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ORIGINAL ARTICLE

Mitral valve myxoma: a large-scale collective review

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Summary

Purpose: *Despite the review articles repeatedly published with respect to mitral valve myxomas, hardly could we find one based upon complete literature retrieval. We took an effort on complete literature retrieval and made a comprehensive review of the mitral valve myxomas.*

Methods: *An instant thorough literature retrieval of the heart myxoma was made by using the MEDLINE and EMBASE databases, as well as secondary references cited in the articles obtained from the MEDLINE search. In addition, we searched the Google and HighWire Press.*

Results: *The patients with mitral valve myxoma were young. Their major symptoms were cerebrovascular, cardiovascular, or constitutional. The tumors had small sizes, predilection of mitral leaflet location, solitary and pedicled nature, and good response to surgical resection.*

Conclusion: *These clinical characteristics of mitral valve myxoma may help the differential diagnosis between mitral valve myxoma and other valvular lesions, and help making a decision of a surgical treatment.*

Key words: cardiac surgical procedures, mitral valve, myxoma

Introduction

Cardiac myxomas are the most common, accounting for 50% of primary cardiac tumors [1]. Most cardiac myxomas arise from the left side of the interatrial septum near fossa ovalis with a narrow stalk [2]. They are most commonly located in the left atrium (75%), less commonly in the right atrium (15-20%), and least commonly in either the left or the right ventricle [3]. They can also originate, in descending order of frequency, from the posterior atrial wall, the anterior atrial wall, and the atrial appendage [3]. Most of them are solitary, but occasionally they are multilocular [3].

Despite the review articles repeatedly published with respect to mitral valve myxomas, hardly could we find one based upon complete literature retrieval. We thus took an effort on complete literature retrieval and made a comprehensive review of the mitral valve myxomas.

Methods

An instant thorough literature retrieval of the heart myxomas was started on December 27, 2007, and ended on May 15, 2011, by using the MEDLINE and EMBASE databases, as well as secondary references cited in the articles obtained from the MEDLINE search. In addition, we searched the Google and HighWire Press. Articles with ambiguous descriptions of the location of the myxomas [4], or with inaccurate case number of discrete valve myxomas, for example "cardiac myxomas originated from cardiac valves in 5 patients" [5], published in Mandarin or Russian, and in a format of an internet discussion forum between the physicians and the patients, were excluded. Repetitive publications were carefully screened [6-8] and only the updated information from the last reports was retained.

Definition

Mitral valve myxoma is defined as a myxoma arising from the mitral leaflet, annulus, commissure, junction area or subvalvular apparatus (chorda or papillary muscle) with a stalk or presenting as a broad-based one. Myxomas originating from other locations of the left heart chamber but with adherence with the mitral valve or apparatus were excluded.

Statistics

Data were expressed in mean ± standard deviation and Student t-test was used to evaluate intergroup differences. A p-value < 0.05 was considered as statistically significant.

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Results

From 1905 to present, 250 cases of mitral valve myxomas were described by 185 reports [9-189]. The patient age was 39.37 ± 19.92 years (range 0-86; median 38). Of the 140 patients whose gender was recorded, 53 (37.86%) were males and 87 (62.14%) females with a male-to-female ratio of 1:1.64. There was no significant difference in patient age between males and females (39.33 ± 19.25 vs. 39.10 ± 20.48 years, p = 0.9474).

The onset of symptoms was sudden in 7 patients. One patient presented with two episodes of transient facial and left arm weakness. In the remaining 56 patients with the duration of the presenting symptoms available in the reports, the disease course ranged from 30-60 min to 11 years (mean 2.17 ± 3.65 years; median 3 months). Symptoms were described in 113 patients. Of them, 49 (43.36%) were cerebrovascular, 55 (48.67%) cardiovascular, 9 (7.96%) constitutional, and 26 (23.01%) patients were asymptomatic at physical examination or at screening for Cushing's syndrome or congenital heart disease (Table 1). In 28 (11.2%) patients, a heart murmur was recorded (in 16/28 [57.14%] systolic, in 10/28 [35.71%] diastolic, and in 2/28 [7.14%] both systolic and diastolic). In the very early days, the diagnosis of mitral valve myxoma was usually accidentally found at autopsy, by heart surgery exploration, histological inspections, or invasive examinations. With the development of noninvasive diagnostic tools, such as 2-D echo, transthoracic echocardiography, transesophageal echocardiography, computed tomography and magnetic resonance imaging, the lesions can be documented during routine examinations (Table 2). Mitral regurgitation and left ventricular outflow obstruction were the most commonly hemodynamic disorders associated with mitral valve myxoma (Table 3).

