrial septum by a stalk. Prompt diagnosis and treatment are crucial for all cardiac myxomas since they have a high risk of serious complications like embolism, heart failure, or sudden death. Although early imaging, such as MRI and echocardiography, is crucial, surgical excision remains the gold standard treatment procedure and is often curative. Recurrence is uncommon; however, it can occur, particularly in patients with genetic predispositions such as Carney complex. Although rare, recurrence is possible, especially in patients with genetic predispositions like Carney complex and for such patient, postoperative monitoring is crucial for identifying possible recurrence [13].

CM often produces serious complications due to its asymptomatic nature. Because of the high blood flow dynamics, tumour fragments may detach and frequently embolize to the systemic circulation mimicking an aggressive malignant tumour. Therefore, patients with an undetected cardiac myxoma are at a significant risk of experiencing intracardiac obstruction and pulmonary and systemic embolism resulting in a significant increase in morbidity and mortality especially if not detected early or if not properly resected [14, 15].

The scope of this review will focus on cardiac myxoma, providing information on the epidemiology, molecular genetics, clinical presentation, imaging, histopathologic findings, differential diagnosis, complications, treatment, and prognosis. This will guide the physicians in understanding the basic pathology of this condition, make a timely diagnosis, and institute the right treatment or possibly consider an early referral to cardiac centers to avoid the fatal complications associated with this tumour.

Epidemiology

Cardiac myxoma is still an uncommon tumour whose precise prevalence is unclear. It has been observed that the incidence rate in the general population from surgically resected specimens is 0.5–0.7% per million inhabitants and the prevalence is less than 5 per 10,000 [16], and between 0.0017% and 0.03% in postmortem series [17]. A systematic review and meta-analysis study of 74 articles involving 8,849 patients reported that 7484 (84.6%) were benign primary cardiac tumours of which 5140 (68.7%) were cardiac myxomas [10]. The frequency is unclear in Africa with only a few cases reported [18, 19].

Although cardiac myxoma often affects all age groups, majority manifests in the third to sixth decade of life with a mean age at diagnosis at 50 years and there is a slight preponderance in women in a ratio of 2:1 [4]. The majority of cardiac myxomas are sporadic and isolated, while only 5–10% having familial pattern of inheritance and usually develop in the atria (75% from the left atrium and 18% from the right atrium). CM has been reported as a component of genetic diseases such as the Carney complex in young patients without sex predilection and such cases often develop CM around the age of 20 years [14, 17, 20]. According to autopsy data, the incidence of cardiac tumours throughout fetal life is 0.14%. Furthermore, myxomas are the most prevalent primary tumours in adults, making up 40% of benign tumours, according to a small number of studies. Conversely, they are incredibly uncommon in fetuses and newborns but commonly diagnosed in children around a mean age of 9–10 years [21, 22].

Pathophysiology

The precise aetiology of CM is still under study with early debate on whether cardiac myxomas were neoplastic structures or organized thrombi have also been reported [23]. However, several studies on the origin of myxoma cells have been reported and they include:

Molecular and immunohistochemistry study

Recent gene expression profiles and immunohistochemical findings have proposed that cardiac myxomas take their origin from entrapped embryonic foregut tissue, including multipotent mesenchymal cells with the capability of differentiating into neural and epithelial cells [16, 23–25].

Origin from cardiac stem cells

Similar to other studies that demonstrated that a certain subpopulation of cells known as "tumour-initiating cells or cancer stem cells" (CaSCs) show stem cell properties including, self-renewal ability, clonogenicity, and multipotent differentiation similar to normal stem cells are present in some malignant tumours [23]. The potential of the adult mammalian heart to produce new cardiomyocytes and microvasculature throughout life has been demonstrated, even though it was once thought to be a terminally differentiated organ. The discovery of endogenous cardiac stem cells (CSCs) or progenitor cells in the adult heart raises the possibility that replicating myocytes are a subset of proliferating cells that grow quickly and originate from more primitive cells. Recent studies have demonstrated that these CSCs are distributed throughout the heart and show commitment toward differentiating

between blood and endothelial cell lineage. These CSCs are characterized by heterogenous expression of the c-kit (also known as CD117) positive cell population, negative for CD45 and CD31 [23, 24, 26, 27]. Some studies have demonstrated that myxoma cells express CD44 which is a widely used cancer stem cell marker and this expression may indicate their malignant potential. Furthermore, myxoma cells have been found to express transcription factors that are unique to the phenotype of primitive cardiomyocytes, suggesting that multipotential mesenchymal progenitors with a cardiomyogenic lineage are the source of cardiac myxoma development [25].

