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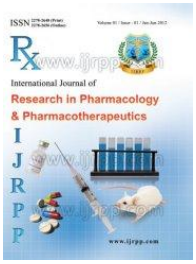

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Review article ***Open Access***

A comprehensive review on atrial myxoma

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ABSTRACT

An atrial myxoma is a noncancerous tumor in the upper left or right side of the heart. It grows on the wall that separates the two sides of the heart. This wall is called the atrial septum. Atrial myxomas are the most common primary heart tumours. It usually arises as a polypoid, gelatinous structure attached by a pedicle to the left atrium. Myxomas may arise less commonly in the right atrium or the ventricles. From an epidemiologic perspective, cardiac myxomas are divided into the following 2 categories, those that arise sporadically (non-familial myxomas), which account for about 95% of cases, and those that occur in association with a so-called myxoma syndrome (familial myxomas), which account for about 5%. Sudden death may occur in 15% patients with atrial myxoma. Sporadic cardiac myxomas occur approximately twice as often in women as in men. The exact origin of myxoma cells remains uncertain, but they are thought to arise from remnants of subendocardial cells or Multipotential mesenchymal cells in the region of the fossa ovalis, which can differentiate along a variety of cell lines. Signs and symptoms of mitral stenosis, endocarditis, mitral regurgitation, and collagen vascular disease can simulate those of atrial myxoma. The treatment of choice for myxomas is surgical removal. It is usually curative. After the diagnosis has been established, surgery should be performed promptly because of possibility of embolic complications or sudden death. The aim of this review is to find the cause, symptoms and treatment of atrial myxoma, also to make the aware of atrial myxoma.

Keywords: Atrial myxoma, Sneddon syndrome, Fossa ovalis, PRKAR1α, Pluripotential stem cell, Tumor plop

INTRODUCTION

MYXOMA

Myxomas (New Latin from Greek 'muxa' for mucus) are the most common type of primary cardiac tumours in all age groups accounting for one-third to one-half of cases at postmortum and for about three quarter of tumours treated surgically [1].

Myxomas are polypoid, round, or oval. They are gelatinous with a smooth or lobulated surface and usually are white, yellowish, or brown. The mobility of the tumor depends upon the extent of attachment to the interatrial septum and the length of the stalk [2].

A Cardiac myxoma is a benign gelatinous growth composed of primitive connective tissue cells and stroma resembling mesenchyme, this usually pedunculated and usually arises from the interatrial septum, near the fossa ovalis .The majority arise within the atrium. They may be distinguished from thrombi by their endothelial lining and the presence of endothelium-lined crevices and clefts on their surface. For a time, myxomas were thought to arise from minute endocardial endothelial structures known as Prichard structures, located primarily in the fossa ovalis. However, this theory has now been largely discredited by studies that show no relation between the seemingly age-related Prichard structures and myxomas [3].

Although myxomas are known as benign tumours, they can grow quite large, and can interfere with how the heart works causing problems with the pumping actions of the heart muscle and abnormal heart rhythms. Sometimes small pieces of tumor can break off and fall into the atrium or ventricle of the heart. If this happens, they may block an artery elsewhere in the body such as brain or in lungs [4].

ATRIAL MYXOMA

An atrial myxoma is a noncancerous tumor in the upper left or right side of the heart. It grows on the wall that separates the two sides of the heart. This wall is called the atrial septum [5]. Atrial myxomas are the most common primary heart tumours. It usually arises as a polypoid, gelatinous structure attached by a pedicle to the left atrium. Myxomas may arise less commonly in the right atrium or the ventricles.

These tumors tend to occur most often in people with a family history of cardiac tumors, but also seem to have in increased incidence in those with histories of embolic disorders. They also occur with more frequency in those with mitral stenosis or atrial fibrillation [6].

Left atrial myxoma

Myxoma of the left atrium is the commonest primary cardiac neoplasm.

