



Atrial Myxoma: From Diagnosis to Management

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Abstract

The purpose of this paper is to review and discuss all the topics and issues related to the diagnosis and management of atrial myxomas. These tumors represent the most common primary heart tumors and may present with a wide range of symptom spectrum making the diagnosis sometimes difficult. Echocardiography is the gold standard tool for diagnosis as well as follow-up. Due to its potential serious consequences, myxoma should be removed as soon as possible. While surgery results in excellent overall survival and freedom from reoperation rates, annual follow-up is recommended particularly in familial cases.

Keywords: Myxoma; Cardiac tumor; Carney complex

Introduction

Myxoma is a neoplasm composed of stellate to plump cytologically bland mesenchymal cells set in a myxoid stroma [1]. Myxoma was first diagnosed in 1952 by Goldberg [2]. This neoplasm is the most common cardiac benign tumor. Nevertheless, many of its features still remain unknown or controversial. In this paper, we review recent scientific data concerning diagnosis and management modalities of myxomas.

Epidemiology

Myxomas represent 0.25% of all heart diseases [3]. Even if their annual incidence rarely exceeds 0.5 to 1 case per million individuals [4,5], myxomas are the most frequent primary cardiac tumors in adults and represent more than 50% to 85% of benign ones [2,6,7].

Epidemiologically, myxomas show a female predominance with a sex ratio of 3:1 [4,5] and are generally classified into two main epidemiologic forms: the familial and the sporadic. On one hand, the latter type, representing 95% of all cases [7], affects mainly middle age women. Tumor is more commonly unique and localized in the left atrium. On the other hand, the familial type affects more frequently young males. Tumors are usually multiple and may occur in other cardiac chambers. This type has autosomal dominant inheritance and falls under Carney's syndrome. The latter was described in 1985 and combines cardiac and extracardiac myxomas as well as cutaneous pigmentation (lentiginosis periorificial, café-au-lait spots, blue nevi) and endocrine tumors (Cushing syndrome, breast fibroadenoma, testicular tumor, acromegaly...) [8,9]. Carney complex is a multiple neoplasia syndrome caused by PRKARIA, inactivating mutations associated with chromosome 17q22-q24. These genes encode the cAMP's (cyclic adenosine monophosphate) regulatory subunit of the dependent protein kinase A. Nevertheless, their role still remains imprecisely known [10,11].

Histogenesis

Myxoma's origin remains inadequately understood as the theory stating that it derives from thrombi is progressively rejected [12,13]. Furthermore, myxomas were alleged to arise from microscopic endocardial structures located in the fossa ovalis, known as Prichard structures [14]. By detecting the antigens and genetic material of the Herpes simplex virus type 1 (HSV1) in 70% of cases of operated myxoma, Li et al. [15] suggest that cardiac myxomas could result from chronic inflammation of the endocardium induced by viral infection.

The conflicting hypotheses on the histogenesis of cardiac myxoma originate from two main contributing factors: the heterogeneous phenotype of myxoma cells, as well as the different approaches in their morphological and immuno-histochemical characterization. Nevertheless, it is relevant to point out that, currently, most authors believe myxoma derives from multipotent mesenchymal stem cells [16]. Indeed, myxoma tumoral cells exhibit two characteristics. On one hand, it exhibits the phenotypic markers of embryonic endothelial-to-mesenchymal transformation, which precedes terminal differentiation of endocardial cushion formation involved in cardiac septation and valve

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formation. On the other hand, it displays markers of primitive cardiac mesenchymal differentiation [17]. This hypothesis is further supported by the presence of substantial similarities between the following three types of cells: the endothelial lining ones, the cells within the cushion tissue and finally the cardiac myxoma's lepidic ones [6]. However, it still remains unclear from which the cardiac myxoma derives from but there are currently three main leads. The first one is the embryonic remnants of cardiac cushions, the second, the primitive multi-potential mesenchymal cells existing in adult hearts and the third, the ectopic de novo re-expression of early cardiomyogenic phenotype in adult cardiac cells [17].

Finally, other authors support the nervous origin of myxomas. Based on immuno-histochemical data, Krikler et al. [18] affirm that myxomas originate from a neuroendocrine tissue. The observed pattern of neuroendocrine markers and distribution of VWF/FVIII, CD34 and SMA (smooth muscle actin) led Krikler et al. [18] to suggest a possible neuroendocrine origin of cardiac myxoma. This origin was further supported by the findings of Teraccianno et al. [19]. In fact, they detected strong and diffuse immune-histochemical staining of CALB2 (calretinin/calbindin 2 protein normally detected in the cells of the central and peripheral neural tissue) in the cytoplasm and nucleus of neoplastic cells in all examined sporadic cardiac myxoma cases [20].

