Central Nervous System Manifestations of Cardiac Myxoma

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Background: Neurologic complications can be the initial manifestation of atrial myxoma. Prompt diagnosis is of paramount significance to prevent recurrent complications.

Objective: To identify patients with neurologic complications attributed to atrial myxoma.

Design, Setting, and Patients: With institutional review board approval, we retrospectively reviewed the medical records of 74 consecutive patients with pathologically confirmed cardiac myxoma at the Mayo Clinic from January 1, 1993, through December 31, 2004.

Main Outcome Measures: Discharge and follow-up modified Rankin score.

Results: Nine of the 74 patients with cardiac myxoma (12%) presented with neurologic manifestations in the setting of atrial myxoma. Mean age was 48.5 years (range, 17-70 years). There were 6 females and 3 males. Among patients with myxoma and neurologic symptoms, ischemic cerebral infarct was the most common neurologic manifestation (8 patients [89%]). No patients had concomitant cardiac symptoms. The size of the atrial myxoma was variable, with a mean diameter of 2.7 (range, 0.4-6.5) cm. Most of the atrial myxomas causing neurologic symptoms demonstrated a mobile component on transesophageal echocardiography (8 patients [89%]). Two patients (22%) had pathologic evidence of systemic myxomatous emboli. One patient with intracerebral hemorrhage had pathologically confirmed intracranial metastatic myxoma and myxoma-induced aneurysmal dilatation.

Conclusions: Neurologic complications are associated with cardiac myxoma in some patients with myxoma and, when they occur, frequently present with cerebral infarction. The mobility, not the size, of the myxoma appears to be related to embolic potential. Potential delayed neurologic complications relevant to patients with tumor embolization include myxoma-induced cerebral aneurysm and myxomatous metastasis, which can mimic the clinical picture of central nervous system vasculitis or infective endocarditis.

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MYXOMAS ARE GENERALLY thought to originate from multipotential mesenchymal cells of the endocardium.1 Cardiac myxomas are the most common primary cardiac tumor in adults, representing as many as 83% of all primary tumors of the heart.2 Myxomas are particularly frequent from the third to the sixth decades of life and show a 2:1 female predominance.1,3 Most myxomas occur in the left atrium (83%-88%).2,3,7 Although the occurrence of atrial myxoma is normally sporadic, as many as 7% of cases are familial, with the most notable condition being Carney syndrome, an autosomal dominant complex of cutaneous and cardiac myxomas, pigmentation, and endocrine abnormalities.8,9 Transesophageal echocardiography (TEE) has proved superior to transthoracic echocardiography in the diagnosis and characterization of cardiac mass lesions.10-12 In general, the outcome after cardiac myxoma resection is favorable, with a 20-year survival rate of 85%, and the recurrence rate of atrial myxoma after resection is low (5%).3,7 As many as 10% of patients with atrial myxoma present with no symptoms.3 However, in most patients, left atrial myxomas produce symptoms via the following 3 principal mechanisms: obstruction of the mitral valve, systemic embolization (peripheral or cerebral), and constitutional symptoms. The most common initial symptom that provokes the diagnosis is related to mitral valve obstruction and can include dizziness, palpitations, dyspnea, and congestive heart failure.3 Obstructive cardiac symptoms are the provoking symptoms in approximately 50% of pa-
tients, but may be present at any time in as many as 70%.3,6,7 Constitutional symptoms (eg, fever, fatigue, and weight loss) are the provoking symptoms in 50% but can be present at any time in as many as 58%.3,6,7 Systemic embolization is the provoking symptom in 16%, but may be present at any time in as many as one-third of patients.3,6,7 Neurologic symptoms have been reported in 26% to 45% of patients, with embolic cerebral infarct being the most frequently observed event.3,13,14 We report the largest descriptive clinical case series of neurologic complications related to atrial myxoma seen during an 11-year period at the Mayo Clinic.

### METHODS

Using the pathology database of biopsy and autopsy specimens, we searched for the diagnosis myxoma and then confirmed a cardiac origin in 74 patients. With institutional review board approval, we reviewed medical records to identify patients who underwent neurologic testing (computed tomography or magnetic resonance imaging of the brain, magnetic resonance angiography, or cerebral angiography) or neurologic consultation. One of us (V.H.L.) reviewed the medical records to identify patients with neurologic complications attributable to cardiac myxoma. Two patients with neurologic complications were excluded. The first patient had a possible amaurosis of the right eye in the setting of a right atrial myxoma without intracardiac shunt. The second patient had an intracranial mass that was pathologically confirmed to be myxoma without evidence of an atrial mass.

