Atrial myxomas

Atrial myxomas are the most common primary heart tumors. They are benign intracavitary cardiac neoplasms and accounting for one-third to one-half of cases at postmortem and for about three quarter of tumors treated surgically (**Braunwald 2001**). Because of nonspecific symptoms, early diagnosis may be a challenge. Left atrial myxoma may or may not produce characteristic findings on auscultation. Most atrial myxomas, whether left or right, arise from the atrial septum, usually from the region of the limbus of fossa ovalis. About 10% have other sites of origin, particularly posterior wall, anterior wall and the appendages (in order of frequency) (**McAllister 1979**). ‘Two-dimensional echocardiography is the diagnostic procedure of choice. Most atrial myxomas are benign and can be removed by surgical resection.

Pathophysiology

Myxomas account for 40-50% of primary cardiac tumors. Approximately 90% are solitary and pedunculated, and 75-85% occur in the left atrial cavity. Up to 25% of cases are found in the right atrium. Most cases are sporadic. Approximately 10% are familial and are transmitted in an autosomal dominant mode. Multiple tumors occur in approximately 50% of familial cases and are more frequently located in the ventricle (13% vs 2% in sporadic cases).

Myxomas are polypoid, round, or oval. They are gelatinous with a smooth or lobulated surface and usually are white, yellowish, or brown such as of the figures 1 and 2

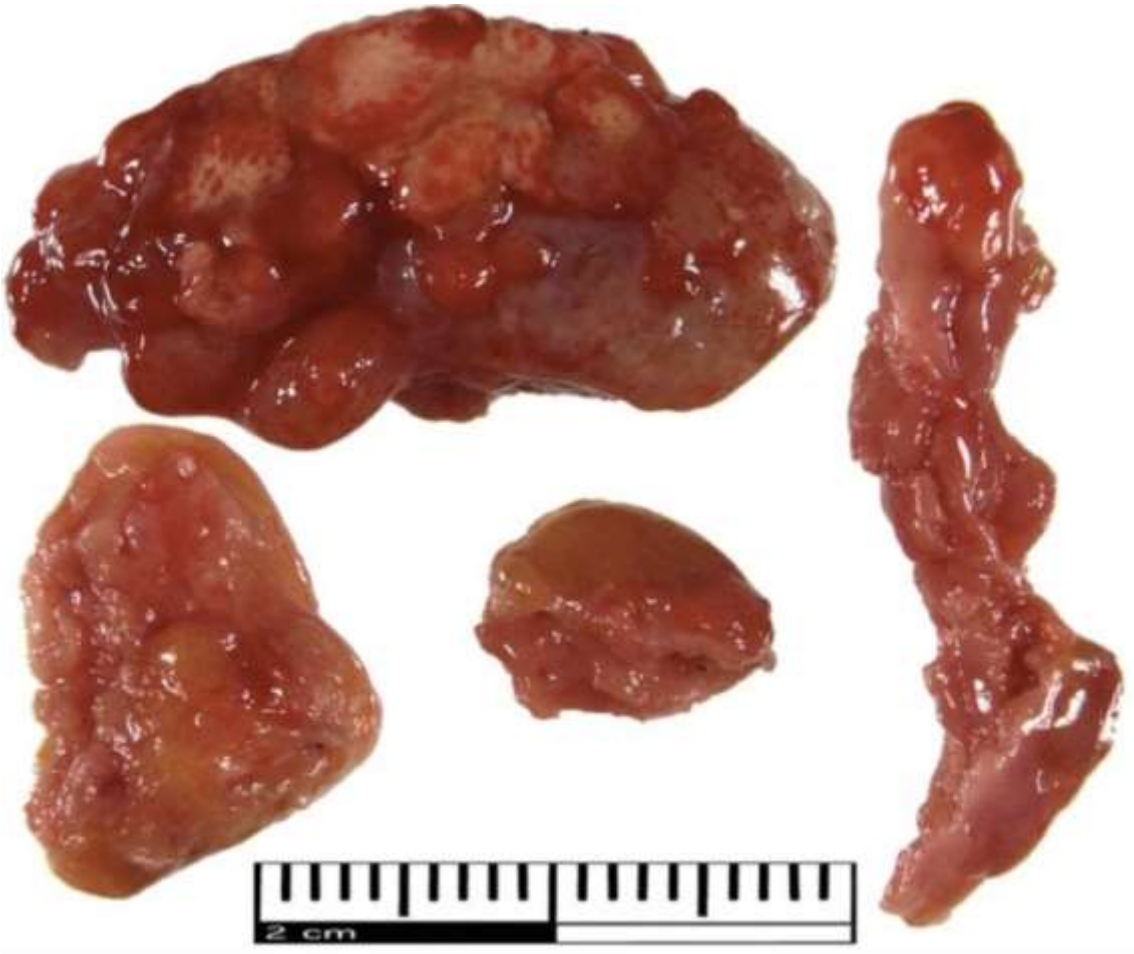


Fig. 1 Pathology specimens of multiple small myxomas resected from the right atrial surface.