Anatomical Pathology

Myxomas are intra-cavitary tumors that mainly affect atrial chamber (75% LA and 18% RA). They arise from inter-atrial septum near the fossa ovalis but rarely anteriorly or posteriorly to the atrial walls, or even auricles. In 6% of cases, these tumors originate in the ventricles (RV 8%, 4% LV) or in the atrioventricular valves (1%). Complementarily, myxomas can be bi-atrial or, more rarely, multi-focal [21].

Macroscopically, the myxomas' size varies from 1 to 15 cm, with an average of 5 cm to 6 cm [22,23]. Myxomas can be either pedunculated or have a wide base of implantation.

St. John Sutton's classification distinguishes between two forms of myxomas: solid and papillary [24]. The first group represents 2/3 of myxomas and corresponds to solid tumors, sometimes polypoid, with unstriated and smooth surfaces related to a high superficial collagenation. Papillary myxomas are brittle and characterized by their irregular shape. One particular characteristic, explained by the secretory activity of these tumors, is the release of metalloproteinase and enzymes which degrades continuously the extracellular matrix and therefore creates an imbalance between the process of synthesis and tissue fragmentation [25]. These characteristics explain why obstructive heart failure is usually associated with solid tumors while embolic events represent the most common clinical feature of fragile papillary myxoma [26] (Figure 1).

The histology of cardiac myxoma resembles closely the mesenchymal tissue, forming vascular structures. It is characterized by a myxoma stroma rich in elastin, collagen and proteoglycans in which reside small fusiform or stellate cells with round or oval nuclei and scarce eosinophilic cytoplasm [27]. These cells are sometimes multi-nucleated. They are shaped and structured in chained rings, or in nests all around the capillaries. Other cells can also be observed like lymphocytes, plasma cells, histiocytes and mast cells, which may all together contribute to systemic manifestations [27].

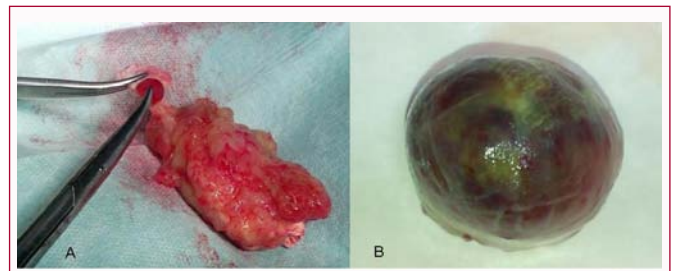


Figure 1: Macroscopic features of atrial myxoma: solid vs. papillary forms.

Myxomas are often infused by thin-walled vessels lacking pericytes, versus thick-walled ones located at the implantation base. The tumor surface is often covered with a layer of flattened endothelial cells which form small vascular spaces or invaginations. In some locations, this endothelium is covered by lipid cells.

Most authors agree on the benign aspect of myxomas. Nevertheless, these tumors have a local and remote extensive potential [8]. As a consequence, myxomas are considered biologically benign but "*functionally malignant*" tumors. In fact, many brain metastases localizations, as well as arterial and bone (sternum, spine and pelvis...) have been described in the literature [28-30]. Some authors believe that these metastases result from the persistence within the tumor fragments disseminated of live tumor cells capable to grow and multiply [31]. This tumor progression is promoted by the autocrine expression of growth factors and angiogenesis (VEGF, vascular endothelial growth factor and PDGF, platelet-derived growth factor), which acts upon the cytoplasmic receptors [32-35]. Similarly, inflammatory cytokine (IL6, IL8), abundantly secreted by the neoplastic tissue, may also enhance CM (cardiac myxoma) vascularization and migration as well as proliferation of their cells [21]. Furthermore, others antigenic signals are induced by monocyte chemotactic protein-1 (MCP-1) and thymidine phosphorylase (TP) which are expressed by myxoma cells [36]. Further studies are needed to prove, first, the involvement of other markers such as MIA and S100 in tumoral growth; second, the recurrence or even the exact nature of the extra-cardiac dissemination or malignant potential of cardiac myxoma [21].

