



Original Article

Surgical management of atrial myxoma and study of its inflammatory status: A single center study

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Abstract

Background: Cardiac myxomas are rare tumors mostly located in the left atrium, less often in right atrium and occasionally in all heart chambers. The aim of the present study is to report on the early outcomes and expression of inflammatory markers associated with the surgical treatment of myxoma patients between years 2018 up to 2023.

Methods: The study included thirteen patients diagnosed with atrial myxoma. Five patients were retrospective cases under follow up and eight patients underwent prospective surgery. All patients were diagnosed by transthoracic echocardiography, then underwent median sternotomy for complete tumor resection. Left atrial myxoma was found in eleven cases while right atrial myxoma were found in two cases. Blood samples were obtained pre- and post-operatively from the eight prospective cases to determine the protein levels inflammatory markers IL-6 and TNF- α in addition to mRNA levels of IL-6.

Results: Female patients represented 69.23% of total patients. Shortness of breath was involved in 61.53%, palpitation in 15.38% and atrial fibrillation in 15.38%. of patients. Mean tumor size was 3.75 ± 1.6 cm. No recurrence or mortality were recorded and only one case of wound infection was found (7.69%). Biochemical results revealed significant increase ($p < 0.05$) in IL-6 levels pre-operatively (99.25 ± 8.78 pg/mL) compared to post-operatively (41.13 ± 10.40 pg/mL). Moreover, IL-6 gene expression showed down-regulation in post-operative blood samples ($p < 0.05$). In addition, TNF- α levels were significantly increased ($p < 0.05$) pre-

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operatively (97.5 ± 16.34 pg/mL) compared to post-operatively (42.38 ± 8.03 pg/mL).

Conclusion: Transthoracic echocardiography is the best diagnostic tool for myxoma diagnosis, median sternotomy with complete tumor resection decrease the rate of recurrence and mortality. Moreover, cardiac myxomas are associated with a distinct inflammatory state, evident by increased circulating inflammatory mediators as IL-6 and TNF- α which may act as markers in follow up to avoid recurrence.

Introduction

Cardiac tumors are rare, representing only 0.2% of overall tumors [1]. The most common cardiac tumor is myxoma, mostly found in the left atrium (75-80%), sometimes in the right atrium (15-20%) [2] and very rare in all four-heart chambers [1, 3]. Cardiac myxoma could be sometimes asymptomatic or symptomatic in the form of embolization, heart failure, sudden cardiac death and arrhythmia [4].

There are many surgical approaches used in the excision of atrial myxoma. In a previous clinical study, which extended over 9 years, it was reported that echocardiography is the best tool for diagnosis and follow up of atrial myxoma. Surgical excision is indicated for all patients with low rate of mortality and morbidity [5]. Siminelakis et al (2013) after thirteen years of follow up in patients with heart myxoma, concluded that right atrial or both atrial incision is the best approach with excision of the fossa ovalis and its surrounding tissues and closure with a pericardial patch [6].

The hallmark of cardiac myxoma is a distinct inflammatory state affecting most patients. This manifests as general constitutional symptoms and is associated with elevated levels of circulating inflammatory mediators [7, 8]. Khan et al 2013, explained that the fever, coma, fatigue and loss of weight in myxomatous patients may be due to the inflammatory impact of the tumor [5].

The aim of the present study is to report on the early outcomes and expression of inflammatory markers associated with the surgical treatment of myxoma patients.

Patients and Methods

Patients Characteristics

The present study is a longitudinal study carried out in the Cardiothoracic surgery Department, Heart hospital, Faculty of Medicine. The study included thirteen patients diagnosed with atrial myxoma. Five patients were retrospective cases under follow up and eight patients underwent prospective surgery. Patients were diagnosed with preoperative transthoracic echocardiogram showing a space-occupying lesion either in left or right atrium (Figure 1).



Figure 1: Transthoracic echocardiography showing dilated cardiac chambers, globally impaired LV and RV contractility, globally impaired LV systolic function (Ef: 32% by M-mode) and globally impaired RV systolic function (TAMPE:12mm). A huge mass is shown in LA attached to the IAS with a short pedicle prolapsing in LV through MV causing severe eccentric MR. The mass has well defined border with some calcification.

