Oncotic (Myxomatous) Aneurysms: A Review of Management

Aneurismas oncóticos (mixomatosos): Revisão das opções de tratamento

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Abstract

Atrial myxomas are the most common primary cardiac tumors and may manifest with neurological symptoms in ~ 30% of cases. Cerebral ischemia, aneurysmal formation, and extravascular metastases are mechanisms that lead to these neurological manifestations. Perilesional changes on computed tomography (CT) and magnetic resonance imaging (MRI) may help in the diagnosis of myxomatous aneurysms, which are usually located in the distal middle cerebral artery (MCA) and in the posterior cerebral artery (PCA) circulation territories. Careful resection of the cardiac lesion is essential for preventing embolism. However, treatment of myxomatous aneurysms is controversial due to the limited understanding of the natural history of this condition. Treatment may include clinical observation in asymptomatic patients, surgical resection, endovascular approaches, adjuvant chemotherapy, and low-dose radiation therapy. We present one case of a female patient with myxomatous aneurysm secondary to an atrial myxoma who presented with neurological symptoms and another case of a female patient who developed neurological symptoms after initial surgical treatment of the primary lesion. Lesion growth rate, topography, morphology, and the patient's clinical condition must be considered when choosing a therapeutical method. Further clinical studies are needed to achieve a better understanding and treatment of this disease.

Keywords  ➤ oncotic aneurysm ➤ myxomatous aneurysm ➤ intracranial aneurysm ➤ fusiform aneurysm ➤ atrial myxoma ➤ embolization

Resumo

Mixomas atriais são os tumores primários cardíacos mais comuns. Podem levar as manifestações neurológicas em cerca de 30% dos pacientes devido a: isquemia cerebral, formação de aneurismas e metástases extravasculares. Alterações perilesionais encontradas tanto nas de tomografia (TC) ou ressonância magnética (RM) podem...
Atrial myxomas are the most common primary cardiac tumors, and usually arise in the left atrium. Complete surgical resection can cure these lesions, but embolism can occur before and during total resection. Most importantly, cranial metastasis can occur even after years of total resection of the tumor, without any evidence of remaining atrial lesion. Therefore, neurological deficits may appear long after a successful removal of the primary cardiac tumor, stressing the need of long-term neurological follow-up.

Subendocardial multipotent mesenchymal cells originate these tumors. Macroscopically, these lesions are generally soft and pedunculated. They occur between the 3rd and 6th decade of life and show a 2:1 female-to-male ratio. The cranial vasculature is one of the most susceptible areas to myxoma embolization, most often resulting in ischemic strokes. Atrial myxomas are diagnosed by echocardiography. Atrial myxomas with walls with irregular surface are associated with a high risk of embolic events. Early diagnosis and treatment of these cardiac lesions is essential to the prevention of embolic events. There is controversy about the pathogenesis and treatment of secondary cerebral lesions. We report two cases and review the literature on the pathogenesis, clinical-radiological aspects, and management of intracranial myxomatous aneurysms.

Methods

We present a series of two consecutive cases cared for by the main author and obtained from the neurosurgical databases of the institutions where the present study was conducted. These databases are approved by the Ethics and Research Committee of both institutions. The inclusion criteria were patients with cardiac myxoma and intracranial aneurysms.

A systematic review was performed using the PubMed and Scielo databases. To perform the search, the keywords onotic AND myxomatous AND intracranial aneurysm were used, including the past 25 years in English publications.

After magnetic resonance imaging (MRI) studies, we performed digital 3D subtraction angiography, and the location of the lesions was classified as follows: internal carotid artery (ICA), anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA), basilar artery (BA), and posterior inferior cerebellar artery (PICA).

Case Reports

Case 1

A 14-year-old girl presented with sudden-onset aphasia and right-sided weakness. She had a history of generalized tonic-clonic epileptic seizures from the age of 11.

A computed tomography (CT) scan showed hypodensity in the left MCA territory. On echocardiography, a 39 × 17 mm tumor in the left atrium was identified, suggesting atrial myxoma. Surgical excision of the myxoma was performed in another hospital. The neurological condition of the patient improved, but a learning disability ensued, as well as preserved oral comprehension with slower verbal information processing and oral expression characterized by hesitation and moderate anoma. Speech therapy and persistence of school activities enabled continued improvement.

On digital cerebral angiography performed after the cardiac surgery, multiple aneurysmatic lesions in the anterior and posterior circulations were identified. The most evident lesions were in the bifurcation of the left MCA, in the A2 and A3 segments of the ACA, and in the right PICA (Fig. 1). We proposed endovascular treatment, preceded by a test occlusion and occlusion, if possible, but the parents did not accept the risks of a cerebellar infarction even after explanation of the hemorrhagic risk and its consequences. Therefore, a conservative treatment was chosen.