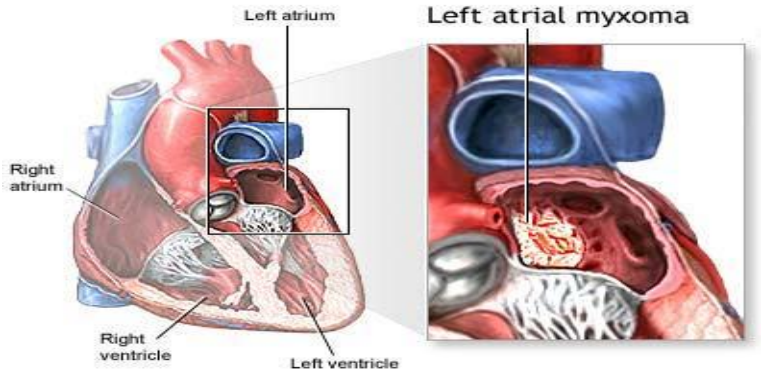

Figure.1: Left atrial myxoma

Left atrial myxomas have been confused with inflammatory disease, such as lupus erythematosus, Hamman-Rich syndrome, myocarditis, subacute bacterial endocarditis, or even acute rheumatic fever. Hyperglobulinaemia has been reported, but has not been emphasized as much as the haemodynamic and embolic aspects of the disease [2].

Right atrial/ventricular myxoma

Right atrial and ventricular myxomas are very rare.

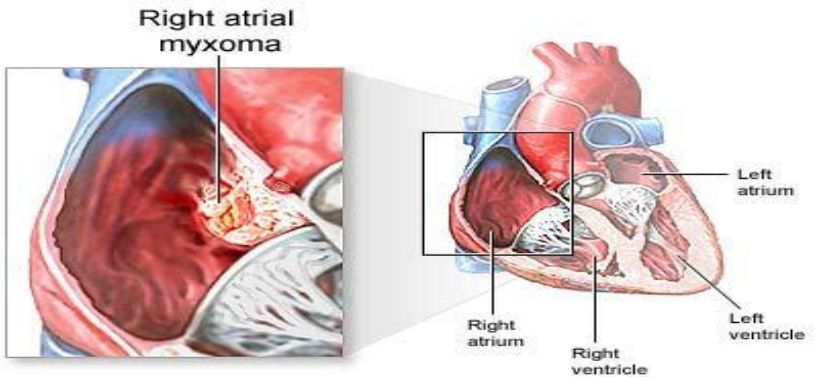

Figure .2: Right atrial myxoma

Right atrial myxomas rarely produce symptoms until they have grown to be atleast 13cm (about 5 inches) wide.

HISTORICAL NOTE AND NOMENCLATURE

History of myxoma

A British surgeon in 1845 described a ‘’vascular growth” in the heart and concluded those to be cadaveric clots. Subsequently, in the first half of the twentieth century, a multitude of papers tried to demonstrate the nature of the myxomas as being the product of an organized intracardiac thrombus. The earliest report to suggest the neoplastic nature of the myxoma was in 1924, labelling those lesions endo-cardial tumors. In the latter decades of this century, sophisticated studies of myxoma, including histochemistry, specific biologic immune marker studies, electron-microscopy and tissue cultures, revealed and documented the neoplastic nature of the myxoma. Those studies set to rest the century old controversy of the nature of the myxoma, establishing it to be of true neoplastic origin rather than of thrombotic origin. The origin of the myxoma appears to be related to the omnipotent (pluripotential) Mesenchymal vasoformative cells of the atrial subendocardium. Those cells also have been called subendocardial cushion cells.

History of left atrial myxoma

Left atrial myxoma was first described over 150 years ago (King 1845)3. The first antemortem diagnosis, by angiocardiography, was in 1952 (Knepper et al 1988)4, and the first surgical excision documented 3 years later (Crafoord 1955) [7].

The first documented association between nonembolic dermatologic manifestations and atrial myxomas was made in 1973. The nevus, atrial myxoma, myxoid neurofibromata, ephelides syndrome; lentigines, atrial myxoma, blue nevi syndrome; and Carney complex (a multiple neoplasia and lentiginosis syndrome) were first reported in 1980, 1984, and 1985, respectively (Greeson et al 1998) [8]. Sneddon syndrome, which commonly presents with a livedo-type rash and diffuse cerebrovascular disease associated with atrial myxoma [9].