We identified 74 consecutive patients with pathologically proved cardiac myxoma who underwent cardiac myxoma resection at the Mayo Clinic from January 1, 1993, through December 31, 2004. Transesophageal echocardiography was performed on all patients before surgery. The mean age was 59.1 (range, 12-92) years, with a female predominance (43 patients [58%]). The left atrium (LA) was the most commonly observed location of cardiac myxomas (60 patients [81%]), followed by the right atrium (8 [11%]) and the ventricles (5 [7%]).

### RESULTS

We identified central nervous system complications of cardiac myxoma in 9 patients (12%), including 6 females and 3 males (Table 1). The mean age at the time of cardiac tumor resection in patients with neurologic complications was 48.5 years (range, 17-79 years). Four patients had no significant prior medical conditions. In the remaining 5 patients, the following stroke risk factors were present: hyperlipidemia (n=4), hypertension...
(n=3), active tobacco use (n=2), paroxysmal atrial fibrillation (n=1), diabetes mellitus (n=1), and coronary artery disease (n=1). One patient was diagnosed as having Carney syndrome (case 5).

**CLINICAL PRESENTATION**

In 7 patients with atrial myxoma who developed neurologic complications (78%), the provoking neurologic symptoms were the initial manifestation. Only 2 patients had the following neurologic events preceding the provoking neurologic symptom: patient 2 had a history of transient ischemic attack and patient 7 had a history of stroke and seizure. None of the patients with atrial myxoma and neurologic symptoms presented with cardiac symptoms.

Only 2 patients (cases 7 and 9) had evidence of pathologically confirmed systemic embolization of myxomatous emboli. Patient 7 (Figure 1) had a prior presumptive diagnosis of central nervous system vasculitis empirically treated with corticosteroids and cyclophosphamide; she then subsequently developed headache and left hemiparesis owing to a right frontal intracerebral hemorrhage. Case patient 9 with pathologically confirmed myxomatous embolization (Figure 2), presented with lower back pain and acute weakness of the bilateral lower extremities owing to an acute infrarenal aortic thrombus. He also developed splenic and renal emboli and underwent aortic embolectomy, bilateral femoral thromboembolectomy, and bilateral lower extremity fasciotomies.

**NEUROIMAGING**

Neuroimaging was performed on all patients with neurologic complications related to cardiac myxoma. Three patients had only computed tomography studies available; in 6 patients, magnetic resonance imaging studies were also available. Neuroimaging findings were consistent with ischemic cerebral infarction in 8 patients and intracerebral hemorrhage in 1 patient. Six patients (67%) had single-vessel territory ischemic events on neuroimaging findings. Only 3 patients (33%) had neuroimaging results that showed involvement of multiple vascular territories distinctive for a proximal embolic source (cases 3, 7, and 9).

Case 7 involved the only patient with intraparenchymal hemorrhage confirmed on computed tomography and magnetic resonance imaging of the brain (Figure 1). The patient in case 7 also had unusual magnetic resonance imaging findings, including multiple punctate areas of hemosiderin outside the area of the initial hemorrhage, and details of this case have been previously published. A cerebral angiogram in case 7 demonstrated a 3-mm wide-necked left internal carotid artery aneurysm arising proximal to the left ophthalmic artery in the region of the distal cavernous left internal carotid artery. There was also mild luminal irregularity with a more focal zone of dilatation involving 2 distal branches of the left middle cerebral artery in the region of the posterior aspect of the sylvian fissure. Cerebral angiogram data were available in 1 additional patient (case 4) and were unremarkable.

![Image](image_url)
TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Transesophageal echocardiography results were available in all 9 patients (Table 2). Eight patients (89%) had mobile or highly mobile masses. All 9 patients with neurologic manifestations had myxomas originating in the atrium. The size of the atrial myxoma was variable, with a mean diameter of 2.7 cm (range, 0.4-6.5 cm). Three patients had unusual echocardiographic features, including frondlike projections and a multilobulated appearance. Eight of the atrial myxomas causing neurologic symptoms (89%) demonstrated a mobile component on TEE. All patients had a normal or a mildly reduced ejection fraction (≥40%). In 3 patients, the atrial mass prolapsed through the mitral valve during diastole, but none of the patients demonstrated inflow obstruction of the mitral valve. Multiple TEEs were necessary before a diagnosis was reached in 1 patient (case 7).