Origin from Prichard structures

In 1951 Prichard identified certain microscopic endocardial structures of the atrial septum, which were proposed to be related to cardiac myxomas [28]. Myxomas were once thought to have originated from these microscopic endocardial/endothelial structures known as Prichard structures. These structures, which are age-related alterations of unclear origin, are made up of tiny endocardial malformations in the fossa ovalis that have capillary-sized lacunas lined by plump endothelial cells [29].

Thrombotic origin

Myxomas may initially form from thrombus or blood clots, which eventually undergo dysplastic changes resulting in tumour-like features. On this basis, chronic cellular stress may stimulate the endothelial cells covering a thrombus to become transformed, leading to abnormal cell proliferation and myxoid stroma secretion. This theory is supported by the fact that myxomas in low-flow areas like the atrial septum may promote thrombus formation. Additionally, myxomas' propensity to generate emboli points to a thromboembolic component of their pathogenesis [13].

Metaplastic origin

According to the metaplastic concept, cardiac myxomas arise from metaplasia, which is a reversible change in which one adult differentiated cell type (epithelial or mesenchymal) is replaced by another adult cell type within the endocardial tissues. Mechanical stress, inflammation, or genetic changes that cause a change in cellular phenotype may be triggers resulting in the production of myxomas. Myxoma cell's histological similarities to endothelial and mesenchymal cells, which point to a shared origin and subsequent metaplastic change, lend credence to the notion. Furthermore, the cytokines and growth factors secreted by myxoma cells suggest an environment that promotes the creation of extracellular matrix and cellular transformation [13].

Inflammatory origin

Cardiac myxoma has been found to produce growth factors, interleukin 6 (IL-6), matrix metalloproteases including chondroitin-6-sulfate, hyaluronic acid, and chondroitin-4-sulfate all of which make up to 90% of tumour glycosaminoglycans (GAGs) [13, 30, 31]. IL-6 contributes to systemic inflammatory responses, including fever and the increased inflammatory markers seen in myxoma patients. It is believed that immune-mediated mechanisms or chronic inflammation may indirectly contribute to the development or maintenance of myxomas. The inflammatory microenvironment may additionally provide signals that promote angiogenesis and cellular proliferation, indirectly promoting tumour growth [13]. Furthermore, studies have also revealed the existence of herpes simplex virus type 1 (HSV1) genetic material and viral antigens in myxomas, and the pathophysiologic mechanism for these viral infections is the induction of persistent chronic inflammatory lesions in endocardial tissue [32]. On the flip side, an immunohistochemical investigation conducted on seventy individuals diagnosed with cardiac myxoma showed no connection between HSV1 and the development of CMs [33]. In my opinion, this viewpoint is still unclear, and will need more studies to prove the involvement of HSV1 in the pathogenesis of CM.

Genetics of myxoma

It will be recalled that 10% of myxomas are inherited via an autosomal dominant condition called Carney's complex syndrome (CNC), while the bulk occurs sporadically [4]. Carney complex is a rare X-linked autosomal dominant disorder with diverse phenotypic expression but with complete penetrance [34]. This disorder is characterized by the following: cardiac myxoma, extracardiac myxoma e.g. cutaneous and breast myxomas, osteochondromyxoma, myxomatous tumors of the breast, ductal adenoma of the breast, blue nevi, endocrine overactivity and tumours (hypercortisolism, pituitary adenoma with acromegaly or gigantism, thyroid tumours, testicular large cell calcifying Sertoli cell tumours (LCCST), psammomatous melanotic schwannoma (PMS) and paradoxical positive response of urinary glucocorticoids to dexamethasone administration (PPNAD) during Liddle's test [4, 11, 34, 35]. The tumour suppressor gene protein kinase A (PKA) type-1 regulatory subunit (R1A) PRKAR1A linked to chromosome 17q24 has an inactivating mutation in CNC [4, 35, 36].

The diagnosis of Carney complex (CNC) is made when there are two or more clinical presentations of the syndrome, or when there is an inactivating mutation of PRKAR1A (regulatory subunit of cyclic AMP-dependent protein kinase type I-alpha) in a patient [34].