The mitral valve myxoma was solitary in 188 (75.2%) patients, and broad-based extending onto more

Table 1. Symptoms of 113 patients

Symptom	*N (%)*
1. Cerebrovascular	49 (43.36)
Transient ischemic attack	6 (5.31)
Stroke	6 (5.31)
Syncope	4 (3.54)
Focal seizure	2 (1.77)
Other cerebrovascular attack	7 (6.19)
Right/left-sided hemiparesis	11 (9.73)
Right/left-sided weakness	4 (3.54)
Ataxia	1 (0.88)
Dizziness and loss of balance	1 (0.88)
Convulsion	1 (0.88)
Worsening confusion	1 (0.88)
Leg pain	1 (0.88)
Painful finger tips	2 (1.77)
Face numbness	2 (1.77)
2. Cardiovascular	55 (48.67)
Dyspnea	22 (19.47)
Shortness of breath	7 (6.19)
Palpitation	7 (6.19)
Chest pain	6 (5.31)
Chest discomfort	3 (2.65)
Embolic event	6 (5.31)
Cough	2 (1.77)
Episode of cardiac arrest	1 (0.88)
Congestive heart failure	1 (0.88)
3. Constitutional	9 (7.96)
Fever and sweating	5 (4.42)
Fever of unknown origin	1 (0.88)
Arthralgias	1 (0.88)
Malaise	1 (0.88)
Anorexia	1 (0.88)
4. Asymptomatic	26 (23.01)

Table 2. Diagnostic methods of mitral myxoma of 144 patients

Diagnostic methods	*N (%)*
By autopsy	8 (5.56)
By surgical exploration	2 (1.39)
By angiocardiography	1 (0.69)
By donor heart inspection	1 (0.69)
By histologic examination of emboli removed from the right internal carotid and the left proximal brachial arteries	1 (0.69)
2-D echo	10 (6.94)
Transgastric echo	1 (0.69)
TTE	64 (44.44)
TEE	15 (10.42)
TTE + TEE	30 (20.83)
TTE + angiography	3 (2.08)
TTE + CT	1 (0.69)
TTE + MRI	3 (2.08)
TTE + electron beam CT	1 (0.69)
TTE + electron beam MRI + magnetic	1 (0.69)
TTE + TEE + 3D TEE	1 (0.69)
TTE + TEE + 3D TTE+3D TEE	1 (0.69)

TEE: transesophageal echocardiography, TTE: transthoracic echocardiography, CT: computed tomography, MRI: magnetic resonance imaging

Table 3. Hemodynamic disorders of 42 patients with mitral valve myxoma

Hemodynamic disorders	*N (%)*
Mitral regurgitation	20 (50)
trivial	1 (2.5)
mild	7 (17.5)
moderate	11 (27.5)
severe	1 (2.5)
Left ventricular outflow tract obstruction	7 (17.5)
Left ventricular outflow tract obstruction + mitral stenosis	1 (2.5)
Left ventricular outflow tract obstruction + mitral regurgitation	1 (2.5)
Mitral stenosis	3 (7.5)
Mitral stenosis + mitral regurgitation	2 (5)
Mitral regurgitation + tricuspid regurgitation	2 (5)
Mitral obstruction	4 (10)

than one cardiac structures in 17 (6.8%) patients. There were one or more multiple cardiac myxomas in 40 (16%) patients, and one or more multiple and recurrent cardiac myxomas in 5 (2%) patients. The recurrence frequency of myxomas was 1.60 ± 0.89 (range 1-3). There were 102 (80.95%) mitral myxomas originated from the atrial side and 24 (19.05%) from the ventricular side with an atrial-to-ventricular ratio of 4.25:1. One hundred and thirty-eight (55.2%) mitral myxomas originated from the mitral leaflet, with 94 (68.12%) on the anterior and 44 (31.88%) on the posterior leaflet, with a ratio of 2.14:1.

Mitral valve myxomas may be concurrent with some other diseases, including Carney's syndrome, Cushing's syndrome etc. Table 4 describes the associated lesions with mitral valve myxomas. The distribution of the locations of the mitral valve myxomas is listed in Table 5. Mitral leaflet and annulus were the locations where mitral valve myxomas developed most commonly.