Left atrial myxoma was found in eleven cases while right atrial myxoma were found in two cases. Full history including family history was obtained from every patient. ECG, Chest X ray, Echocardiography, Coronary angiography if there were any changes in ECG or Echocardiography and if the patients age was more than 40 years old, CT scan ultrasonographic examination on femoral vessels was performed. Also, routine laboratory tests included liver and kidney function tests, blood Sugar, PT, aPTT, ESR, CRP and cardiac enzymes assay were performed.

Patients with severe coronary stenosis, severe lung diseases, or previous right thoracic surgery adhesion, severe calcification or stenosis in femoral vessels, simultaneous coronary artery bypass grafting, or any organ failure were excluded from this study.

All study protocols were approved (No. 04-2023-300332) by the Ethical committee.

Tissue Collection and Handling

Five milliliters of blood were extracted from each patient pre-operatively and one-week post-operatively, then were divided into two test tubes. 2.5 mL were placed in a plain test tube, sera were separated and frozen at -80°C for immunoassays. The other 2.5 mL were preserved in an EDTA tube and deeply frozen at -80°C for Real-Time quantitative PCR (RT qPCR).

Enzyme-Linked Immunosorbent Assay (ELISA)

Tumor Necrosis factor α (TNF- α) and Interleukin-6 (IL-6) were estimated by ELISA technique using kits purchased from Biosource international Inc. CA, USA (Catalog numbers: MBS355371 and MBS5726707 respectively) according to the manufacturer's instructions.

RNA Extraction and RT qPCR

Total RNA was extracted using an RNA isolation kit (Qiagen RNeasy, Cat. No. 74104, Qiagen, Germany) according to the manufacturer guidelines. This was followed by synthesis of cDNA using the Super Script First Strand synthesis system (Cat. No. 18080051, Invitrogen, USA). For

RT qPCR experiment, Power SYBR Green PCR master mix was used (Cat. No. 4368577, Applied Biosystems, Germany). The primer pair for IL-6 expression were as follows: Forward: 5-ACAAAGCCAGAGTCCTCAG-3 and Reverse: 5-AGAGCATGGAAATTGGGT-3. IL-6 mRNA was quantified relative to the house-keeping glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene. The primer pair used for GAPDH expression were as follows: Forward: 5-CACGATGGAGGGGACTCATC-3 and Reverse: 5-TAAAGACCTCTATGCCAACACAGT-3. Relative gene expression (fold change) was calculated using the $2^{-\Delta\Delta\text{Ct}}$ formulae.

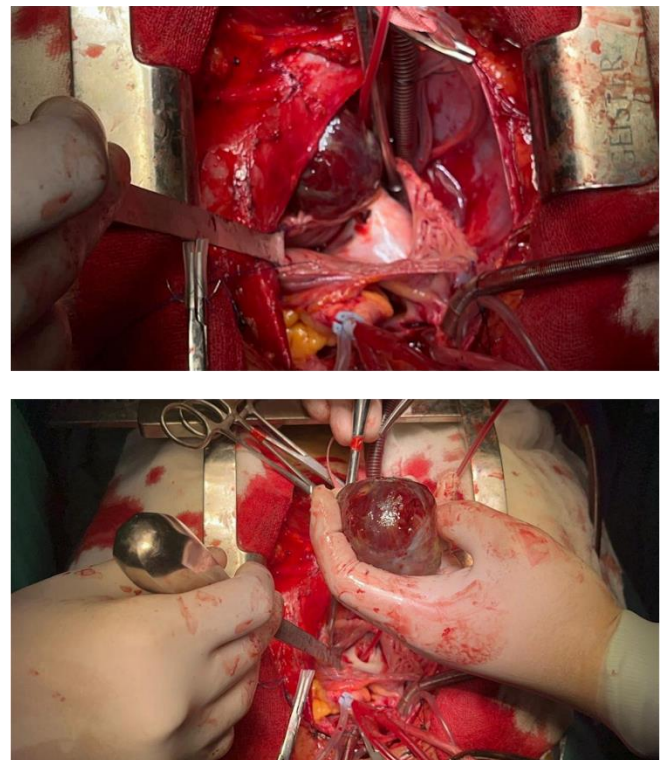


Figure 2: Operative intervention showing removal of left atrial myxoma

Surgical techniques (Median sternotomy)