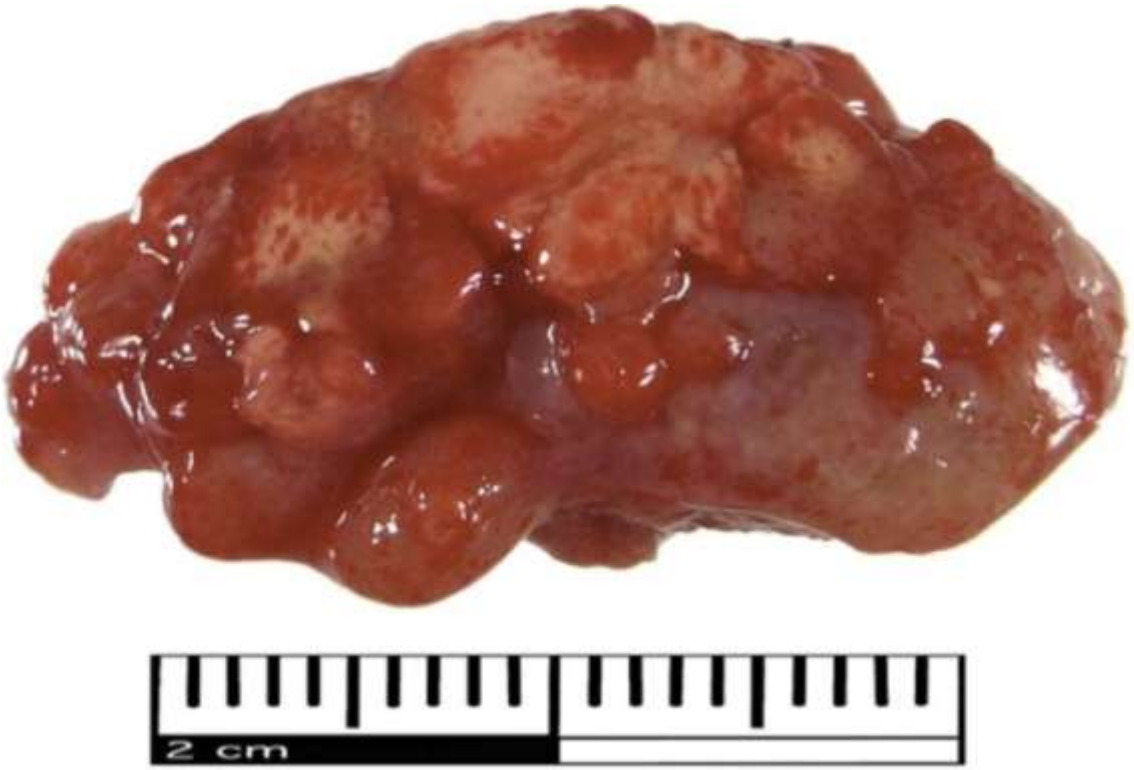


Fig. 2 Pathology specimen of myxoma from the vicinity of the interatrial groove, after near-total resection.

. The most common site of attachment is at the border of the fossa ovalis in the left atrium, although myxomas can also originate from the posterior atrial wall, the anterior atrial wall, or the atrial appendage. The mobility of the tumor depends upon the extent of attachment to the interatrial septum and the length of the stalk.

Although atrial myxomas are typically benign, local recurrence due to inadequate resection or malignant change has been reported. Occasionally, atrial myxomas recur at a distant site because of intravascular tumor embolization. The risk of recurrence is higher in the familial myxoma syndrome (**Larsson 1989**).

Symptoms from a cardiac myxoma are produced by mechanical interference with cardiac function or embolization and more pronounced when the myxomas are left-sided, racemosus, and over 5 cm in diameter (**Obrenovic-Kircanski 2013**). Because the tumors are intravascular and friable, myxomas account for most cases of tumor embolism, which occurs in about 30-40% of patients. The site of embolism is dependent on the tumor location (left or right atrium) and the presence of an intracardiac shunt. A case of multiple peripheral pulmonary artery aneurysms has been reported in association with a right atrial myxoma (**Dong 2016**). Most of the aneurysms had thrombi and became smaller following

disappearance of thrombi after resection of the right atrial myxoma. However, some aneurysms became slightly larger (**Dong 2016**).

Ha et al. reported a more frequent occurrence of systemic embolism in polypoid tumors as compared to round (58% vs 0%) (**Ha 1999**). Also, polypoid tumors more frequently prolapse into the ventricle. Prolapse of a tumor through the mitral or tricuspid valve may result in the destruction of the annulus or valve leaflets. In one study, 19% of the patients had atrial fibrillation associated with large atrial myxomas. Tumors vary widely in size, ranging from 1 to 15 cm in diameter, with the rate of growth not exactly known. In one case report, right atrial myxomas had a growth rate of 1.36 × 0.03 cm/mo. The myxomas are vascular tumors and may be neovascularized by a branch of a coronary artery (**Hasdemir 2011**). A case of hemorrhage in a left atrial myxoma has been reported (**Park 2011**). Kelli et al (**Kelli 2011**) described a large right atrial myxoma with fast growth rate.