EPIDEMIOLOGY

The incidence of atrial myxomas found at autopsy is 0.03%10. It is the most common primary tumor of the heart in adults but comprises only 10% of primary Intra cardiactumors in children. Overall, they represent 50% of all primary cardiac tumors [11].

From an epidemiologic perspective, cardiac myxomas are best divided into the following 2 categories: Those that arise sporadically (non-familial myxomas), which account for about 95% of cases and those that occur in association with a so-called myxoma syndrome (familial myxomas), which account for about 5%.

Mortality/Morbidity

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 [12].

Sex

Sporadic cardiac myxomas occur approximately twice as often in women as in men. Female sex predominance is less pronounced in familial atrial myxomas.

Age

Myxomas have been reported in patients aged 3-83 years. The mean age for sporadic cases is 56 years. Patients with familial cardiac myxomas are generally younger at first diagnosis than those patients presenting with sporadic cardiac myxomas. The mean age for familial cases is 25 years [13].

ETIOLOGY

Numerous theories have been postulated regarding the etiology of cardiac myxomas. For a time, cardiac myxomas were believed to arise from mural thrombi. However, the differences between myxomas and thrombi are substantial. Although mural thrombi tend to occur in individuals with underlying heart disease and in many locations within the heart (eg, atrial appendages, atria, and ventricles), myxomas arise with astonishing consistency in 1 location: primarily adjacent to the fossa ovalis [14].

Furthermore, histologically, myxomas do not organize into fibrous tissue or show stratification, a classic feature of mural thrombi. Cardiac myxomas also behave differently from thrombi in tissue culture studies. This body of evidence in support of the neoplastic nature of myxomas has led to the consensus that cardiac myxomas are not of thrombotic origin and are, indeed, neoplastic. The impetus for this neoplastic transformation is equally unclear.

Regardless of the precise etiology of cardiac myxomas, the morphologic, ultrastructural, and immunoperoxidase studies done to date suggest that the neoplastic cells originate from mesenchymal cells capable of endothelial differentiation [15]. These cells can differentiate into endothelial tissue. Immunohistochemical reactivity has been shown to be similar to human gut epithelium [16]. Myxoma cells also have phenotypic markers of the embryonic endothelial-to-mesenchymal transformation that precedes terminal differentiation of endocardial cushions. This finding supports the hypothesis that cardiac myxoma cells derive from adult developmental remnants [17].

Although genetic factors Clearly play a role in myxoma , they do not appear to offer a consistent explanation in sporadic cases.

Carney Syndrome is thought to be responsible for most of the familial cases of cardiac myxoma and may represent as many as 7% of all the cases. Carney Syndrome is an autosomal dominant syndrome characterized by Cardiac myxoma formation, spotty skin pigmentation, endocrine hyperactivity and other tumors such as testicular Sertoli cell tumor, Psammomatous melanotic schwannoma, pituitary adenoma, and thyroid tumors. Mutations in the PRKAR1α gene encoding the R1α regulatory subunit of protein kinase A cause familial cardiac myxomas in autosomal dominant Carney complex. Individuals with familial myxoma were described as having either the nevi, atrial myxoma, Myxoid neurofibroma, and ephelides (NAME) syndrome or the lentigines, atrial myxoma, and blue nevi (LAMB) syndrome [18].

Patient treated with Immunosuppressive agent during heart transplantation are also found to be susceptible to atrial myxoma.

PATHOPHYSIOLOGY

The exact origin of myxoma cells remains uncertain, but they are thought to arise from remnants of subendocardial cells or Multipotent mesenchymal cells in the region of the fossa ovalis, which can differentiate along a variety of cell lines. The hypothesis is that cardiac myxoma originates from a pluripotential stem cell, and myxoma cells express a variety of antigens and other endothelial markers.

Myxomas can be formed by pedunculation with a short broad base (85% of myxomas), but sessile forms can also occur. Myxomas are yellowish, white, or brownish, and are frequently covered with thrombus. The tumour size ranges from 1 cm to 15 cm and can weigh from 15 g to 180 g. The surface of the myxoma is smooth in the majority of the cases but can also be friable or villous. The villous or papillary form of myxoma has a surface that consists of multiple fine or very fine villous, gelatinous, and fragile extensions that have a tendency to fragment spontaneously and are associated with embolic phenomena. Histologically, myxomas are composed

of myxoma (lepidic) cells, endothelial cells, smooth muscle cells, and an undifferentiated form embedded within an acid mucopolysaccharide ground substance and covered by endothelium [19].