After appropriate IV access, arterial lines were established, and general anesthetic was administered with endotracheal intubation. A central line was placed. To evaluate cardiac function and anatomy, transthoracic echocardiogram was inserted. Transesophageal echocardiogram was used on three occasions intraoperatively. Median sternotomy was done, and the phrenic nerves were identified and protected. Opening of the pericardium was performed with harvesting of separate patch to be used later on for atrial septal repair (Figure 2).

Circumferentially dissection of both superior vena cava and aorta were done and the pulmonary artery was also dissected up to the level of the ligamentum arteriosum. In ascending aorta and both superior (SVC) and inferior vena cava (IVC), purse string sutures were placed followed by direct aorto-bicaval cannulation. Cardiopulmonary bypass was initiated after confirmation of adequate activated clotting time (ACT).

Starting at the right atrial appendage, an incision was made in the right atrium with moving obliquely towards the IVC. The atrial mass was identified using atrial retractor. A 15-blade scalpel was then used to excise the mass off the atrial wall with part of the intra atrial septum, 1 cm margin of myocardial tissue was obtained.

Artificial atrial septal defect (ASD) was closed by using continuous 4/0 prolene sutures, using the previously harvested pericardial patch, and rewarm began systemically. The cooling temperature before by pass was 32.

Additional de-airing was accomplished via the ascending aorta and confirmed with TEE. The aortic cross-clamp was removed, and a normal sinus rhythm returned rapidly.

The right atriotomy was approximated using running polypropylene (4/0) and decannulation and hemostasis was done. A test dose of protamine was given, and the patient was monitored for any hemodynamic affection. Temporary atrial and ventricular pacing wires were placed, and drains were inserted (mediastinal and/or pleural)

Hemostasis then started for all suture lines and paraital tissue sternum was approximated using stainless steel wires. Hemostasis of wire sites was then assessed. The overlying fascia and soft tissue and skin were approximated using absorbable sutures in a running fashion. The patients were then transferred to the Cardiac Surgery Intensive Care Unit in a stable condition.

No residual atrial septal defect with normal functioning tricuspid valve and acceptable velocity

across the right ventricular outflow tract were checked by post-operative TTE assessment. Patients were discharged from hospital mostly after 7 days. Follow up by TTE was done.

Table 1: Patient Characteristics

Parameter	Range (Mean \pm SD)
Age (years)	35–57 (45.38 \pm 8.92)
Parameter	Number (Percentage)
Sex	
• Male	4 (30.76%)
• Female	9 (69.23%)
Shortness of breath	8 (61.53 %)
Palpitation	2 (15.38 %)
Hypertension	4 (30.76 %)
Diabetes mellitus	3 (23.7%)
Atrial fibrillation	2 (15.38 %)
Fever (low grade)	3 (23.7%)
Fatigue	3 (23.7%)
Location	
• Left atrium	11 (84.61%)
• Right atrium	2 (15.38%)
Both	Nil

Histopathological study

The mass was serially cut and submitted in representative section in plastic cassettes, immersed to be fixed in formaldehyde 10% overnight and further dehydrated in ascending alcohol solution (70% ,80% ,85% ,90% ,95%) one hour for each. Then it was put in a xylene jar and further immersed in wax to form paraffin embedded block. After cooling, the block was cut by microtome into thin 4 μ m thick sections where were put on glass slides. Then the sections were rehydrated and stained by H&E stain for histological microscopic evaluation.

Statistical analysis

All study data were analyzed using the IBM SPSS software package version 25.0. Normality of distribution was verified using the Kolmogorov-Smirnov test. Quantitative data were demonstrated using range (minimum and maximum) mean, and standard deviation, median and interquartile range. Pre- and post-operative cytokine levels were compared using Wilcoxon Sign test. Significance of the obtained results was judged at the 5% level.