Myxomas have been demonstrated to produce numerous growth factors and cytokines, including vascular endothelial growth factor, resulting in angiogenesis and tumor growth and an increased expression of the inflammatory cytokine, interleukin-6 (**Sakamoto2004**; **Mendoza2001; Kono 2000.**)

Most cases of atrial myxoma are sporadic, and the exact etiology is unknown.

Familial atrial myxomas have an autosomal dominant transmission. Carney syndrome is genetically heterogenous and is caused by a defect in more than one gene. It is estimated to account for 7% of all atrial myxomas without any predilection for age. Cardiac myxoma is more common in young women, and often complicated with cerebral infarction (**Cao 2017**). Abnormalities in the short arm of chromosome 2 (Carney) and chromosome 12 (Ki-*ras* oncogene) have been described. In one case report, a frame-shift mutation was found in exon 2 in the causative gene of Carney complex, protein kinase A regulatory subunit 1 alpha (*PRKAR1A*) (**Imai 2005**).

At present, there does not appear to be an association between cardiac myxomas and herpes simplex types 1 and 2 (**Anvari 2017**).

Epidemiology

United States statistics

Based upon the data of 22 large autopsy series, the prevalence of primary cardiac tumors is approximately 0.02% (200 tumors per million autopsies). About 75% of primary

tumors are benign, and 50% of benign tumors are myxomas, resulting in 75 cases of myxoma per million autopsies.

International statistics

Surgical incidence in the Republic of Ireland from 1977-1991 was 0.50 atrial myxomas per million population per year.

Sex- and age-related demographics

Approximately 75% of sporadic myxomas occur in females. In a series of 66 cardiac myxomas, the female-to-male ratio was 2.7:1(**Zheng 2013**). However, female sex predominance is less pronounced in familial atrial myxomas. In a retrospective analysis of 367 patients, there were 28 cases of right atrial myxoma, of which 16 occurred in males and 12 in females (**Li 2016**).

Myxomas have been reported in patients aged 3-83 years. The mean age for sporadic cases is 56 years; whereas it is 25 years for familial cases. In a retrospective review of 171 patients from India, the mean age of presentation was 37.1 years. Most of these patients were symptomatic; dyspnea was the most common symptom (**Aggarwal 2007**).

Symptoms/ History

Symptoms range from nonspecific and constitutional to sudden cardiac death (**Rios 2016**). In about 20% of cases, myxomas may be asymptomatic and discovered as an incidental finding. Signs and symptoms of mitral stenosis, endocarditis, mitral regurgitation, and collagen vascular disease can simulate those of atrial myxoma. A high index of suspicion aids in diagnosis. Table 1 shows the % of each symptom.

Table 1. Preoperative clinical symptoms and signs (Lee 2017)

Symptom/sign N (%)	
Dyspnea	**36 (38.7)**
Chest pain	**20 (21.5)**

Palpitation	**8 (8.6)**
Stroke	**10 (10.8)**
Syncope	**5 (5.4)**
Fever	**1 (1.1)**
Cough	**1 (1.1)**
Headache	**1 (1.1)**

Symptom/sign n (%)

Symptoms of left-sided heart failure include the following:

- Dyspnea on exertion (75%) that may progress to orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema is observed (**Fisicaro 2013; Pergolini 2015**).
- Symptoms are caused by obstruction at the mitral valve orifice. Valve damage may result in mitral regurgitation.
- Cerebral infarction is the first clinical manifestation in one-third of cases (**Sha 2014**). Because surgical resection is highly effective in left atrial myxoma, Zeng et al (**Zheng 2014**) should strive for early diagnosis in order to shorten the duration of symptoms and to avoid worse neurologic damage in patients in whom an embolic event is the initial manifestation. The myxomas with an irregular or villous surface have more frequently embolism.

Symptoms of right-sided heart failure include the following:

- Patients experience fatigue and peripheral edema.

- Abdominal distension due to ascites is rare; however, it is more common in slowly growing right-sided tumors (**Jha 2014**).
- These symptoms are also observed in the later stage of progressive heart failure associated with left atrial myxomas.

Severe dizziness/syncope is experienced by approximately 20% of patients. The most frequent cause in patients with left atrial myxomas is obstruction of the mitral valve. Symptoms may change as the patient changes positions.

