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NEUROLOGY OF SYSTEMIC DISEASES (J. BILLER, SECTION EDITOR)

Neurological Complications of Cardiac Tumors

Madalena Rosário [1] · Ana Catarina Fonseca [1,2] · Filipa Dourado Sotero [1] · José M. Ferro [1,2]

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Abstract

Purpose of Review This article reviews recent literature regarding the neurological manifestations of cardiac tumors, including diagnosis, pathophysiology, and treatment.

Recent Findings Clinical cases of patients with acute ischemic stroke due to cardiac tumors who were treated with intravenous alteplase show a favorable safety profile. Mechanical thrombectomy seems to be a reasonable treatment alternative for these patients, when there is a large vessel occlusion. Histopathology analysis of mechanical thrombectomy specimens may allow the diagnosis of a cardiac tumor. Prolonged time interval between stroke and tumor excision surgery is significantly associated with stroke recurrence. Myxomatous aneurysms are a late complication of cardiac myxomas, which commonly demand imaging follow-up after excision of the primary tumor. Aneurysms are more frequent in patients who present with other embolic complications. Conservative treatment of myxomatous aneurysms is a reasonable strategy, as the majority of aneurysms remain stable over many years. Spontaneous regression of these formations has been documented after excision of the primary tumor. Other complications recently described include acute psychosis and mononeuropathy multiplex.

Summary Cardiac tumors are rare. There are mainly case reports and retrospective case series describing the neurological manifestations of cardiac tumors. Hyperacute stroke treatment seems to be safe, and mechanical thrombectomy is a reasonable treatment. A conservative approach towards myxomatous aneurysms should be considered.

Keywords Cardiac tumors · Stroke · Aneurysms · Fibroelastoma · Myxoma

Introduction

Cardiac tumors can be categorized according to their origin as primary or secondary lesions (metastasis). The reported incidence of primary cardiac tumors is 1 per 100.000 inhabitants. Autopsy studies show a prevalence of primary cardiac tumors of 1:2000 and of secondary tumors of 1:100, with a secondary/primary ratio of 20:1. Ten percent of primary cardiac tumors are malignant and 90% benign (Table 1) [1]. The most common benign tumors are myxomas, followed by fibromas and papillary fibroelastomas (Table 1).

Myxomas comprise 80% of primary benign cardiac tumors [2•]. These tumors have a mesenchymal origin and are typically sporadic. They affect mainly patients in their third to sixth decades, and have a female preponderance [3, 4•, 5, 6]. More rarely, cardiac myxomas can present as part of an autosomal dominant syndrome titled Carney's complex. This syndrome is comprised by multiple and recurrent cardiac and skin

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✉ José M. Ferro
jmferro@medicina.ulisboa.pt

Madalena Rosário
madalena.rosario@gmail.com

Ana Catarina Fonseca
catarinagfonseca@gmail.com

Filipa Dourado Sotero
fdouradosotero@gmail.com

[1] Department of Neurosciences and Mental Health, Neurology Service, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal

[2] Faculdade de Medicina, Hospital de Santa Maria, Universidade de Lisboa, Neurology 6th floor, Avenida Professor Egas Moniz s/n, 1649-035 Lisbon, Portugal

Table 1 Primary cardiac tumors

Primary cardiac tumors	
Benign (90%)	Malignant (10%)
Myxoma	Angiosarcoma
Fibroelastoma	Sarcoma
Lipoma	Myxofibrosarcoma
Fibroma	Rhabdomyosarcoma
Rhabdomyoma	Leiomyosarcoma
Hemangioma	Cardiac lymphoma
Cystic tumor of atrioventricular nodal region	
Paraganglioma	

myxomas, hyperpigmentation of the skin (lentiginosis), and endocrine disorders. Mutations in the *PRKAR1A* gene have been found in 40% of patients with Carney's complex [3, 7, 8].

Although myxomas can grow anywhere in the heart, they are more commonly located in the left atrium, attached by a pedicle to the interatrial septum, near the fossa ovalis [3, 9]. Two anatomic types of myxomas can be considered, with implications for the clinical manifestations of the tumor: a solid type, which embolizes infrequently, and a papillary type, which can fracture due to its friable surface and embolizes distally [7].

Papillary fibroelastomas are the most common type of cardiac valvular tumors, typically involving the left side of the heart [10]. They affect men and women equally and the mean age of diagnosis is 60 years old.