We performed a control MRI angiography, that showed the aforementioned lesions with no significant change compared with the previous test, and an additional lesion located inside a sulcus in the posterior temporal region. Digital

Palavras-chave

- aneurisma oncótico
- aneurisma mixomatoso
- aneurisma intracraniano
- aneurisma fusiforme
- mixoma atrial
- embolização

Introduction

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Subendocardial multipotent mesenchymal cells originate these tumors. Macroscopically, these lesions are generally soft and pedunculated. They occur between the 3rd and 6th decade of life and show a 2:1 female-to-male ratio. The cranial vasculature is one of the most susceptible areas to myxoma embolization, most often resulting in ischemic strokes. Atrial myxomas are diagnosed by echocardiography. Atrial myxomas with walls with irregular surface are associated with a high risk of embolic events. Early diagnosis and treatment of these cardiac lesions is essential to the prevention of embolic events. There is controversy about the pathogenesis and treatment of secondary cerebral lesions. We report two cases and review the literature on the pathogenesis, clinical-radiological aspects, and management of intracranial myxomatous aneurysms.
cerebral angiography showed stable lesions, and there was no increase in size or number of lesions in a 2-year outpatient follow-up.

**Case 2**

A 47-year-old woman was admitted to our hospital with generalized tonic-clonic seizures. A CT scan showed two areas of hemorrhagic stroke on the right parietal lobe, on the posterior right MCA territory. The patient was awake and oriented, with a slight left hemiparesis on physical examination. She had a history of a cardiac myxoma surgery 3 months before, without surgical or postsurgical complications.

Magnetic resonance imaging depicted multiple foci of sulcal and intraparenchymal lesions, one of which showed evidence of hemorrhage (a small 1 cm parietal hematoma), suggesting multiple intracranial cavernomas. The clinical information provided to the radiology did not mention her cardiac history.

Clinical treatment of the low volume hematoma was chosen, with general clinical improvement, cessation of seizures, and residual occasional headaches.

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After 2 months, the headaches worsened, and a follow-up MRI made in another institution (►Fig. 2) depicted several foci seen before, but which now showed an increase in volume in 2 lesions, with perilesional hemorrhage in 1 of them. Gadolinium-enhanced T1 images showed continuity of the lesions with distal blood vessels, suggesting fusiform aneurysms, the larger one located in the right precentral gyrus, with vasogenic edema in the surrounding parenchyma. Minute hypointense foci in SWI-weighted imaging in the cerebellum, brainstem, and cerebral hemispheres suggested microhemorrhages.

Digital subtraction 3D angiography (3D DSA) showed 7 fusiform aneurysms in the territory of the right MCA (►Fig. 3), 5 in the left MCA territory and four aneurysms in the distal PCA territory (2 on the left and 2 on the right side). Most of these lesions remained opacified until the late venous phase.

A diagnostic echocardiography showed no remaining atrial myxomas. Based on the symptoms and on the findings of increased lesion volume, a multidisciplinary team comprised of therapeutical neuroradiologists, oncologists and radiation therapists chose radiation therapy as the best course of action. Two lesions were irradiated, 1 in the frontal and another in the parietal region, measuring 1.6 and 1.3 cm, respectively. The treatment was performed with stereotactic ablative radiotherapy (SABR, also known as radiosurgery), with a single dose of 1200 cGy, in a linear accelerator with Agility multileaf collimators (Elekta Corporation, Stockholm, Sweden). We decided to only treat these lesions due to the evidence of volumetric progression when compared with previous diagnostic images, which was lacking in the other lesions.

Follow-up brain MRI and cerebral angiogram performed after 2 years of follow-up, in January 2021, showed stability of both treated and untreated lesions, with no evidence of disease progression or new lesions. The patient was clinically...
stable, without new seizures. Annual MRI and MRA follow-up was decided as the management strategy for the patient, with digital subtraction angiography as a possible choice in case the noninvasive images showed progression of the lesions.

Discussion

Clinical Presentation and Pathogenesis

Cardiac myxomas are benign lesions originated from subendocardial mesenchymal cells commonly located in the left atrium, at or near the interatrial septum. There is a female-to-male ratio of 2:1 and they are more frequent between the 3rd and 6th decades of life, although children and elderly individuals may be affected. They can be solid or soft (papillary subtype) and, in these cases, they may be pedunculated, and intermittently stop the flow across the mitral valve, leading to syncope. Most of the times the lesions are benign but may recur after initial surgical treatment if incompletely resected. Malignant transformation has been reported. Recurrence has been reported in the familial myxoma syndrome.

