Intracranial Aneurysms in Patients with Atrial Myxoma: a systematic review of the literature

Aneurismas Intracranianos em Pacientes com Mixoma Atrial: uma revisão sistemática da literatura

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ABSTRACT

Introduction: more than half of primary cardiac tumors are atrial myxomas (AM) and they may cause neurological complications. However, intracranial aneurysms (IAs) related to these tumors are rare. The pathogenesis of IAs associated with AM is not well established. IA diagnosis can occur before or after myxoma resection. There are no well-defined management guidelines for these patients. Objective: this study aims to assess the occurrence of IAs in patients with AMs, as well as their clinical characteristics and outcomes. Methods: this is a systematic review, performed in the databases PubMed, LILACS, Scielo, DOAJ and Cochrane, using different combinations of the keywords, atrial myxoma, neurological complications, myxoma, aneurysm, intracranial aneurysm in both AND and OR combinations. Results: a total of 62 case reports were analyzed, and 72.6% of patients were women, mean age of 46.31 years. A total of 64.5% of aneurysms were diagnosed after myxoma resection. Fusiform aneurysms affecting the middle cerebral artery predominated (66.1%). Headache, visual changes, and speech disturbances were the main symptoms. Neurological examination was normal in 17.7%. From these patients 40.3% presented with some neurological event and 35.4% received conservative treatment. Deaths were infrequent. Conclusion: IAs in patients with AM are rare. Women are more affected than men, especially around the age of 50, men were more affected at age of 60. Middle cerebral artery aneurysms were more prevalent. Headache was the main symptom. Management is controversial, and less than a third received a surgical approach. Overall, there is neurological improvement and hospital discharge.

Keywords: Atrial myxoma; Neurological complications; Myxoma; Aneurysm; Intracranial aneurysm
Atrial Myxoma (AM) corresponds to more than half of primary cardiac tumors (50-80% of cases). Despite being benign tumors, they can cause embolic phenomena, which affect the vascular system and provoke infarctions. The true incidence of intracranial aneurysms (IAs) formation after an embolic phenomenon is not known, but the association between these events has already been evidenced. Commonly, myxomas occur in the left atrium, creating symptoms by obstruction of the mitral valve, systemic embolization, and constitutional symptoms. Nevertheless, 10% of patients can be asymptomatic.

More than 50% of cases can course with neurological complications. Headache, nausea/vomiting, limbs/body weakness, numbness and seizure are some manifestations of central nervous system involvement. Cerebral embolism is the main neurological complication, intracerebral hemorrhage (parenchymal and subarachnoid hemorrhage) has a lower incidence and is associated with aneurysm formation. Myxomatous metastasis and cerebral cavernous formation are also described as complications of cardiac myxoma.

Cerebral artery aneurysms related to atrial myxoma are rare. The pathogenesis of myxomatous aneurysms formation is not well established. It can be associated with embolic myxoma cells invasion of vessel walls, which damage the vessel and create a subintimal growth. Myxoma cells have also been detected in the wall of aneurysm at the same region of a cerebral infarction. It was once theorized that tumor cells could keep spreading after invading the vessel wall, which causes a fibroblastic proliferation and weakens the vessel creating aneurysmal dilatation, but some patients developed aneurysms without embolic signs and some others after the tumor resection. Interleukin-6 (IL-6) may also have a role in aneurysm formation. Myxoma cells produce IL-6, and high levels of these in the cerebrospinal fluid has been reported. It is theorized that IL-6 up-regulates the expression and activity of metalloproteinases and promotes invasion of myxomatous cells into cerebral arteries. Most studies in patients with atrial myxoma describe fusiform aneurysms, but a few others found saccular aneurysms.

These associations can occur before or many years after myxoma’s diagnosis or resection. Currently, there are few studies about the risk of cerebral myxomatous aneurysm rupture, and there is no established management guidelines for patients with intracranial aneurysms and atrial myxoma.