SYMPTOMS

Symptoms of CM mainly depend on the location, size, and mobility of the neoplasm Symptoms range from nonspecific and constitutional to sudden cardiac death. In about 20% of cases, myxoma 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.

Symptoms of left-sided heart failure

- Dyspnea on exertion (75%) that may progress to orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema is observed.
- Symptoms are caused by obstruction at the mitral valve orifice. Valve damage may result in mitral regurgitation.

Symptoms of right-sided heart failure

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

Symptoms related to embolization

Embolisation is due to the degradation of extracellular matrix of myxoma cells by matrix metalloproteinase enzyme.

- Systemic or pulmonary embolization may occur from left- or right-sided tumors.
- Left-sided symptoms are produced from the infarction or hemorrhage of viscera.
- Embolization to the central nervous system may result in transient ischemic attack, stroke, or seizure.
- Strokes are often recurrent and symptomatic but may occur asymptomatically and resulting multi-infarct dementia.
- Embolisation to the spinal cord leads to neurological symptoms with resultant paraplegia.
- Cerebral infarction.
- Myxoma-induced cerebral aneurysm.
- Involvement of the retinal arteries may result in vision loss.
- Systemic embolization 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.
- Embolic phenomena may result in numerous cutaneous manifestations including petechiae, cyanosis, splinter haemorrhages, livedo, reticularis and Raynaud's phenomenon.
- Small bowel obstruction caused by a metastasizing atrial myxoma may also occur [20].

Constitutional symptoms

These symptoms may be related to overproduction of interleukin-6.

- Fever
- Weight loss
- Arthralgias (pain in joints esp. When there is no inflammation)
- Raynaud phenomenon (intermittent attacks of ischaemia of the extremities of the body)
- Hemoptysis (coughing up of blood from respiratory tract) due to pulmonary edema or infarction
- Chest pain is infrequent8.

Severe dizziness/syncope

- This is experienced by approximately 20% of patients.
- Symptoms may vary depending on size and position of myxoma [21].

DIAGNOSIS

Diagnosis of atrial myxoma is done by

1. General physical examination
2. Laboratory studies
3. Imaging studies
4. Histological studies
5. Miscellaneous

General physical examination

In many patients, early diastolic sound, called a tumour plop is heard. This sound is produced by the impact of the tumour against the endocardial wall or when its excursion is halted. If there is valve damage from tumour, mitral regurgitation may cause systolic murmur at apex. Right atrial tumour may cause a diastolic rumble or holosystolic murmur due to tricuspid regurgitation.

Laboratory Studies

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

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

The health care provider will listen to the heart with stethoscope. A "tumor plop" (a sound related to movement of the tumor), abnormal heart sounds, or murmur may be heard. These sounds may change when the patient changes position.

Imaging studies

- Chest radiography

It may show

- Cardiomegaly
- Abnormal cardiac silhouette, mimicking mitral stenosis.
- Unusual intracardiac tumour calcification.
- Pulmonary edema
- Biventricular hypertrophy with or without LA enlargement.

- 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.

Histological studies

These are characterized by the presence of lipidic cells embedded in myxoid stoma.

Other tests

If petechiae are present, a skin biopsy may reveal the presence of elongated or spindle-shaped, myxomatous, endothelial-like cells with round or oval nuclei and prominent nucleoli [22].

TREATMENT

The treatment of choice for myxomas is surgical removal. It is usually curative. After the diagnosis has been established, surgery should be performed promptly because of possibility of embolic complications or sudden death. The root of the pedicle and the full thickness of the adjacent interatrial septum should be excised. The resulting atrial septal defect caused by the excision of tumour can be closed by direct suturing or if too large, with a pericardial or Dacron patch.

Mitral valvuloplasty or valve re- placement may be necessary if the mitral valve or chordae tendineae, or both, have been damaged by the tumour.

Recurrence is usually attributable to incomplete excision of tumour, growth from second focus or intracardiac implantation from primary tumour [23].