Symptoms related to embolization include the following:

- Systemic or pulmonary embolization may occur from left- or right-sided tumors.
- Embolization to the central nervous system may result in transient ischemic attack, stroke, or seizure. In an analysis of 113 cases of atrial myxoma with neurologic presentation, 83% of patients presented with ischemic stroke, most often in multiple sites (43%). Twelve percent of patients presented with seizures. In a retrospective review of 74 patients with atrial myxoma, 12% had neurologic manifestations (**Lee 2007**). Cerebral infarction was present in 89% of the cases and most myxomas (89%) demonstrated a mobile component on transesophageal echocardiography. Other complications include myxoma-induced cerebral aneurysm and myxomatous metastasis that can mimic vasculitis or endocarditis (**Singh 2013**).
- Involvement of the retinal arteries may result in vision loss.
- Systemic embolization that causes occlusion of any artery, including coronary, aortic, renal, visceral, or peripheral, may result in infarction or ischemia of the corresponding organ.
- On the right side, embolization results in pulmonary embolism and infarction.
- Multiple, recurrent small emboli may result in pulmonary hypertension and cor pulmonale.
- Presence of an intracardiac shunt (atrial septal defect or patent foramen ovale) may result in a paradoxical embolism.

Constitutional symptoms that include fever, weight loss, arthralgias, and Raynaud phenomenon are observed in 50% of patients. These symptoms may be related to overproduction of interleukin-6.

Physical Examination

Note the following:

- Jugular venous pressure may be elevated, and a prominent A wave may be present.
- A loud S_1 is caused by a delay in mitral valve closure due to the prolapse of the tumor into the mitral valve orifice (mimicking mitral stenosis).
- P_2 may be delayed. Its intensity may be normal or increased, depending on the presence of pulmonary hypertension.
- In many cases, an early diastolic sound, called a tumor plop, is heard. This sound is produced by the impact of the tumor against the endocardial wall or when its excursion is halted.
- An S_3 or S_4 may be audible.
- A diastolic atrial rumble may be heard if the tumor is obstructing the mitral or tricuspid valve.
- If there is valve damage from the tumor, mitral regurgitation may cause a systolic murmur at the apex.
- A right atrial tumor may cause a diastolic rumble (due to obstruction of the tricuspid valve) or holosystolic murmur (due to tricuspid regurgitation).
- General examination may reveal fever, cyanosis, digital clubbing, rash, or petechiae.

Patients with familial myxoma may have a variety of features called syndrome myxoma or Carney syndrome (**Lanjewar 2014**), as follows:

- Myxomas in breast, skin, thyroid gland, or neural tissue
- Spotty pigmentation such as lentigines (ie, flat brown discoloration of skin), pigmented nevi, or both
- Endocrine hyperactivity such as Cushing syndrome
- Multiple cerebral fusiform aneurysms may be seen in patients with Carney syndrome (**Ryou 2008**).

Other described syndromes associated with atrial myxomas include the following:

- NAME syndrome features nevi, atrial myxoma, myxoid neurofibroma, and ephelides (ie, freckles [tanned macules found on the skin]).
- LAMB syndrome features lentigines, atrial myxoma, and blue nevi.

Laboratory Studies

Laboratory Studies are non-specific and non-diagnostic. If present, abnormalities may include the following:

- - Elevated erythrocyte sedimentation rate (ESR) and elevated C-reactive protein and serum globulin levels.
- - Leucocytosis.
- - Anemia may be normochromic or hypochromic. Hemolytic anemia may occur because of the mechanical destruction of erythrocytes by the tumor.
- - Serum interleukin-6 level may be raised and can be used as a marker of recurrence.

Chest radiography may show

- Cardiomegaly

- Abnormal cardiac silhouette, mimicking mitral stenosis.

- Unusual intracardiac tumour calcification.

- Pulmonary edema

- Biventricular hypertrophy with or without LA enlargement.