This systematic literature review has the objective of assessing the occurrence of intracranial aneurysms in patients with atrial myxoma, as well as describing their clinical characteristics and outcomes.
METHODS

This study corresponds to a broad systematic review performed in the databases PubMed, LILACS, Scielo, DOAJ (Directory of Open Access Journals) and Cochrane, using different combined keywords of atrial myxoma, neurological complications and the mesh terms myxoma, aneurysm, intracranial aneurysm (and its entry terms brain aneurysm, cerebral aneurysm), hemorrhage stroke, subarachnoid hemorrhage, embolism, metastasis in both AND and OR combinations. Pubmed search strategy: (("atrialisation"[All Fields] OR "atrialization"[All Fields] OR "atrialized"[All Fields] OR "atrially"[All Fields] OR "heart atria"[MeSH Terms] OR ("heart"[All Fields] AND "atria"[All Fields]) OR "atria"[All Fields] OR "heart atrial"[All Fields] OR "atrial"[All Fields]) AND ("myxoma"[MeSH Terms] OR "myxoma"[All Fields] OR "myxomas"[All Fields]) AND ("intracranial aneurysm"[MeSH Terms] OR ("intracranial"[All Fields] AND "aneurysm"[All Fields]) OR "intracranial aneurysm"[All Fields]) AND ((y_5[Filter]) AND (english[Filter] OR portuguese[Filter] OR spanish[Filter]))). The correspondents in Portuguese language of the terms were also used. We search for articles in Portuguese, English or Spanish.

Articles were included if they focused on patients with intracranial aneurysm and atrial myxoma, regardless of the study design. Articles were excluded if they were about patients with other neurological diseases rather than aneurysms. Articles which were not completely available online, not available in English, Portuguese or Spanish languages, book chapters and other reviews were also excluded.

RESULTS

The research strategy yielded 243 results, 28 of these were duplicated, and 144 did not satisfy the selection criteria or matched the exclusion criteria, resulting in 71 articles analyzed. There were 62 case reports from these 71 studies.

The majority of patients were women, nearly 72.6% of the total. Male patients were described in 25.8% reports and two studies (about 3.2%) did not report the biological gender of the patient.

Ages of occurrence were diverse: the youngest woman was 14-year-old and the older one was 73 years; men's ages varied from 11 to 58-year-old. Patients' age from one of the reports that didn't mention their sex was 68-year-old, and the other one is a patient who had been followed since she was 17-year-old with aneurysm detection 12 years after that. As a result, the mean age of occurrence was 46.31 years for women (population standard deviation: 16.23) and 36.1 years for men (population standard deviation: 16.28). Table 1 shows the distribution of cases according to age.

Most of the aneurysms were diagnosed after the myxoma's resection (about 64.5%). The time gap between myxoma resection and aneurysm diagnosis was 25 years. Table 2 shows the percentage of patients with aneurysm diagnosis after myxoma's resection, according to the period between these events. One study did not report the time gap between myxoma resection and aneurysm diagnosis.

Aneurysms affected mainly the middle cerebral artery and its branches, followed by anterior and posterior cerebral arteries. Basilar, posterior inferior cerebellar artery and other vessels were also affected, but occurrence was quite smaller. In 66.1% of the studies the aneurysms were fusiform, 12.9% studies reported saccular aneurysms and 17.7% didn't characterize the aneurysms. Also, in most of the reports (88.7%) the patients had more than one aneurysm.

Headache was the most recurrent symptom being present in 38.7% reports. In general, patients complained of progressive headache,
blunt headache, or thunderclap headache. Table 3 shows the main clinical manifestations. Visual symptoms were described as blurred vision, scintillations in the right visual field, and homonymous quadrantanopia. Motor aphasia, dysarthria, slurred speech are some related speech disorders. People complained of weakness in a variety way: one-sided limb weakness, weakness in lower or upper extremities, and only weakness. Seizures presented as generalized tonic clonic seizures, secondary generalized, focal seizure, motor seizures with secondary generalization, right upper extremity seizure followed by paralysis. Facial changes were inferolateral deviation of the right eye, deviation of angle of mouth, facial palsy, right facial pain and left ptosis. Other symptoms like behavior changes, dyspnea or respiratory distress, nausea/vomiting were also related.

In 17.7% of the studies, patients had a normal neurological exam, and the most common abnormalities in patients with an abnormal physical exam were decreased muscle strength, hyperreflexia, and hypertonia. A total of 9.6% of aneurysms were diagnosed in incidental or follow-up exams.