Cardiac myxomas in CNC individuals are typically younger with a median age at diagnosis at 20 years, more often males than females, multicentric tumours, and with an increased risk of recurrence when compared to the sporadic forms [4, 34–36].

Site

CM can develop in any of the cardiac chambers, but predominantly in the left atrium as well as the right atrium, right ventricle, and the valves [17].

Clinical presentation

The triad of intracardiac obstruction, embolization, and constitutional symptoms are characteristic of CM and these vary depending on their location, size, and mobility. A majority of patients will have one of these signs on their first day of clinic visit [4, 37–39].

Large pedunculated polypoid tumours frequently present with clinical manifestations associated with intracardiac obstruction. The symptoms of left atrial myxoma include regurgitation or obstruction of the mitral valve, left-sided heart failure presenting with orthopnea, dyspnea at rest and with exertion, paroxysmal nocturnal dyspnea, dizziness, intermittent positional syncope, sudden death, and pulmonary edema. Secondary pulmonary hypertension may develop [4, 32, 37]. There can also be damage to the tendinous chords of the heart valves [32]. In a similar vein, right-sided myxomas result in right heart failure and tricuspid stenosis or insufficiency. Here, symptoms will include ascites, hepatomegaly, dyspnea, pedal edema, and sudden death [4]. Studies have shown that 20% of patients with cardiac myxomas develop cardiac arrhythmias, such as atrial fibrillation and flutter [39].

Embolization is a frequently reported complication of cardiac myxoma and it is more common in myxomas with irregular surfaces, like those with papillary or villous projections due to their loose consistency, fragility, size, and increased left atrial diameter [4]. The location of the tumour determines the embolization site. Systemic embolism is typically more common in cases of left atrial myxoma (cerebral and peripheral) because of the high blood flow dynamics and the most common sites of embolism include the brain, coronary arteries, aorta, kidney, spleen, extremities, and pulmonary arteries [32, 39]. Cerebral and retinal arteries are affected followed by arteries that supply the lower extremities, visceral, renal, and coronary arteries, and may involve the abdominal aorta. Occlusion to the middle cerebral arteries and supraclinoid internal carotid artery may lead to the development of a progressive headache, nausea or vomiting due to the increase of intracranial pressure, limbs or body weakness or numbness, new onset of seizure, ischaemic cerebrovascular disease, transient ischemic attack, cerebral aneurysm formation, syncope, psychiatric symptoms, brain necrosis, intracranial aneurysms, hemiparesis, aphasia, and progressive dementia [32, 37, 40]. Acute vertigo, nausea, headache, and abnormalities in gait are the most common initial symptoms of a posterior inferior cerebellar artery area infarct with headache as the most common initial symptom [16]. In addition, visual disorders leading to acute and permanent vision loss are caused by central retinal artery occlusion [41–44]. Systemic embolization affecting the lower limbs may be misdiagnosed as peripheral vasculitis (collagen vascular disease) [32], thus, highlighting the significance of a thorough histologic analysis of each embolectomy specimen [45]. Coronary artery embolization may cause a myocardial infarction or severe angina [3, 32]. During surgical excision, cardiac myxoma may also embolize, leading to pulmonary embolism and cardiogenic shock [37]. Also, 10% of embolic events are triggered by right atrial myxoma, which blocks the pulmonary artery and results in pulmonary hypertension or possibly a fatal fulminant lung obstruction [32, 46].

Constitutional symptoms which include physical weakness, lethargy, fatigue, loss of appetite, anorexia, recent and progressive decrease in body weight, persistent and unexplained low-grade fever, arthralgia, and anaemia are present in 90% of cardiac myxoma patients [32, 39]. The constitutional symptoms often result in abnormal laboratory results, including thrombocytopenia, elevated inflammatory markers (leukocytosis, polycythemia/erythrocytosis, and elevated erythrocyte sedimentation rate), high levels of serum C-reactive proteins, and immunoglobulin levels, as well as normochromic and normocytic red cell indices in chronic anaemia [4, 32, 47]. The mechanical destruction of blood components by a mobile intraluminal tumour is thought to be the cause of hemolytic anemia and thrombocytopenia, which are frequently observed in left atrial myxomas [16].

The enhanced release of cytokines by the host's inflammatory and autoimmune responses, such as interleukin-6 (IL-6) and interleukin (IL-8), is the pathophysiologic mechanism explaining these constitutional symptoms. This may be followed by the activation of the complement cascade by circulating antibody-tumour-antigen complexes [4, 48, 49]. Studies have also shown that Il-6 can serve as a better clinical biomarker than C-reactive protein in assessing an affected patient's inflammatory status [4, 37]. Rarely myxomas may mimic other inflammatory conditions of the lungs including pulmonary tuberculosis or bronchial asthma [37].