Table 4. Concurrent disorders of mitral myxoma patients

Associated disorders	*N (%)*
Carney's syndrome	3 (17.65)
Cushing's syndrome	2 (11.76)
Cushing's syndrome with congenital heart disease	1 (5.88)
Carney's syndrome and Cushing's syndrome	1 (5.88)
Infective myxoma	1 (5.88)
Infective endocarditis	3 (17.65)
Coronary artery disease	2 (11.76)
Congenital heart disease	1 (5.88)
Bicuspid aortic valve	1 (5.88)
Left renal infarction	1 (5.88)
Splenic infarction	1 (5.88)

Table 5. The distribution of the locations of the mitral valve myxomas

Location	*N (%)*
1. Leaflet	138 (64.49)
Anterior	94 (43.93)
a.aml	60 (28.04)
v.aml	15 (7.01)
?.aml	19 (8.88)
Posterior	44 (20.56)
a.pml	26 (12.15)
v.pml	6 (2.80)
?.pml	4 (1.87)
2. Subvalvular apparatus	36 (16.82)
Chord	18 (8.41)
Papillary muscle	17 (7.94)
Unidentified subvalvular apparatus	1 (0.47)
3. Other locations	40 (18.69)
Annulus	35 (16.36)
Commissure	9 (4.21)
Junction	6 (2.80)

?.: atrial or ventricular aspect of the mitral leaflet, a.: atrial aspect of the mitral leaflet, aml: anterior mitral leaflet, pml: posterior mitral leaflet, v.: ventricular aspect of the mitral leaflet

The mitral valve myxomas (n=112) measured 2.62 ± 1.53 cm (range 0.22-7; median 2.5). There were no significant difference between the sizes of mitral myxomas in the atrial and ventricular cavity (2.78 ± 1.73 vs. 2.99 ± 1.44 cm, p = 0.6625; Figure 1). A significant difference was noted between the sizes of the mitral myxomas developed on the ventricular side of the anterior mitral leaflet and those on the ventricular side of the posterior mitral leaflet (2.45 ± 1.29 vs. 4.08 ± 1.15 cm, p = 0.0328; Figure 2). No significant differences were found between sizes of mitral myxomas on other locations (Figure 3). Even though benign, mitral valve myx-

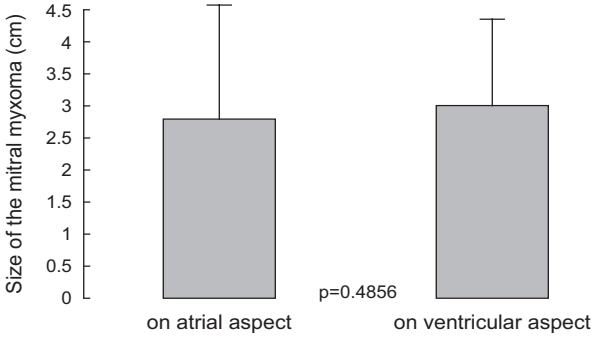

Figure 1. The sizes of mitral myxomas in the atrial and ventricular cavity.

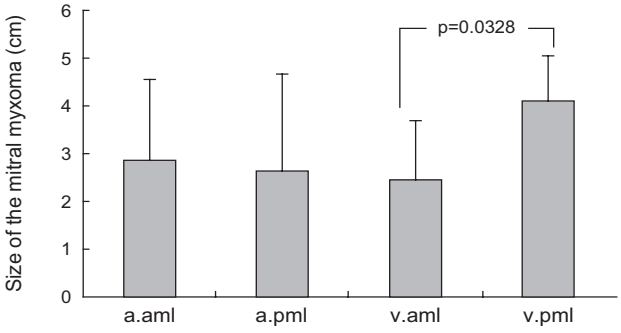

Figure 2. The sizes of the mitral myxomas developed on the ventricular side of the anterior mitral leaflet and those on the ventricular side of the posterior mitral leaflet. For abbreviations see footnote of Table 5.

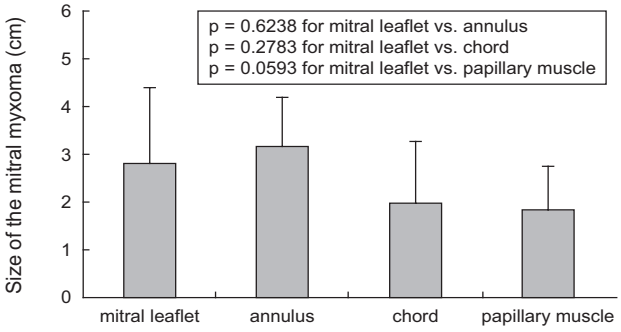

Figure 3. The sizes of the mitral myxomas on other locations.

omas may have a tendency to grow. The tumor growth could be as fast as 1.73 cm/year [171].