At the time of diagnosis of aneurysm, 40.3% of the patients already had a previous brain infarct or an hemorrhagic event, and in 45.1% cases the aneurysm diagnosis happened concurrently with some neurological event such as brain infarct or hemorrhage.

**Management**

We had divided the patient management in surgical or nonsurgical approaches of the aneurysms and those who had radiointervention. Table 4 shows the percentage of cases according to management. The surgical approach described in the case reports were diverse and depended on patients’ features and risks. A total of 8.0% were treated with clipping, 9.6% received an endovascular approach as coil or liquid embolization, 9.6% had a surgical resection, and 1.6% were treated with coagulation via electrocautery.

Radiointervention was also diverse and regarded the same features as surgical approach. Low -dose radiation therapy, frameless stereotactic radiosurgery and whole brain radiation were the techniques reported.

Death was reported in only one study, in the 61 remaining articles patients were discharged from the hospitals and/or required medical follow up. In general, independently of the chosen approach, patients reported improvement symptoms. Complete obliteration of the aneurysms was found in 12.9% of patients, or the same size after management was kept. A few reports described worsening of aneurysms features after some approach.

**DISCUSSION**

Intracardiac tumors can cause life-threatening situations, ordinarily caused by embolic phenomena or as a sequelae of cardiac dysfunction. The central nervous system might be the most affected site of embolism, and one can find as neurological complications of cardiac myxomas: embolism and ischaemia, neoplastic aneurysm formation (these situations can occur with hemorrhagic complications), and intracranial mass formation. Cerebral aneurysm formation as a complication of cardiac...
myxoma is rare, but these patients with cardiac tumors can present with a diversity of neurologic syndromes, even without cardiac symptoms\(^3\), and these disturbances are still underdiagnosed\(^3\).

According to the results presented above, myxomatous aneurysms occur predominantly in adults, mainly women, after cardiac myxoma resection. The disparity of occurrence between genders was already described with cardiac myxoma affecting women twice as much as men\(^4\). The predominant ages of occurrence corresponded to previous reports, between thirty and sixty years old\(^5\). Also, the aneurysms can affect anterior and posterior circulation, and manifest in a diversity of symptoms, such as headache, blurred vision, or aphasia. In most cases aneurysms' diagnosis happens after myxomas resection. It also can happen at the time of a neurological event, or after that. Neurological exam is normal in most patients and non-surgical approach is preferable in these cases.

Atrial myxoma, in addition to atrial fibrillation, acute myocardial infarction, valvular heart disease, infective endocarditis, and nonbacterial thrombotic endocarditis are the main causes of cerebral embolism originating from the heart\(^6\). Previous studies have shown that neurological manifestations occur in 12-45% of patients and aneurysms formation in 1-3%\(^9\). Tumor cells undergo embolization, and reach intracranial vessels, where they are lodged in the smaller and peripheral arteries\(^6\). These cells penetrate and proliferate in the endothelium, leading to weakening and dilatation of arterial walls\(^6\). Some studies also associated myxomatous proliferation inside the vascular lumen with aneurysmal dilatation\(^7\). Therefore, the pathology of formation of myxomatous aneurysm has three steps: arterial embolism and ischaemia, neoplastic aneurysm formation, and intraparenchymal metastases\(^11\). Neoplastic aneurysm formation can happen with or without hemorrhage\(^11\).

The already described characteristics of these aneurysms match with the results of this research: myxomatous aneurysms are multiple, fusiform, located at distal branches on the arterial tree, mostly at the anterior and middle cerebral arteries territories\(^11,12\). Saccular aneurysms were also described. In our study, aneurysms were mostly diagnosed after myxomas resection, but Alrohimi et al.\(^13\) showed that 56% of aneurysms were diagnosed previous to myxomas resection\(^13\).