Finally, although it is uncommon, CM may become secondarily infected. The Streptococcus species—*Streptococcus mutans*, *Streptococcus oralis*, and *Streptococcus viridans*—are the most frequently isolated organisms. Other bacterial and fungal pathogens, including *Candida*

albicans, *Staphylococcus lugdunensis*, *Gemella morbillorum*, *Porphyromonas asaccharolytica*, and *Enterococcus faecalis*, have also been reported in other studies [32, 38, 50, 51]. Peter *et al*., reported a case of an infected left atrial myxoma presenting with acute myocardial infarction following an occlusion to the left anterior descending coronary artery [3]. Severe infections can make a tumour mass more friable and vulnerable to systemic embolization, bacteraemia, and disseminated intravascular coagulation [32, 37, 38].

It is good to note that on clinical examination, left atrial myxoma can mimic several different disease conditions including tricuspid regurgitation, tricuspid stenosis, mitral regurgitation, and pulmonary embolism. There is no pathognomonic physical finding indicative of a CM [16].

Diagnosis

Histology is necessary for the diagnosis of cardiac myxoma and this is typically carried out on surgically excised tumours. Endomyocardial biopsies may be done in cases with atypical presentations [17].

Imaging

Echocardiography is the primary diagnostic method used in the initial assessment of cardiac tumours including myxomas and it is non-invasive, safe, and accurate. It identifies the site, size, attachment, and mobility of a CM and can macroscopically rule out the possibilities of vegetation or a thrombus. Transthoracic and transesophageal echocardiography is more useful in providing adequate details for good surgical tumour resection because it is used to establish the diagnosis and ascertain tumour locations, dimensions, shapes, and connections to surrounding structures [52].

For increased sensitivity and specificity, transesophageal echocardiography is preferable since it identifies smaller atrial tumours, tumours located at unusual sites, and multi-chambered myxomas. Other methods used include; three-dimensional transthoracic echocardiography and transoesophageal echocardiography [14, 20, 37, 39]. Echocardiography features of a myxoma include polypoid or papillary heterogenous mobile mass connected by a stalk to the interatrial septum's limbus fossa ovalis and exhibiting characteristic mobility with back and forth movement into the cavity, occasionally extending across the atrioventricular valve into the corresponding ventricular cavity. Larger, polypoid myxomas have a smooth exterior and a rough center with lucencies and cystic areas from bleeding and necrosis. Papillary myxomas are usually smaller in size and seem stretched with numerous villi. There can be calcifications or areas of liquefaction [37, 53]. Doppler echocardiography can also be used to assess stenosis or related valvular regurgitation [39].

Additionally, the location of the tumour is often reflected in the radiographic features of cardiac myxoma. The chest radiographic appearance of left atrial myxoma patients is identical to that of patients with mitral valve disease, including left atrial enlargement, pulmonary venous hypertension with pulmonary vascular redistribution, and interstitial edema. Other chest radiograph findings include; cardiomegaly, abnormal cardiac silhouette resembling mitral stenosis, intracardiac tumuor calcification, and biventricular hypertrophy with or without left atrial (LA) enlargement, which are pathologically more common in right atrial myxomas than in the left. Sometimes pleural effusions are seen. A tiny myxoma that does not cause blockage could result in normal chest radiography findings [39, 52].

Depending on the mass's perfusion, contrast echocardiography can help with intracardiac mass differential diagnosis. While myxomas display partial perfusion and less contrast enhancement than the surrounding myocardium, thrombi are avascular with a complete absence of perfusion, and malignant tumours are often highly vascular and exhibit greater contrast enhancement than the surrounding myocardium [37]. The hemodynamic effects of atrial myxoma are demonstrated by Doppler echocardiography [37].

On computed tomography (CT), cardiac myxomas usually appear as well-defined spherical or ovoid masses, with smooth or lobulated contours. It may be pedunculated or sessile. Contrast-enhanced CTs usually show heterogenous enhancement, with the majority highlighting the mass as a lower attenuation lesion surrounded by enhanced intracardiac blood than the adjacent myocardium. Sometimes calcification is observed, which is more typical in myxomas that originate in the right atrium [13, 54].