Besides, it was found that some recurrent lesions may exhibit more aggressive histology and significantly faster cell proliferation [37-39]. While some authors suggest successive malignant alteration of benign myxomas, others think that these tumors correspond to undiagnosed malignant primary tumors [40-43].

Diagnosis

Clinical presentations of cardiac myxomas are polymorphic and unspecific. They depend for the most part on their base, shape, size and mobility. As a consequence, a wide spectrum of clinical manifestations ranging from asymptomatic forms, identified erratically, to severe ones with complications involving life-threatening prognosis. While in the series of Beghetti et al. [44] more than half of the patients were diagnosed during a routine examination, others stated that only 10% to 15% of myxomas are asymptomatic and constitute the prerogative of small tumors [21]. The data in the literature related to the myxoma's growth remains imprecise but it can be inferred from a certain set of observations. Oldershaw et al. [45] reported three cases of myxoma quiescent in patients ranging from 7 to 16 years! Roudaut and Allal reported respectively 1 and 3 cases of left atrial myxomas which developed within the 8, 11, 12 and 14 months following the

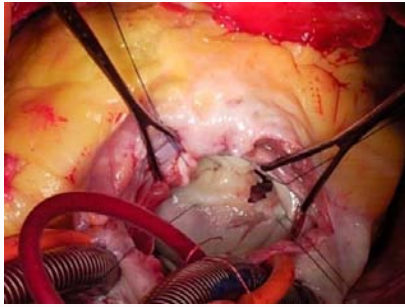


Figure 2: Operative view showing mitral valve injury after removal of left atrial myxomas.

first echocardiography without visible image [46-47]. The reported growth rate of left atrial myxomas varies from 0 to 1.3 - 7mm/month [48-49].

Hemodynamic consequences

The hemodynamic consequences reflect in signs of left heart failure (dyspnea, paroxysmal nocturnal dyspnea, orthopnea or pulmonary edema) or right one (venous hyper pressure, lower limb edema, and hepatomegaly). The symptoms are often progressive but may have a positional character. Because of their atrial localization, myxomas can compromise systemic or pulmonary venous drainage or hinder valve motion. On one hand, they can create a barrier to the passage of blood from the atria to the ventricles. This obstruction, progressive or intermittent, often simulates a mitral or tricuspid stenosis and can cause dyspnea, malaise, or sudden death [50]. This intra-cardiac obstruction is found in approximately 50% of cases, but may appear later in the disease evolution [24,51]. On the other hand, these tumors can cause atrioventricular valvular regurgitation mainly due to impairment of valve closure or even leaflet damage [52]. Indeed, several valvular destruction mechanisms have been reported: mechanical destruction, chemical or infectious. In our experience, we have operated a young patient for whom we discovered a small crack in the mitral valve after resection of left atrial myxoma. Mitral valve repair was performed with a satisfactory result (Figure 2).

Embolic events

Embolic complications represent a serious complication of myxoma. This phenomenon is related to the migration of the tumor or its fragmentation, or even the posting of thrombi and vegetations adherent to the tumor surface.

Patients (30% to 45%) with left atrial myxoma get complicated with systemic emboli [53]. While all organs may be affected, nevertheless, the central nervous system remains the most affected (more than 50% of cases) [54-57]. Cases of retinal emboli, renal mesenteric coronary or lower limbs have been reported [55,58-63].

It's widely admitted to consider at high risk of embolism, patients presenting with some threatening echocardiographic images papillary of large multi-lobed tumors, or intermittently prolapsing mass [64]. Keeling searching for common characteristics of patients who experienced embolic events in their series, highlighted pedunculated myxoma (76.9%), an atrial tachyarrhythmia in six (46.2%), involvement of mitral valve tissue (38.5%), as well as prolapse through the mitral valve (30.8%). Moreover, the combination of two factors was detected in almost all patients [5].

Right atrial myxomas seem to be less emboligenic. Although it

affects only 10% of cases, this complication can cause massive and fatal pulmonary embolism or pulmonary arterial obstruction with secondary pulmonary hypertension. Furthermore, paradoxical embolisms seem to be rare [65].

General signs

General signs appear in approximately 90% of patients and may be the sole symptoms in 30% of cases [7,66]. It generally consists of fever, weight loss, Raynaud's phenomenon, arthralgia and myalgia. These symptoms are often accompanied by a procession of biological abnormalities, such as chronic anemia, thrombocytopenia, or the inflammatory syndrome (leukocytosis, elevated ESR and CRP as well as hypergammaglobulinemia).