It is known that aneurysms can be a late manifestation of cardiac tumors, and the latency period between tumor resection and aneurysm detection varies between 2 and 300 months, an average of 36 months, and it occurs even in the absence of other risk factors\(^6\). Aneurysms may develop after many years, since tumor's resection, as a delayed complication, owing to slowness of the pathological process that involves its formation\(^7\). Myxomatous metastasis is also a delayed complication, and haemorrhagic stroke is not common (in general related to cerebral aneurysms)\(^14\). Neurological manifestations can be acute or chronic\(^12\). The immediate manifestation of tumor embolization is ischemic brain disease because of occlusion and stenosis of the vessels\(^12\).

The clinical manifestations described at this study were reported by patients at the hospital admission resulting in aneurysm diagnosis. Myxoma can present with a range of symptoms, such as neurological deficits, hemorrhages, syncope, psychiatric symptoms, headaches or epilepsy\(^11\). All these manifestations were found in the analyzed cases. Embolic events should be suspected at the sudden onset of neurologic deficit associated with alteration in consciousness, seizures, or hemorrhagic infarction on computerized tomography\(^15\). Patients with myxomatous aneurysms usually have symptoms like cerebral vasculitis or infective endocarditis, so echocardiography, computed tomography and magnetic resonance imaging of the heart are necessary in patients with suspected stroke\(^14\). It has already been demonstrated that aneurysms can present stroke, transient ischaemic attack, subarachnoid hemorrhage, intraparenchymal hemorrhage, headaches, and neurological deficits, similar to the clinical manifestations shown above\(^11\).

There are no guidelines that determine the approach for patients with intracranial aneurysm followed by a cardiac myxoma\(^7\). In general, conservative management is the main choice for these patients, mainly because of the poor existing data about the natural history of myxomatous aneurysms, and the lesions seem to be stable on radiographic follow-up or have a spontaneous regression\(^16\). As usually the aneurysms are multiple and fusiform,
they cannot be coiled or clipped, so if they are stable, conservative management is an appropriate choice. Surgical approach can be considered in patients with hemorrhage, and resection of aneurysms located in non-eloquent areas has been described. The cardiac tumor’s resection can prevent neurological complications but does not prevent the risk of cerebral aneurysm. “Metastasize and Infiltrate” theory is the major explanation for this phenomenon: myxoma fragments metastasize to the brains, these cells infiltrate the vessel walls and damage the elastic lamina, creating vessel dilatation that results in aneurysm formation.

Other options to be considered are chemotherapy and radiointervention: chemotherapy results were questionable; radiation therapy combined with chemotherapy could degrade myxoma metastasis cells, so it can prevent the myxomatous aneurysms. Irradiation with doxorubicin and ifosfamide has better results, compared with chemotherapy.

Medical management, as anticoagulation, is ineffective for the prevention of embolic phenomenons related to cardiac myxoma, therefore echocardiography should be performed in patients with suspected cardioembolic stroke. Penn et al. recommended radiographic follow-up after lesion diagnosis, and if the patient presents with neurological symptoms, MRI and/or MRA, should be performed on presentation and repeat imaging at 3 months. The lesions detected initially demand a closer follow-up with a 3 months interval to confirm stability. Once confirmed stability, 6 months or one-year interval can be considered.

As a result of this study, we observe the knowledge gap about neurological manifestations of atrial myxoma, mainly aneurysm formation. This stems from the rarity of these occurrences, in the meantime it can cause life-threatening situations and/or neurological consequences for patients. In the literature, most studies about this theme are case reports, so it is important to keep watching closely these patients and studying the best way to manage them. The poor quantity and quality of reviews and studies about this condition was the biggest limitation of our study. Updated data about aneurysm formation and patient management are poor. As a result, we did not obtain a large sample of case reports, as we expected, to build this research.

**REFERENCES**


**CONCLUSION**

Intracranial aneurysms in patients with atrial myxoma are a rare condition, but it can cause damage. Women are more affected than men, and the aneurysms occur mostly around the 5th (women) or 6th (men) decades of life. The majority of aneurysms were diagnosed after the myxoma’s resection. In general, they are fusiform, and the most affected vessels are middle cerebral artery and its branches, anterior and posterior cerebral arteries. Headache is the main symptom. Treatment and management are still controversial, only 32.2% were treated surgically. But, in general, patients had a neurological improvement and were discharged from hospitals for follow-up. Death occurred in only one report.


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