The most common primary malignant tumors are undifferentiated pleomorphic sarcomas followed by angiosarcomas and leiomyosarcomas. Rhabdomyomas are more common in children and can be found in tuberous sclerosis.

Secondary cardiac lesions are typically derived from breast or lung carcinomas, melanoma, lymphoma, leukemias, or sarcomas [7]. The incidence of cardiac metastases ranges from 2.3 to 18.3% of patients with extracardiac malignancies.

Clinical Manifestations

The classic triad of cardiac tumors manifestations was initially described in patients with cardiac myxomas and includes embolic phenomena, cardiac obstructive symptoms, and constitutional symptoms. However, these rarely present simultaneously [7]. Another possible manifestation is electrical or mechanical cardiac dysfunction [1]. Clinical presentation has a good correlation with the anatomic type of tumor. Solid tumors tend to present with symptoms of congestive heart failure, while papillary tumors typically embolize to the cerebral and peripheral vessels [4•].

Embolization of tumor fragments or thrombi occurs in up to 45% of patients, half of which to the central nervous system [11]. This is especially common in myxomas and fibroelastomas due to their villous morphology and propensity to embolize [7, 12]. The "at risk" circulation depends on the cardiac chamber affected by the tumor and also on the presence of vascular shunts [8]. As most myxomas are located in the left atrium, systemic embolization is particularly frequent and can also affect cerebral, visceral, renal, and coronary arteries [13].

Cardiac dysfunction includes mitral valve obstruction with symptoms of palpitations, dizziness, dyspnea, cough, heart failure, and syncope [14].

Constitutional symptoms are due to the production of cytokines and affect over 50% of patients. The major complaints consist of fever, fatigue, weight loss, and generalized aching. Occasionally, patients have a clinical picture resembling an immune disease, with arthralgias or rash, and laboratory findings of an increased gamma globulin ratio or an increased erythrocyte sedimentation rate [7]. Although typically reported in cardiac myxomas, these symptoms may also occur in malignant primary and metastatic cardiac tumors [1].

Neurological Complications

Studies reporting neurological manifestations of cardiac tumors generally consist of small series and clinical cases mostly including myxoma patients [2•]. The list of complications is varied and some can be neurologically devastating or even life threatening (Table 2) [7]. Literature reports a frequency of neurological complications in cardiac tumors of 12–45% [11, 14]. The most common neurological manifestation is cerebral infarction/transient ischemic attack which can occur in 30–40% of myxoma patients [7]. Repeated embolic strokes can also present with epileptic seizures and multi-infarct

Table 2 Neurological manifestations of cardiac tumors

Neurological manifestations of cardiac tumors
Ischemic stroke
Transient ischemic attack
Intracranial aneurysm (ruptured/unruptured)
Hemorrhagic stroke—due to intracranial aneurysms or metastasis
Spinal cord ischemia
Monocular vision loss
Seizures
Dementia
Psychosis
Delirium
Neuropathy (polyneuropathy, mononeuropathy multiplex)
Syncope

dementia [11]. Other manifestations include syncope, aneurysms, intracerebral hemorrhage, brain metastasis, and psychiatric symptoms [6, 14].

Neurological complications can be the initial presentation of the cardiac tumor in up to 80% of cases [14].

Neurological complications of cardiac tumors can be understood as a continuum, from acute onset to late-onset presentations. Typically, patients are admitted with an ischemic stroke or transient ischemic attack during active embolization of the cardiac tumor. Later, patients may develop aneurysms with hemorrhagic stroke or brain metastasis after the slow growth of the embolic material [5, 7].

Patients with neurological complications tend to be younger than those without. As embolism is the main neurological complication, Andreu et al. hypothesized that, in cardiac tumor with embolic potential, time to diagnosis will be shorter than in other patients [15]. Also, patients with neurological embolic symptoms typically have cardiac tumors of papillary type, as mentioned before [4•]. The mobility and morphology of the tumor, but not the size, appear to be related to its embolic potential [16].

Some studies report that female patients with cardiac tumors and neurological complications seem to have a more severe prognosis, with higher mortality, from 72% in women as compared with 25% in men [7].

Ischemic Stroke and Transient Ischemic Attack

The most common neurological complications of cardiac tumors are ischemic strokes and transient ischemic attacks (Figure 1) [17, 18]. Embolization to the central nervous system occurs in approximately 30% of patients with cardiac tumors, especially in myxomas. These patients are mostly young, with a female predominance. Cardiac tumors are a rare cause, but an important etiology and treatable condition causing stroke in the young. A third of patients have one or more predisposing risk factors of stroke, more commonly hypertension [5].