These events reflect an inflammatory response as well as immune reaction against the tumor, or even immune response reaction to the heart muscle mediated by the presence of neoplasm [5]. These reactions involve the activation of numerous humoral and cellular cascades but they can also be explained by embolic or mechanical phenomena (destruction of blood elements) [7,21,68].

All constitutional manifestations are usually reversible and completely resolved after complete surgical excision of tumor tissue. However, these parameters may undergo a change in cases of recurrence of the disease [5].

Rarely, myxoma can become infected. This added infection making the tumor more friable increases the embolic risk. Streptococcus is the most frequently incriminated germ. More rarely, other bacterial or fungal agents were found (*Enterococcus faecalis*, *Staphylococcus lugdunensis*, *Gemella morbillorum*, *Porphyromonas asaccharolytica*, *Candida albicans* and *Histoplasma capsulatum*) [69-70].

Paraclinical investigations

The diagnostic significance of the ECG (electrocardiography) and chest X-ray remains very limited. These two para-clinical tests provide only non-specific signs. Illustratively, ECG may show atrial fibrillation, bundle branch block or even abnormal P waves. Similarly, the chest radiograph can emphasize on cardiomegaly secondary to atrial cavities enlargement.

Currently, echocardiography remains the key examination tool for the diagnosis of atrial myxoma. It enables the diagnosis and determines the localization, shape, and size of the tumor and its various connections with the adjacent cardiac structures (Figure 3 and 4).

Trans-thoracic echocardiography is the most commonly used. It typically provides all the information necessary prior to surgical resection, but transesophageal echocardiography has, to our knowledge, enhanced specificity and sensitivity. Transesophageal echocardiograms detect tumors as small as 1-3 mm in diameter. It is particularly helpful to evaluate the posterior left atrial wall, atrial septum, and right atrium, which often are not well displayed on trans-thoracic examination, in order to potentially exclude the possibility of bi-atrial multiple tumors [71]. Ultra-fast CT, PET (Positron Emission Tomography) scan and especially cardiac MRI (Magnetic Resonance Imaging) provide also complementary information on myxomas. However, these investigations should be reserved for cases in which the diagnosis or characterization of the tumor remains unclear after an echocardiographic evaluation [72]. In exceptional cases, the diagnosis is made on the basis of the embolic material's histological examination [73].

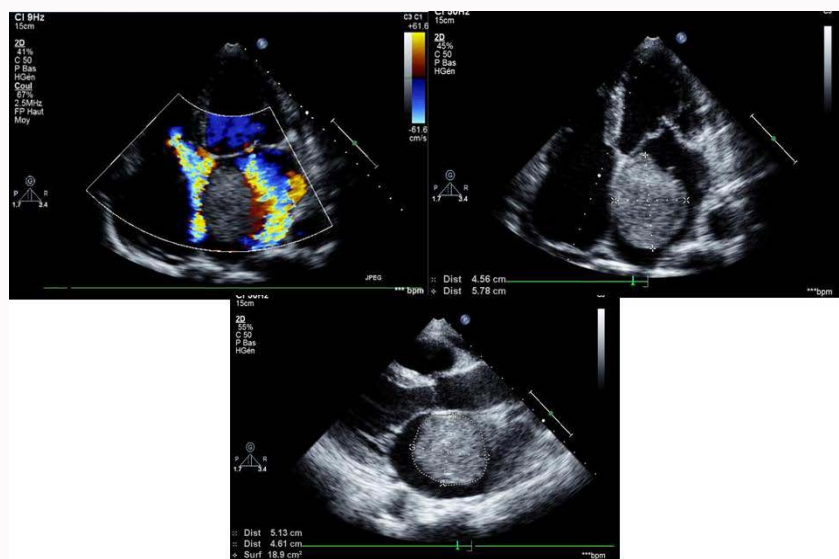


Figure 3: Echocardiographic views showing left atrial myxomas.



Figure 4: Echocardiographic views showing right atrial myxomas.

Natural History & Surgery

In general terms, myxoma represents an emergency. Typically, the treatment has to be provided subsequent to the diagnosis given the sudden death risk and embolism affecting approximately 10% of patients waiting for surgery [74]. This approach is widely accepted; however, some authors think that emergency management appears to be less clearly indicated in some stable patients having tumors less than 2 cm large [64]. In such patients, the risk of embolism seems to be low and is not amplified by a 2 days' preoperative assessment. The latter will allow performing surgery under better conditions and, obviously, with improved outcomes, particularly in elderly or high risk patients [64].