On cardiac MRI imaging, myxomas often show heterogenous signal intensity (isointense or hyperintense lesion) reflecting the underlying components of the mass [54]. While low signal intensity on post-contrast imaging may indicate areas of necrosis, higher enhancement may indicate areas of enhanced vascularity and inflammation [54]. Because of their imaging properties, CT and MRI modalities can be more effective than transthoracic echocardiograms in the diagnosis and examination of cardiac masses. The most sensitive diagnostic technique is contrast magnetic resonance imaging (MRI) while the gold standard for diagnosis is a histological biopsy [22].

Other imaging modalities used for diagnosis include; Chest skiagram, Fluorodeoxyglucose positron emission tomography scanning, and Angiocardiography [2, 37].

Haematological investigations

C-reactive protein and erythrocyte sedimentation rates are typically higher. However, anaemia, leukocytosis,

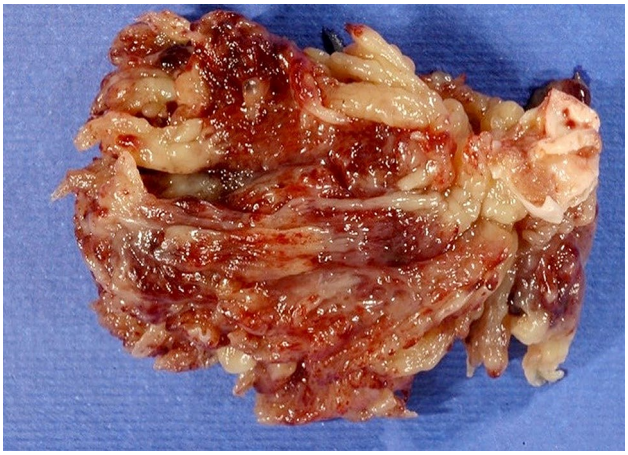

Fig. 1 Gross picture of cardiac myxoma with villous projections. © Pucci A, Bartoloni G. Cardiac myxoma. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/hearttumormyxoma.html. Accessed December 13th, 2024. This work is licensed under CC BY-NC-SA 4.0. To view a copy of this license, visit https://creativecommons.org/licenses/by-nc-sa/4.0/

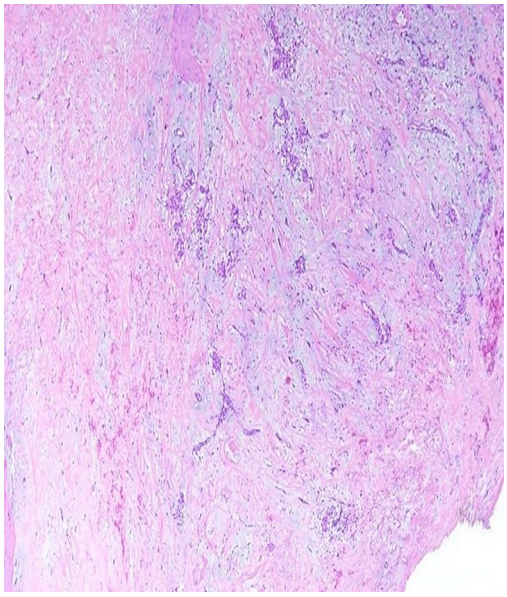

Fig. 2 Low magnification of a left atrial myxoma displaying tumour cells within a myxoid matrix. © Pucci A, Bartoloni G. Cardiac myxoma. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/hearttumormyxoma.html. Accessed December 13th, 2024. This work is licensed under CC BY-NC-SA 4.0. To view a copy of this license, visit https://creativecommons.org/licenses/by-nc-sa/4.0/

thrombocytopenia, increased gamma globulin, and elevated IL-6 predominantly in the presence of constitutional symptoms can be present [13, 37].

Gross pathology

Although, cardiac myxomas can affect any of the heart chambers, however, they most often affect the left atrium. According to research, the left atrium (75%), right atrium (15-20%); left ventricle (3-4%), and right ventricle (3-4%) are all involved. Atrioventricular valves are more commonly afflicted than aortic or pulmonary valves in valvular myxomas, which are extremely rare (< 1%). The tricuspid, aortic, and pulmonary valves are impacted more frequently than the mitral valve [4, 38].