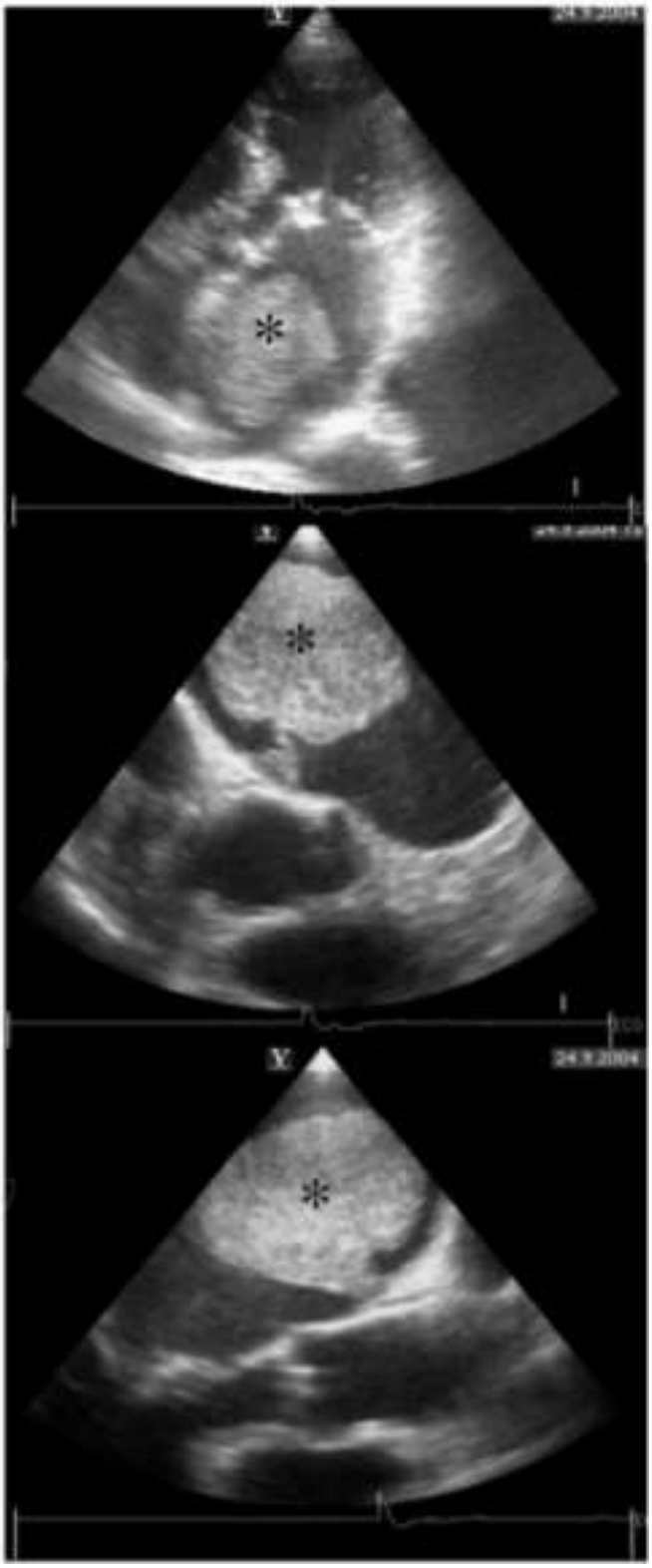
Transthoracic echocardiography

- Although transesophageal echocardiography is more sensitive, 2-dimensional echocardiography is usually adequate for diagnosis.
- All four chambers should be visualized because of multicentricity of tumour.

Transesophageal echocardiography

It has better specificity and 100% sensitivity compared to transthoracic echocardiography. Has good resolution of both atria and atrial septum and better anatomic details. Reveals smaller (1–3mm in diameter) vegetations or tumour and detects shunting. Figure 3