The clinical presentation may range from asymptomatic to sudden death. Cardiac symptoms such as dyspnea, syncope, and cardiac murmur may occur when the tumor is solid, and/or embolization when the papillary subtype is involved.

The triad of symptoms of cardiac myxoma include:

1. Inflammatory syndrome, with symptoms such as myalgia, arthralgia, fever, with elevated erythrocyte sedimentation rate and C-reactive protein (CRP) levels.
2. Embolic presentation, most commonly to the brain or systemic circulation, as tumors are often left-sided in the heart
3. Valvular heart obstruction, leading to pulmonary edema with dyspnea and, less commonly, right heart failure.

Myxomas produce growth factors such as vascular endothelial growth factor (VEGF), resulting in angiogenesis, which may explain why they are more invasive to blood vessels than other tumors. They proliferate under the intimal layer of the artery, and may progress to invade the whole vessel wall, leading to rupture.

Overproduction of interleukin-6 (IL-6) could be responsible for the inflammatory presentation, recurrence, and distal embolization of cardiac myxomas. High levels of IL-6 leads to upregulation of matrix metalloproteinases, consequently with degradation of the arterial wall collagen and aneurysmal genesis.

Interleukin-6 may be a more sensitive biomarker than CRP for evaluation of the inflammatory status of patients with cardiac myxoma. The normalization of circulating IL-6 levels can be of value in the follow-up of patients after cardiac tumor resection.

About 30 and 40% of patients will suffer tumor embolism in the lungs, in the brain or in the systemic circulation. Factors associated with an increased risk of embolism include:

1. Echocardiographic irregular tumor surface (polypoid tumors) embolize much more frequently than round tumors (58 versus 0%).
2. Atrial fibrillation, larger tumor size, and an increased left atrial diameter.

The tumor location (left or right atrium) and/or presence of a persistent foramen ovale will determine the site of embolism.

Neurologic symptoms will occur in ~30% of patients with an atrial myxoma, and in almost half of these, the neurologic manifestation will precede the cardiac symptoms.

Three distinct neurological presentations have been described:

1. Embolic ischemic stroke.
2. Intracranial aneurysms.
3. Intracranial metastases (the most uncommon presentation).

The aneurysm cases we present here are of two women, both with multiple lesions. We will summarize the characteristics and treatment options of these aneurysmal lesions.

The initial presentation of both patients was tonic-clonic seizures. Patient 1 did not bleed, but patient 2 had a hemorrhagic stroke due to a ruptured distal fusiform aneurysm. Only after that, the cardiac myxoma was found.

Also, in both patients, the main patterns of aneurysm distribution were multiplicity and always had a distal location. The topography was most frequently in the MCA and PICA territories, but also in the PCA. No aneurysm was found in the ACA territory. The shape of the lesions was always fusiform. In patient 2, there were significant irregularities in the PICA aneurysms (Fig. 1), which indicated test occlusion.
and occlusion, if possible, but the parents did not accept the risks. In patient 2, some aneurysms coexisted with hypodense areas on MRI (old hemorrhagic sites), which presented as gyral pattern of marked signal loss on T2WI and SWI. Of note, homogenous enhancement surrounding the aneurysms was detected on contrast-enhanced MRI.

The neurologic presentation may occur before, at the time, months or even years after the clinical manifestation or diagnosis of the primary tumor. In our cases, the presentation consisted of seizures and only after the imaging features of the brain (MRI angiography) it was thought to be related to an embolic event.

The histopathological type of both tumors was papillary myxoma. The mobility, but not the size of the myxoma appears to be related to the embolic potential, and the friable and gelatinous papillary myxomas embolize more often than solid lesions.

All patients had multiple fusiform aneurysms in distal locations. There are three hypotheses for the genesis of these lesions:

1. Embolic fragments of the tumor leading initially to vascular occlusion and destruction of the arterial wall and/or myxoma cells would proliferate without apoptosis, leading to occlusion.
2. Hematogenous dissemination of lesions with cerebral vasa vasmorum invasion, leading to destruction of the arterial wall, particularly of the internal elastic lamina, resulting in aneurysm formation.
3. A combination of the two mechanisms above: myxomatous tumor emboli leading to invasion of the vasa vasmorum, apoptosis and destruction of the vessel wall, widening of the arterial lumen, and fusiform aneurysm formation.