Macroscopically, cardiac myxomas may be a more solid, polypoid mass, with a smooth glistening surface or focally cystic, friable, sessile, or pedunculated, haemorrhagic, pink to tan, and may have multiple friable papillary projections (Fig. 1) [4, 17, 37]. Normal characteristics of polypoid myxomas include being more densely packed, pedunculated, and less prone to fragmentation and subsequent embolization [37]. Conversely, because of the friable nature of the papillary projections, the papillary or villous myxomas are less compact, brittle, and more susceptible to spontaneously fragment and embolize to the kidney, spleen, coronary arteries, and extremities [4, 37].

Their cut surface is soft, and bosselated, and shows a variegated surface rich in fibrous, gelatinous, myxoid, and hemorrhagic foci [4].

Microscopically, the tumour is composed of mainly polygonal (lepidic) myxoma cells appearing as small stellate to plump spindle-shaped cells arranged either in singles, or forming cords, nests, and trabecules, and they are oriented towards thin-walled vascular channels that lack pericytes (perivascular cuffing). The individual tumour cells have round or ovoid nuclei with a pale open chromatin pattern and occasionally show prominent nucleoli. They have abundant eosinophilic cytoplasm, and indistinct cell borders surrounded by an amorphous myxoid stroma (Figs. 2 and 3) [17]. The stroma is predominantly myxoid and rich in mucopolysaccharides (chondroitin sulfate, hyaluronic acid, chondroitin, and dermatain sulfate), collagen type IV, and elastin. Mitoses are rare, and there is no significant cytologic atypia as well as absence of necrosis. Myxomas are often covered by flattened endothelial cells and are also often perfused with thin-walled blood vessels that lack pericytes [32, 38].

The stroma is often positive for Alcian blue histochemical stain [4, 37, 38]. Other secondary degenerative changes observed in CM include haemorrhage which may be connected with Gamna-Gandy bodies (calcific/siderotic elastic fiber degeneration), fibrosis, thrombosis, calcification, and necrosis [32, 38]. Finally, a small percentage of cardiac myxoma (< 3%) may show glandular elements that are lined by columnar mucinous cells dispersed in a loose myxoid stroma, and these glands are immunoreactive with epithelial markers such as cytokeratin (CK), epithelial membrane antigen (EMA), CAM 5.2, and carcinoembryonic antigen (CEA) [4, 32]. Within cardiac myxomas, the occurrence of heterotopia (or maybe choristoma) is acknowledged as a pathologic coincidence that may complicate the diagnosis. Microscopically,

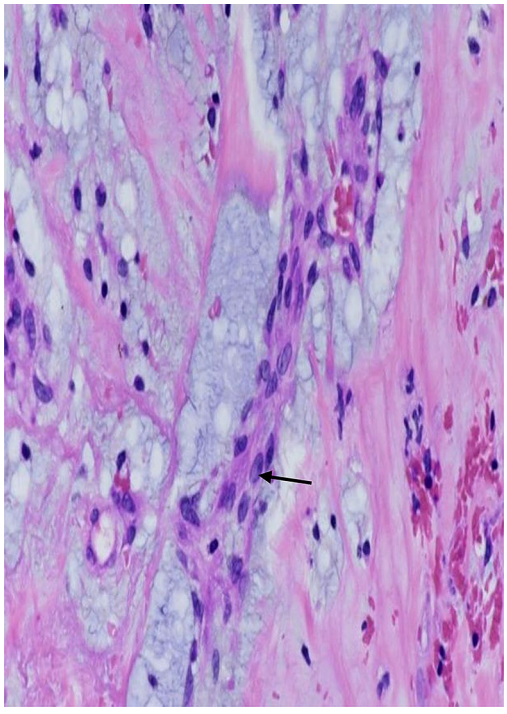

Fig. 3 Myxoma cells forming a perivascular tumour cuff. Arrow showing myxoma (lepidic) cells. © Pucci A, Bartoloni G. Cardiac myxoma. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/hearttumormyxoma.html. Accessed December 13th, 2024. This work is licensed under CC BY-NC-SA 4.0. To view a copy of this license, visit https://creativecommons.org/licenses/by-nc-sa/4.0/

cardiac myxomas may in addition to containing glandular elements, can also contain hematopoietic, chondroid, and thymic tissues. Additionally, there have been reports of intracardiac thyroid heterotopia [55]. Studies have also shown that the neoplastic cells of CM express vascular endothelial growth factor (VEGF) and its receptors, VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1). This VEGF usually acts as an autocrine growth factor for CM. Also, VEGF and mast cell-derived tryptase may play a significant role in angiogenesis and growth of myxoma cells [38].