Figure 3

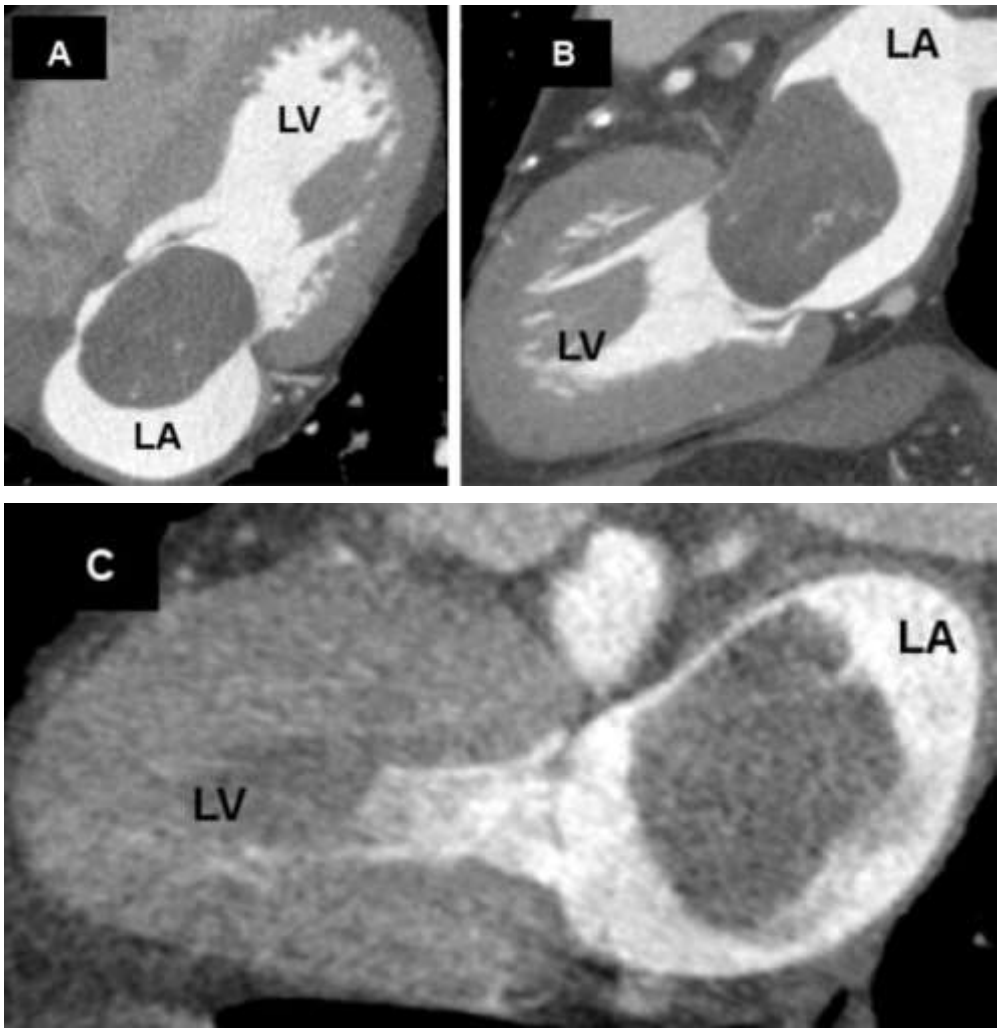


Typical transthoracic (top) and transesophageal (TEE; middle and bottom) echo images. Note the biatrial dilatation and the left atrial mass attached to the cranial part of the interatrial septum (*).

Cardiac Magnetic Resonance Image

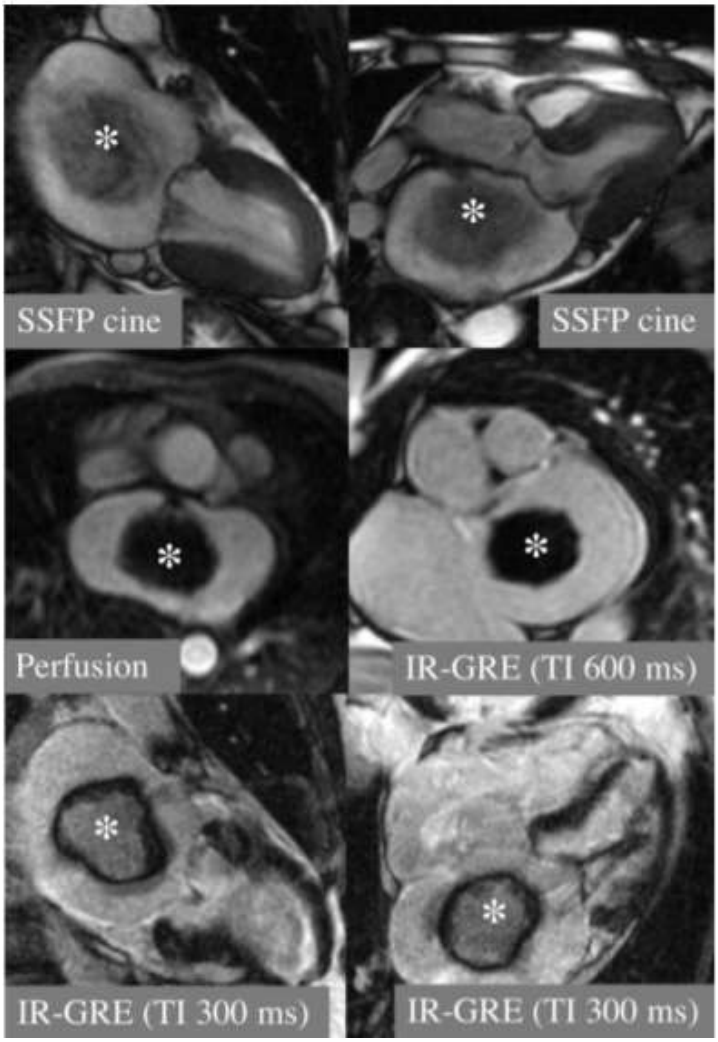
It provides useful information about size, shape and surface characteristics. Information about tissue composition can be used to differentiate a tumor and a thrombus. Figure 4 and 5

Figure 4



Multiplanar reconstruction of the left cardiac chambers. Left atrial myxoma prolapsing into the mitral valve orifice, going into the left ventricle during the diastolic phase of heart cycle (**A** and **B**) and returning into the left atrium during the systolic phase (**C**).

Figure 5



Top, Typical oblique SSFP cine CMR images (2- and 3-chamber view). Note the large mass in the left atrium (*). Because the temporal resolution of CMR is low and the mass does not move synchronized to ECG gating, it appears blurry on the CMR images. First-pass perfusion CMR can be viewed in the left middle panel. The left atrial mass does not show any sign of blood flow, as indicated by low signal during the entire first pass of contrast agent. Right middle and bottom panels depict inversion-recovery gradient-echo CMR images after contrast administration. The inversion time (TI) needed to null the atrial mass was 600 ms (middle right) compared with 300 ms needed to null normal myocardium, indicating that the T1 relaxation time of the mass is not significantly shortened by the gadolinium contrast agent. The black rim around the thrombus visible in the bottom panel at 300 ms is most likely explained by partial volume and the fact that some contrast may have started to diffuse into the outer layers, shortening T1 relaxation in this area.