**Differential Diagnosis**

Echocardiography should be performed in all patients with suspected embolic events, especially when cerebral infarcts or hemorrhages in multiple arterial territories are identified. On noncontrast CT, the aneurysms are spontaneously hyperdense, due to accumulation of myxoid matrix or to calcification in their walls. Also, there are abnormal findings surrounding the myxoid aneurysms, like signal loss on T2-weighted images, enhancement in contrast-enhanced T1 images and on CT, due to myxoid accumulations, angiogenesis, or granulation tissue. These perilesional changes may contribute to differentiate these aneurysms from other lesions, as described below:

- Cavernoma: Cavernomas are not seen on angiography, but on MRI images, both may appear as large-volume lesions surrounded by an irregular hemosiderin ring; different degrees of perilesional edema can exist simultaneously and both show a blooming effect on gradient-echo and susceptibility images, but only the myxoid aneurysms are clearly identifiable on T1-weighted images.

- Myotic aneurysms: angiographic findings of myotic aneurysms are not different from the most common mycotic (septic) aneurysms: multiple lesions that are fusiform in shape and peripheral in topography. The finding of persistent hyperdensity in noncontrast enhanced CT scan may suggest a myxoid origin: histopathological studies showed accumulation of myxoid, hemosiderin, and iron from recurrent chronic hemorrhages, but not calcification. Septic aneurysms are more prone to rupture, resulting in subarachnoid hemorrhage or hematoma around the lesions.

Other neoplastic intracranial aneurysms: choriocarcinoma and lung carcinoma metastases generally are single lesions and may lead more frequently to intracranial hemorrhage (100% in choriocarcinoma and 84% in lung carcinoma). Instead, myxoid aneurysms are almost always multiple and the rate of intracranial hemorrhage is much lower (19.6%).

**Treatment Options for Myxomatous Intracranial Aneurysms**

Early cardiac surgery with extreme caution not to allow the myxoma to embolize intraoperatively is the best treatment to reduce the possibility of embolic complications or sudden death, as well as for optimally preventing these serious lesions from reaching the central nervous system.

After cardiac surgery, these patients need frequent neurological examination, as well as echocardiography, brain MRI and MRA, and must be made aware of the need to seek medical attention should any neurological symptom arise.

In a study of 58 patients with myxomatous intracranial aneurysms, the incidence of rupture was 19.6% in 11 years. A meta-analysis of 37 patients with multiple myxomatous intracranial aneurysms showed 76% of stability or regression of these lesions, enlargement of 21%, and mortality of 3.4%.

The management of intracranial myxomatous aneurysms is controversial. The resection of the atrial lesion does not avoid the continuous growth of these lesions in the central nervous system, if they are already present, with risk of hemorrhage.

There is no definitive guideline available in the current literature, so decisions should be made case by case. Surgery, embolization, and surgery with adjuvant chemotherapy have been proposed, with or without adjuvant low-dose radiation therapy.

**Conservative Treatment**

Given the poor understanding of the natural history of these lesions, a conservative management is mandatory in most asymptomatic patients with stable and nonhemorrhagic lesions.

Follow-up imaging may show stability or even regression of some lesions after cardiac tumor removal. In a series of 37 cases, 78.4% were managed conservatively and 75.9% with stable or even regression, with a mortality of 3.4%. In the present study, 20.7% of the cases demonstrated aneurysmal enlargement, without symptoms or bleeding.

**Noninvasive Methods**

The pathogenesis and further growth of myxomatous aneurysms is linked to the proliferation of neoplastic cells inside the arterial wall. Therefore, radiation and chemotherapy...
have been used in selected cases to try to halt their growth.\textsuperscript{24} There are limited reports of such treatments, so their efficacy remains unproven.

**Radiation Therapy**

The effects of radiation in metastatic myxomas are extrapolated from the response seen in the setting of tumors and especially of brain arteriovenous malformations,\textsuperscript{25} including endothelial damage, arterial wall smooth muscle proliferation, and intraluminal platelet aggregation with microthrombosis, resulting in vessel obliteration. The parent vessel occlusion with radiation has a slow course, allowing for the opening of collateral circulation, avoiding ischemic events. Furthermore, given the differential response to radiation of neoplastic cells, it could interrupt the proliferation of myxomatous cells and, consequently, aneurysmal enlargement.\textsuperscript{24}

There are many reports of successful treatment of metastatic myxoma,\textsuperscript{21} but for the treatment of myxomatous intracranial aneurysms, we have found only two literature reports of radiation therapy for multiple lesions located in eloquent areas, in which parent artery surgical or endovascular ligation would be highly deleterious.