Results

Patient Characteristics

The present study included 13 cases (9 female and 4 male). Out of them, five cases were retrospective, and eight cases were prospective. The mean \pm SD of age was 45.38 ± 8.92 years. The study revealed that eight cases presented with shortness of breath, two cases with atrial fibrillation. Moreover, three cases were diabetic, and four cases had hypertension. Fever and fatigue were reported in three cases. Regarding the tumor location, transthoracic echocardiography, showed that eleven cases had myxoma located in the left atrium while two cases in the right atrium (Table 1).



Figure 3: A) Giant left atrial myxoma, received in formalin lobulated hemorrhagic soft to firm mass, measured 7 x 6 x 5.5 cm in its maximum dimensions, attached to its base by 1 x 0.5 cm part of endomyocardium. B) Right atrial myxoma

Pre-operative and post-operative data

Table 2 shows the pre-operative data where the mean tumor diameter was 3.75 ± 1.6 , time of operation and extubation were from 4-5 hours (hr) and 2-4 hr respectively and mean \pm SD of both aortic cross clamping and cardiopulmonary bypass were 41 ± 2.8 m and 93.6 ± 1.8 m respectively. Meanwhile, growth pathology for the cases showed that eight out of them had smooth border and five cases showed villus appearance (Table 2) and (Figure 3). Microscopic examination revealed presence of ill-defined non capsulated

Table 2: Pre- and post-operative data of patients

Parameter	Results
Type of operation	Median sternotomy
Diameter of tumor (cm)	
Mean \pm SD	3.75 ± 1.6
Time of operation (hours)	4-5 hr
Mean \pm SD	4.2 ± 1.8 hr.
Time of extubation (hours)	2-4 hr
Mean \pm SD	2.8 ± 1 hr.
Time of aortic cross clamping (minutes)	41 ± 2.8 min.
Time of cardiopulmonary bypass (minutes)	93.6 ± 1.8 min.

hypocellular spindle cell neoplasm with bland feature embedded in stroma with congested thick-walled blood vessels, (Figure 4A). Microscopic examination also revealed a fragment of myometrial thickness which is free from tumor tissue that demonstrating to left indicating complete excision of mass with its stalk (Figure 4B).

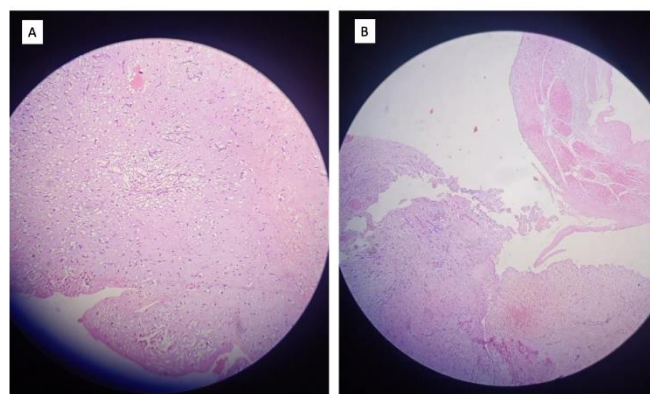


Figure 4: A) Microscopic examination revealed presence of ill-defined non capsulated hypocellular spindle cell neoplasm with bland feature embedded in yoxide stroma with congested thick-walled blood vessels. B) Up to the right; there is a fragment of myometrial thickness which is free from tumor tissue that demonstrating to left indicating complete excision of mass with its stalk

Post-operative data and follow up outcomes

The post-operative data of the current study are showed in Table 3. Mean \pm SD of ICU stay was 48 ± 1.2 hr and hospital stay was 8.0 ± 1.5 days. The study recorded wound infection with re-exploration due to leaking from IVC canulation in one case with no mortality or recurrence with

follow up since 2018 periodically every three months by transthoracic echocardiography.

Table 3: Post-operative and follow up outcomes of patients

Variable	Results
ICU stay (hours)	48±1.2
Mean ± SD	
Hospital stay (days)	8 ± 1.5
Mean ± SD	
Mortality	Nil
Wound infection	1 (7.69%)
Re-exploration	1
Recurrence	Nil
Follow up	From 2018 up to 2023 periodically every 3 months. With asymptomatic cases or slight shortness of breath (NYHA class I), and TTE reveal no recurrence.