Immunohistochemistry and genetics testing

Immunohistochemically, the neoplastic cells in CM are immunoreactive to a wide range of antibodies including S100, smooth muscle myosin, calretinin (strong, diffuse, cytoplasmic, and nuclear staining), vimentin, desmin, cluster of differentiation (CD) CD56, and variable staining for endothelial markers such as CD31, CD34, Factor VIII (FVIII), Friend leukemia virus integration site 1 (Fli-1), and Erythroblast transformation-specific (ETS)-related gene (ERG) [4, 37, 38]. There is negative staining for CD68 (except for associated inflammatory elements) and cytokeratins (except for rare glandular elements) [17].

Mutation of the tumor suppressor gene PRKAR1A, which encodes for c-AMP-dependent protein kinase type I-a regulatory subunit has been found to occur in both familial and sporadic forms of CNC cases and this can be observed through immunohistochemistry and genetic testing [4, 36, 37].

Electron microscope

Myxoma lepidic cells exhibit characteristics of immature mesenchymal cells and are connected with endothelial and smooth muscle cells. Lepidic cells contain numerous smooth and rough endoplasmic reticulum, frequent iron deposits, free ribosomes, polyribosomes, lysosomes, and pinocytic vesicles [17].

Differential diagnosis

Myxoid stroma mural thrombi, papillary fibroelastoma, myxoid sarcomas, angiosarcomas, and epithelioid hemangioendothelioma are among the histopathological differential diagnoses for cardiac myxoma [4]. Mural myxoid thrombi is adherent to the wall of the endocardium, composed of fibrin, and red blood cells, and lack plump tumour cells that are seen in CM as well as calretinin negativity [4]. Papillary fibroelastoma is an endocardia-based papilloma lined by endothelial cells but devoid of the myxoid stroma as well as the large plump neoplastic cells of a myxoma [4].

Malignant tumours that may look like CM include: Myxofibrosarcoma, angiosarcoma, and epithelioid haemangioendothelioma. Myxofibrosarcoma is the most common type of cardiac myxoid sarcoma. These are typically high-grade, pleomorphic, hyperchromatic spindle cells that are embedded in a myxoid stroma that has infiltrated the heart and are mitotically active [4]. Angiosarcoma is a malignant vasoformative tumour composed of malignant cells that line irregular, interconnecting vascular spaces with infiltration into the myocardium. Epithelioid hemangioendothelioma is composed of proliferating large epithelioid cells with densely eosinophilic cytoplasm and may display vacuoles surrounded by a chondrohyaline stroma [4].

Treatment

Surgical treatment

To lower the risk of embolization, cardiac myxoma requires immediate full surgical excision of the tumour, including the attachment point and this should be treated as an emergency. A median sternotomy, cardiopulmonary bypass, and careful tumour excision with a margin of healthy tissue to ensure complete removal are typically part of the surgical procedure. Before surgical excision, coronary angiography (CAG) is also recommended for patients with myxomas to map out the vascular supply to the myxoma and confirm or rule out the presence

of concurrent coronary artery disease (CAD). This will facilitate surgical planning and technique [4, 13, 37].

The cardiac structures often need reconstruction, repair, and post-excision care, especially if the excised tumour has caused significant damage. Patch repair is one technique that uses autologous pericardium or synthetic materials to rebuild the atrial or ventricular walls. The mitral valve may need to be repaired or replaced if it is affected. These reconstructive procedures enable the restoration of normal heart function while preventing complications such as atrial septal abnormalities or valve malfunction [13]. Some patients, especially those who are elderly or have concomitant conditions, may not be good candidates for invasive surgery because of the higher risk of perioperative morbidity and death. Also, the problem of recurrence encountered in familial cases is a challenge. Furthermore, the quality of life and recovery of patients can be greatly impacted by possible postoperative complications such as bleeding, infection, and arrhythmias [56].

Additionally, robotic surgery has been applied more successfully and quickly to restore a normal quality of life [4, 37]. The DaVinci Xi robotic system has been used in some cases and this surgical technique provides excellent visualization and exposure for all surgical teams. The multi-wristed robotic instruments provide a good advantage for easier tumour excision when compared to the long-shafted minimally invasive cardiac surgery (MICS) instrumentation and sternotomy with good results, shorter intensive care unit, and hospital stay, improved postoperative quality of life, and this may be cosmetically advantageous for females if done at an expert center [57–59].