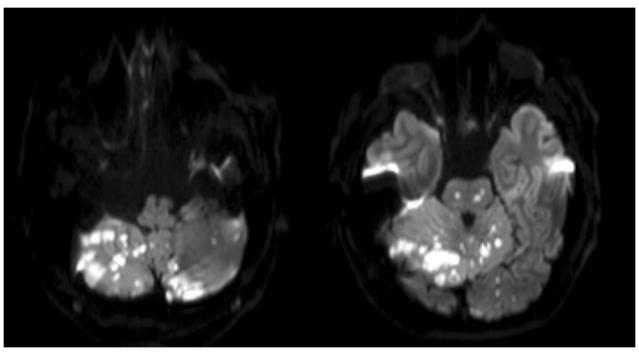

Fig. 1 Brain magnetic resonance imaging with diffusion weighed imaging (DWI) sequence showing multiple ischemic lesions involving both cerebellar hemispheres and pons due to embolization from a cardiac myxoma

A review of published cases of cardiac myxoma stroke, including 83 patients, found the middle cerebral artery to be the most affected vessel, with infarcts localizing to the basal ganglion, cerebellum, parietal, and temporal regions (Fig. 1) [5]. A 2:1 predominance of left-sided abnormalities is also reported in the literature [7].

Neuroimaging will show bilateral, supratentorial, and infratentorial embolic infarcts of multiple ages [4•, 18]. Several studies have demonstrated that between 30 and 50% of patients have infarcts in multiple vascular territories [2•]. Occlusion of proximal arteries has been reported [18].

Occasionally, patients with multiple infarcts present with a multi-infarct dementia [18]. Spinal cord ischemia is a rare but reported an embolic complication. Typically, these patients have also embolic cerebral infarcts [7]. Cardiac tumors can also embolize to the retinal arteries, leading to occlusion of retinal arteries with temporary or permanent visual loss [4•].

Central nervous system infarction in cardiac tumors is thought to be secondary to embolization of tumor particles. Emboli can also be composed of thrombotic material covered with tumor cells [2•]. Up to 41% of atrial myxomas may have surface thrombosis. Histological characteristics of myxomas can provide an estimate of the risk for embolization. Irregular pedunculated myxomas are more likely to embolize than villous or sessile myxomas. The incidence of embolization is unrelated to the size of the cardiac myxoma [19]. It accounts for approximately 75% of all cardiac valvular tumors and affects men and women equally with a mean age of 60 years at diagnosis. In papillary fibroelastomas, tumor mobility has been reported as an independent predictor of death or non-fatal embolism [20]. Ischemic events can also result from episodes of atrial fibrillation caused by the electric interference of the tumor on the heart, typically occurring with solid myxomas [7].

Myxomatous Aneurysms and Intracranial Hemorrhage (Parenchymal or Subarachnoid)

Cerebral aneurysms are typically reported in association with cardiac myxomas. Myxomatous aneurysms are usually fusiform, multiple, and of distal location in the middle, anterior, and/or posterior cerebral arteries, similar to mycotic aneurysms [2•]. Occasionally, saccular aneurysms may occur in distal or proximal branches [7]. Conventional angiography is considered the standard for diagnosis, performing better than magnetic resonance or computerized tomography-based methods [2•].

Myxomatous aneurysms are hyperdense on CT, which is attributed to the accumulation of myxoid matrix in the walls of the aneurysm [21••]. The reported prevalence of myxomatous aneurysms ranges from 2 to 29%, but the true incidence is unknown and may be underestimated as patients were not systematically evaluated by angiographic imaging [2•, 7].

Females are more frequently affected, with an age range between 10 and 69 years [21••].

The pathogenesis of myxomatous aneurysms is not fully understood, and three hypothesis exist for their formation [4•]. Aneurysms are due to scarring and pseudoaneurysm formation following vessel occlusion and altered flow dynamics [16]. Aneurysms result from intimal invasion of the vessel wall by embolic tumor cells, with vessel wall weakening [18]. Aneurysms arise from myxomatous tissue invasion and proliferation in the vasa vasorum and ischemic damage to the vessel wall, with weakening of the subintimal tissue and internal elastic lamina [2•]. Some histopathologic exams of aneurysms showed myxoma cells in the vessel walls, favoring the "neoplastic hypothesis" [21••].