Since the first surgical excision under ECC (extracorporeal circulation) of atrial myxoma by Craaford in 1954 [75], surgery remains the gold standard despite isolated experiences relating the feasibility of percutaneous resection in some particular cases [76].

Surgery is usually performed through a median sternotomy and cardiopulmonary bypass. It is important to minimize cardiac manipulation to prevent embolic complications. Furthermore, the vent should be inserted after aortic clamping in cases of left atrial myxoma.

Minimally, invasive surgery has been increasingly used in the field of cardiac surgery and was applied to excision of myxoma. Ko et al. [77] reported the case of 3 patients who received excision of left atrial myxoma. The procedures were performed through a right anterior

sub-mammary mini thoracotomy or right parasternal incision with the assistance of endoscopy during femoro-femoral cardiopulmonary bypass. Ravikumar et al. [78] reported five consecutive patients with cardiac myxoma who underwent minimally invasive excision of the tumors. In two patients, the approach was the right parasternal mini thoracotomy and the subsequent 3 patients had direct-access partial sternotomy. Yu and colleagues reported the use of extensive thoracoscopic surgery in resecting cardiac myxomas in 12 cases with 10 in the left atria and 2 in the right atria. Extensive thoracoscopic surgical resection of myxoma was successfully performed in all cases through three minimal incisions, with the largest incision being less than 3 cm long. It ensured a safe outcome and achieved complete tumor resection [79].

Despite CPB (cardiopulmonary bypass) and aortic cross clamping durations, these experiences confirm the feasibility and the positive results of this approach. Indeed, minimally invasive surgery can deliver the promise of expediency, safety, minimal discomfort, less postoperative pain, quick functional recuperation, excellent cosmetic healing, shortened hospital stays, and therefore cost savings.

There is no real consensus on the modalities of surgical management of cardiac myxomas. In the study conducted by Jones et al. [80] the frequency of the various operative approaches was as follows: biatrial, 38%; left atriotomy, 34%; and transeptal, 28%.

Jones et al. [80] stated that the surgical approach to atrial myxomas should (1) allow minimal manipulation of the tumor, (2) provide adequate exposure for complete resection of the tumor, (3) allow inspection of all four heart chambers, (4) minimize recurrence, and (5) be safe and efficient. It is therefore conclusive that the left atriotomy by itself is an approach that does not meet all these criteria. The impossibility of an exploration of the four heart chambers can be easily compensated by new methods of medical imaging and echocardiography. However, due to sub-optimal exposure especially in large mass, this route requires an excessive manipulation of the tumor with a risk of secondary fragmentation. The main limitation of the left atriotomy probably remains the impossibility to obtain wide resection of implantation sites with free margins. In fact, 34 to 85% cases had a subendocardial, not full-thickness, resection of the

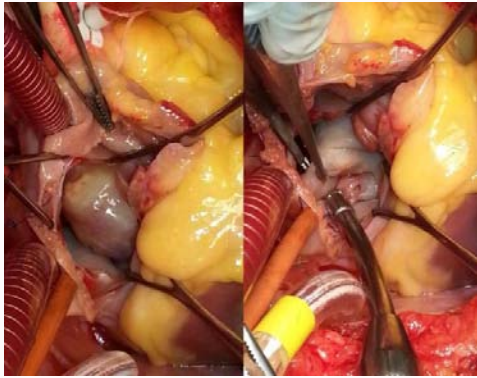


Figure 5: Operative view showing left atrial myxoma approached through Trans septal route.

interatrially based tumor [81,82]. We strongly agree with Garatti and his associates [83] who propose this approach to patients with small myxoma attached to the posterior wall of the left atrium or even the mitral valve.

The bi-atrial approach was introduced and promoted by Cooley in 1973. It brings several advantages: (1) definition of tumor pedicle by direct visualization, (2) minimal manipulation of the tumor, (3) adequate margins of excision (4) inspection of all heart chambers, and (5) secure closure of the atrial septal defect [84]. Trans-septal approach (Figure 5) encompasses all these benefits, even with minimally invasive surgery. Nevertheless, this approach seems to be correlated to a lower risk of bleeding and rhythm disorders, as well as postoperative conduction [85,86].