The appearance of mitral myxomas may be irregular, spherical, ovoid, round or polypoid in shape, glistening, smooth, villous, frond-like, gelatinous, encapsulated, heterogeneous, or lobular in outer appearance, pinkish-yellow, greenish-brown, brownish yellow, brownish tan, tannish, tan-orange, grayish, creamy-brown, white, pink, or slightly blackish in color, friable, soft or firm in hardness, and translucent or semi-translucent in transparency.

Myxomas were pedicled in 48 (60.76%) and sessile in 31 (39.24%) lesions. The majority of patients (94.78%) underwent surgical treatment. Simple tumor resection was the most commonly used surgical fashion for mitral valve myxoma, followed by tumor resection with mitral valve replacement. The surgical approaches were: left atrium in 7, right atrium plus septotomy in 6, biatrial in 6, right atrium in 3, transaortal in 3, right atrium and aorta, biatrial and aorta, and septotomy and aortotomy in 1 patient each, respectively. Minimally invasive surgical approach was applied in 4 patients. Very few patients did not undergo surgical treatment (Table 6).

Follow-up information was available in 60 patients who had a postoperative surveillance of 24.98 ± 38.54 months (range 1-204; median 12) after the surgical resection of a mitral myxoma and showed good results. Four (1.6%) patients died and 5 (2%) had disease recurrence (in 3 of them there was first recurrence, one had second recurrence and one third recurrence).

Table 6. Treatment of choice of mitral valve myxoma

Therapy	*N (%)*
1. Surgery	109 (94.78)
Tumor resection	43 (37.39)
Tumor resection with insertion curette	8 (6.96)
Tumor resection with chord excision	1 (0.87)
Tumor resection with insertion curette and base cauterization	1 (0.87)
Tumor resection with mitral valve repair	15 (13.04)
Tumor resection with mitral valve replacement	35 (30.43)
Tumor resection with mitral annuloplasty and mitral valve replacement	1 (0.87)
Tumor resection with anterior mitral leaflet resection and mitral valve replacement	2 (1.74)
Tumor resection with chordoplasty	1 (0.87)
Partial tumor resection	2 (1.74)
2. Conservative therapy	6 (5.21)
Patient declined the surgery	3 (2.61)
Oral anticoagulation	1 (0.87)
Conservative therapy for transient ischemic attack	1 (0.87)
Follow-up without surgery because of the young age of the patient and unaffected mitral valve functions	1 (0.87)

Discussion

The biological behavior of multiple, recurrent, and "complex" cardiac myxomas have been described by McCarthy et al. [190], who found that multiple and recurrent ones were more often in complex than in sporadic myxomas. This growth predilection of myxomas was proposed to be due to the Prichard's structures of the fossa ovalis, however, which was eventually proved to have no genetic relation with the development of cardiac myxomas by immunohistochemical studies [191]. The underlying etiology of the cardiac myxomas still remain undetermined so far. The clinical manifestations are related with the hemodynamic disorders caused by the myxomas to the cardiac chamber involved [192]. Apart from constitutional symptoms, sudden death, systemic emboli and congestive heart failure due to mitral valve obstruction and atrial arrhythmias may happen [192]. Patients with atrial myxoma may present with atypical symptoms, including recurrent pneumonitis, bronchial asthma, collagenosis, interstitial pulmonary fibrosis and so on, which drove the diagnostic thinking during one year after the initial presentation [193]. Recurrence rates reported for cardiac myxomas are 4-7% for sporadic cases and 10-21% for familial cases. Although recurrence rates are high, second recurrences are rare [173]. More than two-thirds of patients with Carney's complex develop one or more cardiac myxomas [173]. Atrial myxomas are the most common primary cardiac neoplasms. At least 5-10% can be attributed to Carney's complex [194]. The myxomas have different predilections in terms of the lesion locations in children and adults [75]. It has been reported that the mean overall survival was 12.7 years for myxoma patients and 5.6 years for patients with primary malignant cardiac tumors [144].

Gerbode et al. [17] first described a recurrence of left atrial myxoma 4 years after the initial excision. They postulated incomplete removal at the first operation should be responsible for the recurrence of myxoma and thus recommended wide resection of the atrial septum around the base or stalk of the tumor. Besides, totipotent multicentricity was also proposed as a predisposing factor of the recurrence of the cardiac myxomas. O'Neil et al. [195] stated that each recurrence was upstream from the previous one and could therefore not be caused by seeding from an earlier lesion. Jugdutt et al. [196] reported their experience with the surgical resection of a recurrent left atrial myxoma. Considering the surgical results of 9 recurrent left atrial myxomas recorded in the literature, they stressed the importance of the radical excision in the primary surgery in preventing from a cardiac myxoma recurrence.