Myxomatous aneurysms are slow growing lesions, and there can be a long delay between prior successful tumor resection and proper diagnosis of aneurysms, sometimes over 25 years [2•, 21••].

A retrospective study that reviewed 47 patients from a single center found that patients who presented with cerebral infarction or other embolic phenomenon as their initial manifestation of cardiac myxoma were more likely to suffer aneurysm formation (35.7 vs. 6.1%, $p = 0.03$). This suggests that patients who present with embolic complications from cardiac myxoma may potentially benefit from surveillance imaging for the detection of aneurysms, to reduce the risk of intracranial hemorrhage over the long term [2•]. However, currently, there are no guidelines for screening for intracranial aneurysms after a cardiac myxoma.

The natural history of myxomatous aneurysms is reported to be unpredictable [7]. While many stabilize, others may suffer thrombosis, increase, rupture, or even regress in size. In a review of published cases by Zheng et al., approximately 80% of aneurysms were stable or disappeared, with only 20% increasing in size [21••].

Less commonly, cardiac tumors can firstly manifest with hemorrhagic stroke, due to either a subarachnoid hemorrhage or intraparenchymal hematoma. This is in general due to the rupture of a yet unknown aneurysm, normally larger and more proximally located than usual [7, 15, 18].

Metastatic Disease to the Central Nervous System

This is a rare presentation of cardiac tumors. In a retrospective single center case series, 4.3% (2/47) of patients with cardiac myxomas had parenchymal brain metastasis [2•]. Myxomatous metastases are usually hemorrhagic. Cardiac tumor cells penetrate the vessel wall and grow in the parenchyma as an intra-axial mass [8]. This is another reason for a follow-up imaging in patients with embolic complications of cardiac tumors. There are reports of myxomatous lesions discovered from 2 months to as late as 36 months following the initial symptom [2•].

A clinical case of a primary cardiac high-grade myxofibrosarcoma presenting with multiple brain metastases was reported [22]. Also, a primary cardiac intimal sarcoma presenting with a hemorrhagic cystic brain metastasis was described [23].

Syncope

Up to 56% of cardiac tumor patients are reported to have syncope. It is caused by a direct cardiac dysfunction provoked by the tumor, whether in the form of cardiac arrhythmias or valvular obstruction, leading to cerebral hypoperfusion, sometimes with convulsive movements. Syncope is typically linked to fibromas, but has also been reported with rhabdomyomas, large myxomas, and metastatic lesions. The most frequent electrocardiographic changes include supraventricular tachycardias, bradyarrhythmias, and ventricular tachycardias that may require an implantable cardioverter defibrillator device [3, 7].

Neuropathies

In the last years, two cases of peripheral nervous system complications in patients with cardiac tumors were published. One patient presented with a painful mononeuropathy multiplex that preceded by one year the diagnosis of a cardiac myxoma. The presumptive cause was embolism to the vasa nervosum. The symptoms resolved after the surgery of the cardiac tumor. The second patient had a demyelinating polyneuropathy, which was thought to represent an inflammatory manifestation of the atrial myxoma [24].

Neuropsychiatric Manifestations

Neuropsychiatric manifestations are exceedingly rare. Jain et al. report a female patient presenting with acute psychosis that had a previous history of right hemiparesis and dysarthria. The patient was found to have bilateral hemispheric chronic infarcts and an acute infarct in the left periventricular region due to embolism from a left atrial myxoma. Following the surgery, there was a dramatic recovery in the psychotic symptoms without recurrence [11]. Acute confusional states, chronic cognitive impairment, or behavioral abnormalities have also been reported [3].

Diagnosis

Transthoracic echocardiography is the initial diagnostic technique that is used to assess cardiac masses. Transesophageal echocardiography provides superior image resolution and better visualization, especially in patients with suboptimal transthoracic echocardiographic studies. Transesophageal

echocardiography should be performed in patients with multiple cerebral infarctions and multiple aneurysms, especially when aneurysms are distally located. The histopathology analysis of the mechanical thrombectomy specimen allowed the diagnosis of a papillary fibroelastoma in a patient in which transesophageal echocardiogram was unremarkable due to complete embolization of the mass [25].

Treatment

How Can Neurological Complications Be Treated?