Another important problem in the surgical treatment of atrial myxoma is solving the tumor basis in order to prevent tumor recurrence. Thus, ideally, surgery has to allow complete atrial excision of the tumor with an adequate rim of interatrial septum. The site of the attachment should be respected with a clear margin. Myxomas not attached to the septum may undergo a full or a subendocardial wall thickness resection or even thermocauterization. Thereafter, all defects must be repaired by direct closure or by using synthetic or pericardial patch. An inspection of the various cavities and an extensive washing with serum are highly recommended to remove any tumor fragments. Moreover, atrioventricular valves function should be controlled per-operatively with saline and subsequently with transesophageal echocardiography.

Right sided atrial myxomas are approached through right atriotomy. Unless using femoral venous cannulation, both the superior and the inferior venae cavae have to be cannulated directly, and, as much as possible, by using the right angled cannula to avoid tumoral fragmentation and embolization (Figure 6).

We already reported the case of a 57 year-old woman with a large right atrial myxoma and severe left ventricular dysfunction who underwent successful on-pump beating heart resection. The mass was completely removed after a side-clamping of both the base as well as the surrounded atrial septum [87].

Data from the literature show that myxoma's surgery remains associated with low mortality. In most series, hospital mortality rarely exceeds 3% [66]. Virtually all deaths are in patients with advanced disability or old age, the mode of death being generally related not to the atrial myxoma itself but to coexisting cardiac or degenerative disease [66]. The major postoperative complication remains the

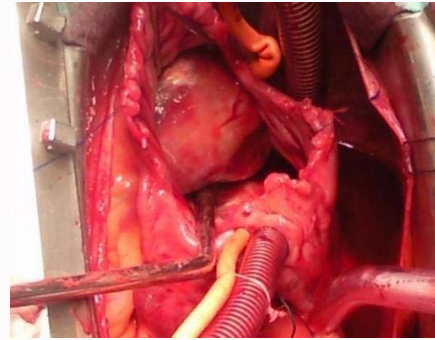


Figure 6: Operative view showing right atrial myxomas.

rhythm disorders. Among the 83 patients who underwent excision of myxoma, Centofanti et al. [88] observed atrial arrhythmias in 31 cases (37.3%). More recently, Garrati et al. [83] and Lad et al. [89] observed transient atrial fibrillation in respectively 6 out of 98 cases and 1 out of 56 cases. The observed low incidence of atrial arrhythmias in these two studies may further strengthen the conservative nature of the trans-septal approach. Moreover, normal sinus rhythm was restored in all these cases using amiodarone [83,88,89].

On the long run, survivors are generally in good health unless they have other disease processes or residual effects from a preoperative embolic event [90]. The most common complication is recurrence. It may occur within just a few months or up to several years after the initial resection (average of 4 years) [21]. There is also a report of a patient whose secondary lesion was diagnosed 20 years after the primary tumor's removal [91]. This complication is more frequent in the familial types (12%–22%) versus the sporadic ones (1%–4%). Similarly, the recurrence rate in sporadic myxomas with abnormal DNA was significantly higher compared to overall sporadic cases (12%–40%) [92]. According to McCarthy and colleagues [93], the risk of tumor recurrence is much higher in the familial variety (10%), in the syndrome of Carney complex (21%), and in the presence of multiple myxomas (33%).

The explanation of the intracardiac recurrence is related to the following features: (1) family predisposition, (2) unrecognized multicentric origin of primary lesion, (3) incomplete resection or intraoperative dissemination of tumor cells, and, (4) the de novo proliferation of the pre-tumor or reserve cells present in the endocardium [94]. The role of incomplete resection still remains controversial since recurrent tumors often do not resurge at the same site of the original lesion. Consequently, it is necessary to perform annual echocardiography throughout a patient's life, and particularly in patients with multifocal, atypical, or familial myxomas. In other cases, echocardiography at 5-year intervals seems adequate [95-99].

Conclusion

Myxomas are the most frequent among cardiac tumors and may present with a wide range of symptom spectrum. Due to their potential fatal consequences, myxomas are usually removed as soon as diagnosed. Early diagnosis is currently obtained by echocardiography which represents the gold standard tool for diagnosis.

Various surgical approaches are possible. Most centers usually prefer the biatrial and transseptal approaches. Surgery with complete excision of the tumor, results in excellent survival rate but do not exclude the risk of reoperation. Thus, annual follow-up is

recommended particularly in familial type. Further studies are still required to assess histogenesis and genetics of atrial myxoma.

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