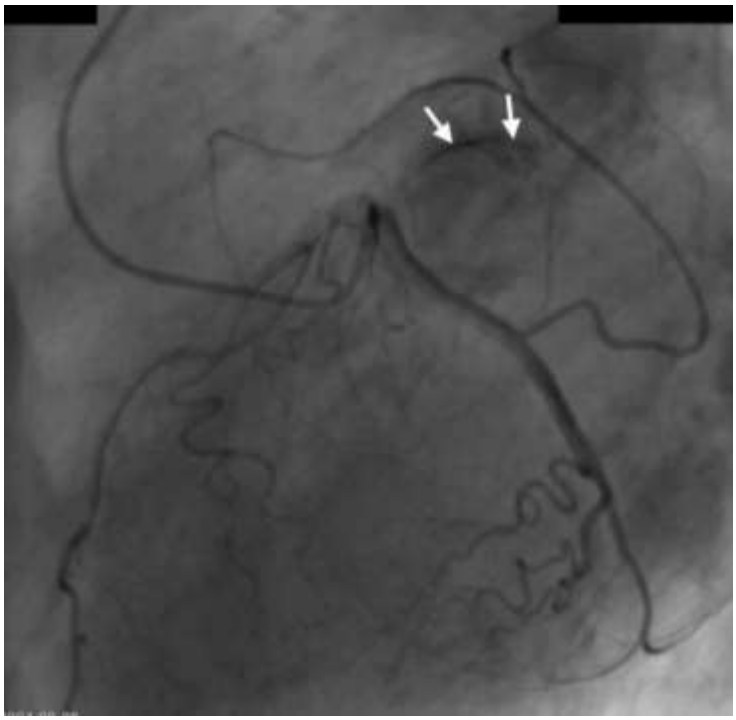
ECG

May show left atrial enlargement, atrial fibrillation, atrial flutter or conduction disturbances. The most common postoperative complication is atrial fibrillation **(Lee 2017**). P-wave dispersion is a simple and useful parameter for the prediction of postoperative AF in patients with LA myxoma **(Sahin 2015)**

Cardiac catheterization

Used in selected patients in case non-invasive evaluation is inadequate. Used to exclude co-existing coronary artery disease in patients of over 40 years of age. Figure 6

Figure 6



Modified late left anterior oblique coronary angiogram visualizing the atrial vascularization originating from the LCX artery. Arrows indicate the presence of several small atypical vessels in the area where the mass is attached to the atrial septum. In addition, small amounts of contrast media appear to leak in to the left atrium in this location.

Histologic features Figure 7

Figure 7

Are characteristic features of myxoma Spindle-shaped cells in a loose matrix. Figure 7

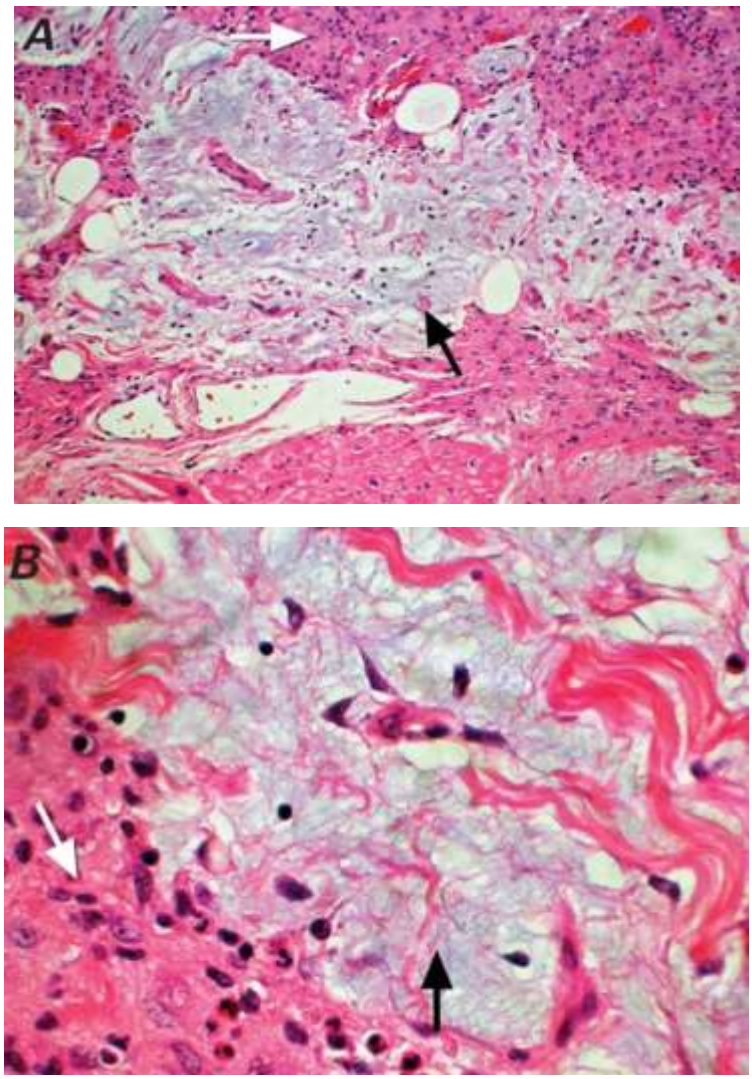


Figure 7 Histologic analysis of all resected specimens showed features characteristic of myxoma. Spindle-shaped cells in a loose matrix of myxoma in both low and high magnifications. A) At the top of the figure is a more stromal cellular area (white arrow); closer to the bottom are cardiomyocytes (black arrow) (H & E, orig. ×10). B) Inflammatory and stromal cells (white arrow) are intermingled within the matrix (H & E, orig. ×40). The black arrow indicates typical myxoma cells.