The treatment of atrial myxoma during pregnancy is dictated by both the maternal and fetal status. Tumor excision during pregnancy, when causing mitral valve obstruction and cerebral emboli, has been reported. If asymptomatic, however, it may be resected postpartum.

Symptomatic treatment

Medical therapy may be required for the treatment of associated conditions, which include arrhythmias, heart failure, and embolism.

- Arrhythmias are treated with the appropriate antiarrhythmic drug until surgery can be performed.
- If there is any evidence of residual heart failure, then appropriate long-term therapies (e.g., beta-blockers, ACE inhibitors, and furosemide) may be needed in individual cases.

- No guidelines or recommendations exist regarding treatment of embolic phenomena in cases of myxoma. The definitive treatment is surgical removal of the cardiac tumor.
- Nonsteroidal anti-inflammatory agents administered for other reasons may mask the systemic symptoms related to atrial myxomas, interfering with the diagnostic process.
- The treatment of embolic phenomena depends on the vascular territory involved. In cases where large vessels are involved, anticoagulation is started based on an initial diagnosis of vascular occlusion, but the definite treatment is surgical removal of myxomatous tissue [24].

The occlusive mass, unlike acute coronary thrombosis, is not composed mainly of platelet-rich thrombus. Hence, both intracoronary thrombolysis and mechanical revascularization may be unsuccessful in patients presenting with MI due to cardiac myxoma.

Emerging Therapies

Cardiac auto transplantation may be considered for complex cases and those carried out in specialized centers. Cardiac auto transplantation is a technique mainly involved for resection of complex cardiac tumors. The technique of auto transplantation involves cardiac explantation, ex vivo tumor resection with cardiac reconstruction, and cardiac reimplantation [25].

Surgical Care

- Operative resection of the myxoma is the treatment of choice.
- The surgery is safe, with an early postoperative mortality of 2.2%. Some authorities believe resection should be performed immediately after the diagnosis is made.
- Because of the risk of tumor fragmentation and embolization, vigorous palpation or manipulation should be performed only after cardioplegia.
- Surgery for sporadic atrial myxoma is usually curative. Long-term prognosis is excellent. In a series of 112 patients, only 4 deaths occurred over a median follow-up of 3 years.

✓ The recurrence rate is 1-5%. Recurrence after 4 years is uncommon.

✓ The recurrence rate of familial patients is 20%.

- Recurrence is usually attributed to incomplete excision of the tumor, growth from a second focus, or intracardiac implantation from the primary tumor.
- Wider resection of the stalk attachment to the endocardium may reduce the burden of pretumorous cells.
- A cloth patch or parietal pericardium is used to close the surgical defect.
- Pretumorous cells around the stalk should be destroyed by laser photocoagulation. This obviates the need for a wide surgical resection.
- To fully visualize both sides of the heart, some surgeons recommend a biatrial approach.
- Damaged valves may require annuloplasty or prosthetic replacement.
- Biannual echocardiograms are useful for early detection of recurrent tumors.

PROGNOSIS

- Although a myxoma is not cancer, complications are common. Untreated, a myxoma can lead to an embolism (tumor cells breaking off and traveling with the bloodstream), which can block blood flow. Myxoma fragments can move to the brain, eye, or limbs.
- If the tumor grows inside the heart, it can block blood flow through the mitral valve and cause symptoms of mitral stenosis. This may require emergency surgery to prevent sudden death [26].

CONCLUSION

Heart is an organ which is not usually affected by tumors. But if affected by tumor, it will lead to serious complications. Atrial myxoma is a non-cancerous primary heart tumor which usually develops in the left upper chamber of the heart and tends to be more common among women. Atril myxoma has been confused with several inflammatory diseases or even acute rheumatic fever. Because of non specific symptom, early diagnosis is a challenge. Although atrial myxoma is typically benign, local recurrence due to resection or malignant change are also reported. Till now surgery is the only treatment for atrial myxoma which frequently evokes post-surgery complaints mainly recurrence and other cardiac problems. So, the need for a better method for treatment has become necessary. But due to rarity of the disease, and unknown biology; drug target are not

yet developed. Awareness of the disorder can make early detection and treatment possible. If it is left untreated it may lead to embolism, which can block the blood flow.

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