In comparison, the valvular myxomas were more uncommon and much smaller than those arising from the heart wall, but with papillary structures [12]. They may grow on all 4 heart valves and were more frequent in the tricuspid valve than in other valves in the early years [12], but nowadays mitral valve myxomas have been increasingly reported and already superseded the tricuspid ones [197]. Mitral valve myxoma has been a topic of investigation due to its clinical peculiarities in comparison with the heart wall myxomas [12]. Mitral valve myxoma was more frequent in females than in males. The size of myxoma in females was larger than in males. They originated more from the atrial side than from the ventricular side. Mitral valve replacement was more frequent for the myxomas which were large in size, originated from the ventricular aspect or were free of embolic manifestations [108]. Fifty-two percent were shaved along their base, and 48% were excised along with the underlying leaflet tissue [34]. Myxomas may originate from the mitral valve either as the primary site or less commonly as the site of recurrence. Because of the high mobility of the mitral leaflets and the high pressure within the left ventricular chamber, patients are at high risk of embolization from tumor fragments [123]. Transesophageal echocardiography is much superior than transthoracic echocardiography in demonstrating tumor attachment and offers additional information of the morphological details and movement behaviors [67]. Mitral myxomas are more likely to develop serious neurological symptoms [52]. Embolization from a mitral valve myxoma might occur more often than from an atrial myxoma due to valvular motion [120]. Valvular myxomas are more uncommon than those in the heart wall, and much smaller in size, usually 6-15 mm. They resemble the larger growths in that they are pedunculated, but show a characteristic papillary structure that the larger ones do not have. They are found on all heart valves but are slightly more common on the tricuspid [12]. The clinical symptoms usually develop in three ways: fragment or embolization; obstruction flow through the valve or cardiac chamber; and constitutional symptoms [19], more likely due to myxoid dysplasia of the valve or incomplete valvular indifference [31].

Molecular biological studies have been applied in the research of cardiac myxoma. Cardiac myxomas may have increased matrix metalloproteinase synthesis and release correlated with enhanced extracellular matrix degradation, which may contribute to the high risk of embolism in cardiac myxomas [198]. Mitral valve myxoma displayed strong mucin (MUC) expression, including MUC1, MUC2 and MUC5AC in comparison with the weakly positive expression in the typical myxoma [134]. Antibodies, such as keratins (AE1/AE3, Cam 5.2, wide spectrum, CK19, CK7), CD57, CD31, CD34, and calretinin showed positive reactions in mitral myxoma cells [199]. The intermediate phenotypic expression of both epithelial and vascular antigens likely reflected the multipotential nature, accounting for the inadequate resection, or multifocal pattern behavior of a benign myxoma [200].

In general, mitral valve myxoma is rare. The patients were young (39.37 ± 19.92 years), and may present with cerebrovascular, cardiovascular, or constitutional symptoms. Mitral valve myxoma can be solitary, broad-based, one or more of the multiple cardiac myxomas, or one or more of the multiple and recurrent cardiac myxomas. The frequency of myxoma recurrence was 1.60 ± 0.89 for the recurrent cases. Most of the mitral myxomas originated from the valve leaflet and a small portion from the annulus or subvalvular apparatus. Mitral valve myxomas may be concurrent with some other diseases, including Carney's syndrome and Cushing's syndrome etc. Mitral valve myxomas were relatively small with a diameter of 2.62 ± 1.53 cm. Although benign, mitral valve myxomas may have a tendency to grow. The myxomas were pedicled in 60.76% and sessile in 39.24% lesions. The majority of the patients (94.78%) were surgically treated: simple tumor resection, or tumor resection with mitral valve replacement, and obtained good results.

The limitation of the present study may lie in an unavoidable incomplete collection due to the fact that inconspicuous cases were occasionally included in original articles and thus led to an innocent omission. Meanwhile, search engines are becoming more and more perfect day after day, and more and more articles could be accessible by various ways of retrieval.

In conclusion, the patients with mitral valve myxoma were young. Their major symptoms were cerebrovascular, cardiovascular, or constitutional. The tumors had small size, predilection of mitral leaflet location, solitary and pedicled nature, and good response to surgical resection. These clinical characteristics may help in the differential diagnosis between mitral valve myxoma and other valvular lesions, and help making a proper decision concerning surgical treatment.

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