Differential diagnosis

I. **Rosai-Dorfman disease, or sinus histiocytosis**: It is a very rare benign multisystemic disorder characterized by histiocytic proliferative disorder that commonly affects the lymph nodes first reported by Rosai and Dorfman in 1969. It is a distinct histioproliferative disorder due to overproduction of histiocytes, which accumulate in lymph nodes (massive lymphadenopathy). The cardiac

involvement of this disease is extremely rare, and until now, only 19 cases have been reported. Khanna et al reported a case of a 53-year-old woman with right atrial mass mimicking myxoma, which the histopathologic evaluation revealed to be Rosai-Dorfman disease of the right atrium (**Khanna 2017**).Rosai-Dorfman disease is a rare, benign histiocytic proliferative disorder that commonly affects the lymph nodes.

II. **Glandular cardiac myxoma** is rare that, represent only 5% of cardiac myxomas. The histological characteristics, the absence of atypia, the absence of tumoral extension or neoplastic lymphatic vascular thrombi in the pedicle or in the interatrial septum, and the finding of typical myxomatous areas supported the diagnosis of cardiac myxoma with glandular component (**Lindner 1999**). Must be distinguished from adenocarcinoma metastatic to the heart. The combination of histopathological features and immunohistochemical profiles should improve the diagnostic accuracy of glandular cardiac myxoma.

III. **Prominent crista terminalis:** Gaudio et al described al the level of the posterior wall of the right atrial (RA) an apparent smooth, bean-like tumor, having a thin pedicle, was identified as a RA mixoma. Cardiac MRI was requested and showed in two sequential slices a muscular ridge, identified as a prominent crista terminalis. Some para-physiological structures sited in the RA may have the appearance of tumors, as crista terminalis, Eustachian valve extending into the RA chambers and Chiari network. The multiplain projections of MRI allow the cardiologist to identify the presence of intracardiac masses and to make a differential diagnosis between neoplasms and variant anatomic structures (**Gaudio 2014**).

IV. **Thrombus**

V. **Endocarditis**

Morbidity/mortality

Sudden death may occur in 15% patients with atrial myxoma. Death is typically caused by coronary or systemic embolization or by obstruction of blood flow at the mitral or tricuspid valve.

Morbidity is related to symptoms produced by tumor embolism, heart failure, mechanical valvular obstruction, and various constitutional symptoms.

In a single-center study of 62 patients with cardiac myxoma, actuarial survival was 96.8 ± 1.8% at 10 years. Most patients were asymptomatic following the surgery, without recurrence. Recurrence occurred only in 2 familial cases of left atrial myxoma. Freedom from reoperation was 98.4 ± 1.3% at 5 years and 96.8 ± 1.8% at 10 years (**Patil 2011**).

Complications

Complications of atrial myxoma include the following:

- Congestive heart failure
- Sudden death
- Cardiac arrhythmias
- Infection
- Embolization
- Rupture (**Yin 2016**)
- Myocardial infarction (**Al-Fakhouri 2017**)

Treatment

No known medical treatment exists for atrial myxomia, drug therapy is used only for complications such as Congestive Heart Failure or cardiac arrhythmias. Long-term survival after myxomas resections are excellents and recurrence are rare (**Lee 2017**). Based on our experience, surgical method did not affect the outcome. Surgical resection of the myxoma is the treatment of choice, surgery being safe with low morbidity and mortality. Pericardial/PTFE patch can be used to close the surgical defect caused by excision of tumor. The risk of tumor fragmentation and embolization, vigorous palpation or manipulation is avoided or performed only after cardioplegia. Damaged valve may require repair or replacement. Recurrence is usually attributable to incomplete excision of tumor, growth from second focus or intracardiac implantation from primary tumor.

Conclusions

Myxomas are the most common tumor of the heart. They are frequently located in left atrium and produce symptoms when they fragment and cause systemic emboli or when they interfere with cardiac valvular function and cause pulmonary congestion. Careful surgical management of these lesions should be curative with minimal early and late morbidity and mortality. Optimal operative technique emphasized minimal manipulation of the heart before institution of cardiopulmonary bypass and aortic cross-clamping and careful examination of intracardiac chambers with meticulous removal of myxomatous debris. Recurrence of atrial myxomas can occur most likely in about 3% of patients. However, extensive resection of the myxoma attached to atrial septum or atrial wall can reduce the likelihood of recurrence to a greater extent. Thus, long term clinical and echocardiographic follow-up is mandatory.

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