Biochemical and Molecular data

The inflammatory status associated with atrial myxoma has been investigated in the eight prospective cases before and after surgery. Results revealed that serum levels of both IL-6, TNF- α in addition to IL-6 mRNA expression significantly decreased in post-operative compared to pre-operative samples ($p < 0.05$). On the other hand, hemoglobin level was significantly increased post-operatively, while ESR and CRP were significantly lower (Table 4). The remaining routine lab analyses results were within the normal ranges (data not showed).

Discussion

Myxomas are rare tumors demonstrating about 5-10 % of all cardiac tumors, mostly in the left atrium and affecting females more than males [4].

The present study includes 13 cases (9 females and 4 males). Five of the cases were retrospective and eight were prospective cases. Regarding location, transthoracic echocardiograph showed that eleven cases had myxoma located in the left atrium and two cases in the right atrium. Our results are in agreement with Alhasso et al 2023

who reported that female patients were predominant over males, and that left atrial myxomas were more prevalent [4].

Cardiac myxoma presentation exhibits clinical heterogeneity, ranging from asymptomatic to symptoms as dyspnea, edema, fever, weight loss in addition to potentially life-threatening manifestations such as embolic events, congestive heart failure, and rhythm disturbances [4]. Asymptomatic myxoma are usually reported during routine checkups and associated with some medical condition as hypertension, chronic liver failure, suppurative lung diseases and different types of cancer [9].

The clinical presentation usually depends on the location, size and mobility of the tumor [1]. Right atrial myxoma can present with obstruction symptoms manifested as tricuspid stenosis [10]. Meanwhile, it was reported that pulmonary embolism is the most serious complication of right atrial myxoma [11]. On the other hand, Zhao et al 2021, reported that the common manifestation of left atrial myxoma were palpitation, shortness of breath and fainting attacks with sudden death. Furthermore, some patients presented with cerebral embolism [12].

The current study results revealed that eight cases presented with shortness of breath and two cases with atrial fibrillation. Moreover, three cases were diabetic, and four cases had hypertension with constitutional symptoms in the form of fever and fatigue.

The conventional surgery for left atrial myxomas is median sternotomy. However, excision of left atrial myxomas under thoracoscopic involves longer extra corporeal circulation duration and aortic cross clamping. Moreover, median sternotomy is required in association with coronary artery stenosis; severe femoral stenosis, right thoracic adhesion, and poor tolerance to one lung ventilation.

In the present study, median sternotomy has been done for all patients for surgical excision of tumors. Pre-operative findings revealed that the mean tumor diameter was 3.75 ± 1.61 , time of

Table 4: Biochemical and molecular data for the eight prospective cases

Parameter (Mean \pm SD)	Pre-operative	Post-operative	p
IL-6 (pg/mL)	99.25 \pm 8.78	41.13 \pm 10.40	p<0.05
TNF- α (pg/mL)	97.5 \pm 16.34	42.38 \pm 8.03	p<0.05
IL-6 mRNA expression (fold change)	2.91 \pm 0.59	1.36 \pm 0.23	p<0.05

operation and extubation were 4-5 hr and 2-4 hr respectively, while mean \pm SD of both aortic cross clamping and cardiopulmonary bypass were 41 \pm 2.8 m and 93.6 \pm 1.8 m respectively. Meanwhile, cross pathology for the 8 prospective cases showed that, six out of them have smooth border and two cases showed villus appearance.

Alhasso et al 2023 concluded that good preparation is very important regarding good results and less complications. They added that transthoracic echocardiography is a very essential tool in order to get low rate of occurrence, embolism and mortality [4]. Our findings are in agreement with the previous statement, since the main tool used in diagnosis in the present study was transthoracic echocardiography eliminating the need for transesophageal echocardiography.

In a previous study that comprised 38 patients of cardiac myxoma whom underwent median sternotomy for tumor excision, authors reported that 20 of the cases were male and 18 were female. The study results also demonstrated that 65.78 % of patients were NYHA class II and 34.2 % were NYHA class III. In addition, 13.15 % of the patients exhibited constitutional symptoms. Moreover, the left atrium was the site of myxoma in 36 patients while only two cases had right atrial myxoma. The authors added that there were two cases reported for early death with 30 day of operation and that post-operative complications occurred in seven patients in the form of super ventricular arrhythmias or atria ventricular block. Finally the authors reported that the majority of patients were asymptomatic or in NYHA class I at follow up [5].