Prompt surgical resection of the cardiac tumor is the treatment of choice for the prevention of neurological complication and symptomatic improvement. However, there are doubts regarding the optimal timing for surgery after neurological complications onset, especially stroke. Open-heart surgery and cardiopulmonary bypass for cardiac tumor resections require systemic anticoagulation during the procedure, which may increase the risk of intracranial hemorrhage. Nonetheless, the procedure is considered to be safe, with most authors recommending emergency excision of the cardiac tumor [7].

Anticoagulants and antiplatelet agents are used while awaiting surgery. In a recent retrospective cohort study of 52 patients with cardiac myxoma, under bridging antithrombotic therapy prior to surgical excision of the tumor, 23% of the patients developed recurrent stroke. Prolonged time interval between stroke and surgery was significantly associated with stroke recurrence ($p = 0.021$). Antithrombotic therapy is not considered an alternative to surgery [26••]. Local recurrence of cardiac myxomas after surgery is uncommon, but may be related to incomplete resection, multicentricity, and genetic conditions. Annual echocardiographic follow-up is recommended for a minimum of 4 years post resection [27].

How to Treat Patients with Acute Ischemic Stroke Due to a Cardiac Tumor?

The American Heart Association/American Stroke Association stroke guidelines consider that thrombolysis might be reasonable in patients with a cardiac myxoma or fibroelastoma presenting with acute ischemic stroke likely to produce severe disability [28].

Some case reports describe the use of intravenous thrombolysis on acute ischemic stroke due to embolization of cardiac tumors. There is conflicting evidence about its safety and efficacy [26••], but it is generally considered an effective procedure, with a favorable functional outcome being reported [29]. Some authors argue that the composition of the emboli could modulate the efficacy of thrombolysis, with tumor emboli being much less likely to lyse than thrombus emboli [7, 30]. Also, even though case reports show limited and small brain hemorrhagic transformations without clinical deterioration after thrombolysis, there is a theoretical hemorrhagic risk in atrial myxomas, as this tumor may be associated with myxomatous aneurysms, a relative contraindication to fibrinolysis [29, 30].

Clinical reports of intraarterial thrombolysis and bridging therapy (intravenous alteplase followed by mechanical thrombectomy) in the setting of large vessel occlusion were published [2•, 18]. Some of these case reports described clot resistance requiring multiple passes for complete clot removal during thrombectomy [30]. Mechanical thrombectomy may be superior to intravenous thrombolysis by minimizing the risk of hemorrhage in the setting of atrial myxoma emboli.

In clinical practice, at the time of stroke onset, the cause of stroke is generally unknown and acute treatment tends to be similar to all other causes, especially if a significant disability is expected.

How to Treat Myxomatous Aneurysms?

There is no consensus regarding the optimal treatment of these aneurysms.

Conservative treatment is a reasonable strategy as the majority of aneurysms can remain stable over many years. Spontaneous regression has been documented after excision of the primary tumor. Open surgery for aneurysms is considered only for ruptured and/or enlarging aneurysms or for diagnostic purpose, as it is associated with high mortality. Endovascular treatment of aneurysms with coiling is usually not feasible due to the fusiform shape of the aneurysms and their distal localization that limits vascular access. However, stenting the artery with a flow diverter could be a reasonable option [19].

Another potential approach, considering the pathophysiology of myxomatous aneurysms, lies in controlling tumor cell proliferation in the vessel wall through chemotherapy or radiotherapy. Results on chemotherapy for treatment of myxomatous aneurysms are equivocal. Regarding radiotherapy, case reports have described its application in treating aneurysms, with good results [21••].

How to Treat Metastatic Disease to the Central Nervous System?

Parenchymal metastases are usually surgically resected. There are some case reports of treatment with radiotherapy and chemotherapy with limited success [2•].

Conclusion

Cardiac tumors are rare in clinical practice. The published literature includes mainly case reports or small case series,

and reports mainly myxoma cases. Neurological complications can be devastating and even life threatening, contributing significantly to the morbidity and mortality of these mainly benign tumors. Most complications demand appropriate treatment according to the clinical presentation, but common to all is the need for surgical excision of the cardiac tumor. These patients should also be evaluated periodically due to the risk of late-onset complications.

Compliance with Ethical Standards

Conflict of Interest Jose Ferro reports grants from Bayer, personal fees from Boehringer Ingelheim, outside the submitted work. Madalena Rosário, Filipa Dourado Sotero and Ana Catarina Fonseca each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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