Medical management

Because of their benign nature and the possibility of radiation-induced heart tissue damage, chemotherapy and radiation therapy are rarely utilized for myxomas. However, these treatment options may be considered in cases where myxomas are part of Carney complex syndrome to manage the associated malignancies as well as in recurrent cases where surgical options are limited [13].

Tyrosine kinase inhibitors (TKIs) are one example of a targeted therapy that is gaining popularity. Targeting particular molecular pathways implicated in tumour growth and recurrence has demonstrated potential for TKIs, such as imatinib. These treatments, which provide a more individualized approach to treatment, are especially pertinent for patients with genetic abnormalities linked to myxomas [13]. Although surgical excision is still the most effective treatment for cardiac myxomas.

Emerging molecular therapies

Although there are still obstacles in their research and use, emerging molecular therapies such as gene editing, RNA-based, microRNA, epigenetic, stem cell, and immunotherapy provide encouraging alternatives to surgical treatment [13, 56, 60, 61].

Prognosis

Cardiac myxoma has an excellent long-term prognosis after complete surgical resection of the tumour mass to avoid/prevent relapse and embolic or systemic symptoms. There is a low rate of operative mortality and a quick postoperative recovery is expected after surgery. After surgery, recurrence may be noticed months or years later. For familial cases, the local recurrence rate is 12–22%, but in sporadic cases, it is 1–4%. This could be due to an undiagnosed multifocal tumor and insufficient surgical tumour removal [4, 12, 39]. Although long-term patient follow-up with serial transthoracic echocardiography is advised in all cases after the initial surgical tumour resection. Echocardiography and postoperative serial follow-up imaging are typically used due to the likelihood of recurrence, particularly in the group of patients with atypical myxomas [39].

Complications

Congestive cardiac failure

Congestive cardiac failure may be a complication of atrial myxomas [4, 37].

Cardiac arrhythmia and valvular defect

A cardiac myxoma may result in the development of valvular heart disease because the tumour can violently enter the mitral valve during the cardiac cycle or surgical resection leading to mitral and tricuspid stenosis or regurgitation [37, 52].

Thromboembolic complications

Following brain embolization left atrial myxomas typically manifest as ischemic stroke and cerebral aneurysm requiring anticoagulation and antiplatelet medication. Both pulmonary embolization and pulmonary atrial aneurysm may arise from right atrial myxoma. Multiple locations, including the coronary, renal, and limb arteries, may be involved in systemic embolization [4, 37]. Embolization leading to central retinal artery occlusion will lead to acute and permanent vision loss [44].

Infections

Sometimes bacteria like *S. faecalis*, *Streptococcus viridans*, or *Staphylococcus aureus* can infect CM patients directly. In these cases, patients can develop symptoms of infectious endocarditis along with high-grade fever, sepsis, and disseminated intravascular coagulation.

Immunosuppression, invasive treatments, and dental work are among the risk factors for infection. In these situations, the patient's life will depend on both surgical resection and broad antibiotic coverage [4, 37].

Central nervous system

Cerebral embolism may result in symptoms of a raised intracranial pressure, cerebral infarction, aneurysm formation, and subsequent subarachnoid or intracerebral hemorrhage [62].

Malignant transformation

Atrial myxoma, although benign, however, the propensity to undergo spontaneous malignant transformation remains uncertain and only very few cases have been documented in the literature. The malignant potential of atrial myxomas is believed to be influenced by strong hereditary factors, multifocal disease, and inadequate surgical excision of the main tumours [63]. The capacity to invade locally, metastasize, and recur both locally and distantly are among the malignant characteristics of atrial myxomas, although it can be challenging to differentiate between benign and malignant cardiac tumours clinically since they present with very similar symptoms, including the typical triad of obstructive, embolic, and constitutional symptoms [63].

Conclusion

Cardiac myxoma is the second most common benign primary cardiac tumours, notwithstanding their rarity. They occur in two forms: familial, such as in Carney complex disorder, and sporadic. CM are intracardiac tumours that are prone to cause intracardiac obstruction and embolization. Additionally, they might be linked to constitutional symptoms that mimic connective tissue and inflammatory diseases. A complete surgical excision of the tumor is the key component of a successful course of treatment. To monitor for tumour recurrence, long-term follow-up is frequently carried out.

Abbreviations

CM	Cardiac myxoma
CT scan	Computed tomography scan
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate

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