The post-operative data from the current study revealed that the mean \pm SD duration was 48 \pm 1.2 hr for ICU stay and 8.0 \pm 1.5 days for hospital stay. The study recorded wound infection with re-exploration in one case (7.69%). On the

other hand, while we did not record any mortality or recurrence in our patients with periodical follow up every three months since 2018 by transthoracic echocardiography, Alhasso et al showed a recurrence rate of 11.25% while the mortality rate was 3.75%.

Lee et al 2017 with his 30-year experience in the resection of cardiac myxoma concluded that hospital mortality was 3.2%. The authors reported that atrial fibrillation was the most common complication postoperatively moreover; the authors said that recurrence occurred in 2.1% of patients 79 months after surgery. Finally, they concluded that long-term survival after resection was excellent, and recurrence was rare [13]. Zhao et al (2021) in his thoracoscopic surgery for treating left atrial myxoma reported that the tumor diameter was 5.3 \pm 4.6 cm, the duration of aortic blockage was 20.6 \pm 6.7 m, the stay in ICU was 14.5 \pm 4.2 hr and the hospital stay was 5.2 \pm 1.2 days [12]. These contradictory results may be mostly due to the surgical technique, in which the nature of the thoracoscopic surgery is less invasive.

A defining feature of cardiac myxomas is a characteristic inflammatory profile observed in the majority of affected individuals. This manifests through non-specific constitutional symptoms and correlates with elevated levels of circulating inflammatory mediators.

Our study showed that myxoma patients showed an inflammatory response, revealed by the significant increase in pro-inflammatory markers, IL-6 and TNF- α pre-operatively compared to one week postoperatively. Moreover IL-6 gene expression was down-regulated postoperatively in the eight prospective cases.

Our results are concomitant with previous reports. Maze et al 2004 in their case study

reported that IL-6 serum levels decreased rapidly two weeks after tumor excision. The authors added that may be a significant correlation between IL-6 levels and tumor size, since their patient surgery showed (4x6 cm) left atria tumor arising from the atrial septum. They also explained that the patient symptoms as fever, elevation of white blood cell count and C-reactive protein were due to the severe inflammatory response associated with myxoma. Finally they concluded that IL-6 might be used as a marker of recurrence [14].

Yalta et al 2021 emphasizes the vital role played by systemic inflammation in rapid recurrence of cardiac myxomas. They reported that IL-6 might have a prominent role in tumour recurrence [15]. Meanwhile, Vito et al 2018 reported that their study of innate immunity in cardiac myxoma revealed that significant correlations between CD117 and tryptase, CD68 and ESR, ESR and RBCs and prothrombin time and platelet count leading to the conclusion that anemia associated with chronic inflammatory disease happens in patients with cardiac myxoma [16]. AL-Ameri and Salerno 2018 in their commentary regarding mystery of cardiac myxomas recorded that fever, malaise, loss of appetite with joints ache and loss of weight associated with elevated ESR and CRP all are related to IL-6 which activates both cell proliferation and differentiation and release of acute phase reactants. Furthermore, elevated levels of IL6 mRNA were detected in cultured myxoma cells [17].

These results collectively highlight the association between systemic inflammation and cardiac myxomas and suggest the importance of measuring levels of inflammatory cytokines as IL-6 in cases of atrial myxoma specially those associated with constitutional symptoms. Moreover, anti-inflammatory drugs may help in the treatment of the constitutional symptoms associated with myxoma.

Limitations

Small number of patients and short period of follow up.

Conclusion

Transthoracic echocardiography is the best diagnostic tool for myxoma diagnosis. Median sternotomy with complete tumor resection decreases the rate of recurrence and mortality of atrial myxoma. Moreover, cardiac myxomas are typically associated with a distinct inflammatory state, evident in most patients by their general symptoms and increased circulating inflammatory mediators as IL-6 which plays a role in release of acute phase reactants and may be a marker in follow up to avoid recurrence.

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