One single case report used 45 Gy low-dose fractionated radiation in multiple myxomatous aneurysms, with occlusion of the lesions and parent vessels on control angiograms.\textsuperscript{17} The other report treated with 14 Gy, obtaining the same effect (aneurysmal and parent vessel occlusion), claiming to minimize the risks of adverse effects of radiation.\textsuperscript{24}

The main issue with monotherapy with radiation is similar to its use in treating hemorrhagic brain arteriovenous malformations\textsuperscript{26}: in hemorrhagic myxomatous aneurysms, the latency period until radiation promotes protection may put the patient at risk of new bleeding episodes.

**Chemotherapy**

In cases of evolving symptomatic masses, chemotherapy might be considered. Etoposide and carboplatin have been used\textsuperscript{27} in severe cases, but their efficacy is poor, and most medical centers are cautious about their use due to a lack of clinical experience and of high-quality studies.

**Invasive Methods**

As most lesions occur in distal branches, surgical excision remains the option of choice in selected cases. In determining the best treatment option, lesion topography, morphology, and clinical and aneurysm size evolution are important factors to help decide between surgical or endovascular approach. The same patient may even need both methods of treatment for multiple lesions.\textsuperscript{28}

**Surgical Treatment**

In cases in which there is significant increase in lesion size, craniotomy may be indicated for decompression. In the subdural space, thrombi may be seen on the brain surface, as well as mucinous masses and yellow staining. It is often not possible to remove the aneurysms due to the eloquent territory irrigated, and the low risk of bleeding. Thus, postoperative MRI or DSA may show persistence of the aneurysms, with amelioration of the mass effect.

In those cases in which the lesion is close to the cortical surface, and with small parent vessels, the use of a neuro-navigational system to guide craniotomy may be chosen, followed by exploration of the sulcus harboring the lesion. After identification of the dilated fusiform artery, coagulation and/or clipping of the afferent and efferent artery is performed, allowing for safe removal of the aneurysm. Bypass should be considered for those lesions in eloquent areas, since clip reconstruction is impossible due to the friability of the aneurysms.\textsuperscript{16,29}

**Endovascular Treatment**

For acute vascular occlusion, intravenous thrombolysis has been attempted in emergency stroke care scenarios, without the knowledge of a cardiac myxoma as the underlying condition.\textsuperscript{10} From a practical standpoint, this can be effective in restoring the blood flow and improve the prognosis in patients with cerebral embolism due to a cardiac myxoma, but the possibility of a hemorrhagic complication in the setting of a coexisting myxoid aneurysm must be remembered.

Consequently, unstable (growing) and symptomatic intracranial myxoid aneurysms, although with a low risk of rupture, may need to be occluded. As a fusiform lesion, they must be occluded sacrificing the artery closely proximal and distally to them (the so-called “deconstructive approach”) with a liquid embolic. This may pose a very difficult decision, as neurological deficits may appear after ligation.

One advantage of the endovascular method is the possibility of performing balloon test occlusion before this decision, with the patient awake, in an attempt to predict the clinical consequence of sacrificing the vessel. Rarely, some deficits may appear lately, only after increased metabolic demands such as that due to physical exercise.

After aneurysm and vessel occlusion, although the hemorrhagic risk is eliminated, the lesion itself or its surroundings may continue to grow as a tumor. This would be the case to treat with chemotherapy or radiotherapy soon, although in most reported cases these embolized lesions remained stable on follow-up after embolization,\textsuperscript{20} possibly because embolization devascularizes the region, causing decreased blood flow to neoplastic cells and lowering the risk of tumoral growth.

**Conclusions**

Myxomatous intracranial aneurysms may present a therapeutic dilemma, as their natural history is relatively unknown. Most of the unruptured cases seem to have a benign course, and all the possible open interventions have potential morbidity (sacrificing the parent artery is almost always necessary).

Once the aneurysmal lesions are diagnosed, periodic follow-up noninvasive images are warranted, as well as close clinical evaluation. Increasing and symptomatic lesions in
low eloquence areas should receive further investigation with DSA followed by treatment with surgery or embolization, and targeted radiation therapy should be considered for lesions in eloquent areas.

There is no time limit to stop follow-up, due to literature cases presenting with hemorrhage decades after tumor removal, as cited above.

Further clinical studies are needed to elucidate the appropriate management of asymptomatic evolving lesions in eloquent areas.

The doubt persists for those increasing lesions in eloquent areas but in asymptomatic patients.

**Conflict of interests**

The authors have no conflict of interests to declare.

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