PATHOLOGICAL FINDINGS

All patients had pathologically confirmed cardiac myxoma. Additional features noted on cardiac pathological examination included an organized thrombus in 2 patients (cases 3 and 8) and myxoma with focal hemorrhage in 1 patient (case 6). Only 2 patients (cases 7 and 9) had evidence of pathologically confirmed systemic embolization of myxomatous material. Pathological examination of the right frontal lesion in case 7 showed myxomatous proliferation inside the vascular lumen associated with aneurysmal dilatation. Despite atrial myxoma resec-

tion, the patient subsequently developed metastatic lesions in the pelvis and proximal femur, confirmed by results of a sacrum biopsy 10 months later. In case 9, pathological examination of the infrarenal segment of the aorta demonstrated embolic myxoma aggregate.

OUTCOME

All patients underwent successful surgical resection of the cardiac myxoma. The median time from the onset of neurologic symptoms to resection was 47 days (range, 2-848 days). The longest delay in diagnosis occurred in case 7, who was presumed to have central nervous system vasculitis. Preoperative medical treatment included warfarin sodium in 1 patient and aspirin in 3. After surgical resection, 5 patients received warfarin and 3 received aspirin. The duration of warfarin therapy was unknown in 2 patients and ranged from 1 to 6 months in the remaining 3 patients (Table 1). On hospital discharge, the mean modified Rankin score was 2 (range, 0-4). Information regarding the length of follow-up after hospital discharge was unavailable in 2 patients; and follow-up ranged from 8 months to 11 years in the remaining patients. A follow-up modified Rankin score was available in 6 patients, who had a mean score of 1 (range, 0-3). No deaths were recorded. Patient 1 had asymptomatic recurrence of myxoma 5 years after her initial presentation and underwent a second atrial myxoma resection.

COMMENT

We present herein, to our knowledge, the largest clinical series of central nervous system neurologic sequelae of atrial myxoma. The ages and sex of the patients with cardiac myxoma were consistent with those of previously reported series, with a female predominance between the third and sixth decades of life.3 Because our series was based on a search of the pathology database, we included all consecutive atrial myxoma resections performed, including asymptomatic presentations. Compared with other series that have reported neurologic symptoms in 26% to 45% of patients with atrial myxoma, the rate of central nervous system complications in our series was lower (9/74 [12%]).3,13,14 In our series, no patients demonstrated symptoms related to mitral valve obstruction or constitutional effects, suggesting that patients with atrial myxoma who develop neurologic complications may lack concomitant cardiac symptoms. Thus, neurologic symptoms can represent the initial clinical manifestation in patients with atrial myxoma. All of the patients in our series had a normal or mildly reduced ejection fraction, and none of the patients demonstrated inflow obstruction of the mitral valve. Multiple TEEs were necessary before a diagnosis was reached in 1 patient (case 7).
nonthrombotic tumors are more likely to be found in older patients.16 Surgical resection of atrial myxoma is curative in most patients, and continued systemic or cerebral embolization after tumor removal is rare.13,17,18 Although surface thrombus embolization may be the suspected mechanism, only one-third of the patients in our series had multiple vascular territory involvement on neuroimaging. Surgical resection is considered curative, and medical management alone may be ineffective. In a case series of 5 patients with atrial myxoma and stroke, cerebral embolization occurred in 2 patients before surgical resection, despite anticoagulation therapy.13 Although anticoagulation therapy may reduce the risk of embolism due to thrombus, it would be mechanistically ineffective in preventing embolism from fragments of the myxomatous tumor.

Only 2 patients (22%) showed evidence of systemic myxomatous tumor embolization. Although rare, myxomatous tumor emboli have been demonstrated histologically in a variety of locations, including the coronary arteries, common iliac arteries, kidney, spleen, pancreas, liver, and brain.3,7,19,20 Compared with nonembolic myxomas, embolic tumors are more likely to have a surface thrombus and myxoid frondlike projections.19 After acute myxomatous emboli, there are 2 potential neurologic complications: myxomatous emboli may invade the vessel walls, inducing cerebral aneurysmal formation, or embolic implants may metastasize and form space-occupying lesions.

Intracranial aneurysms are a rare complication of myxomatous emboli.1,2,10 Pathologically proved myxomatous emboli have been demonstrated in the cerebral vessels.1,9,20,21,22 as was evident in case 7. Histologically, 23% of myxomas have mitotic activity and myxomatous emboli can demonstrate continued growth within vessels.16,24 Myxomatous tumor cells can penetrate the vessel wall at the site of final lodgment, and tumor emboli can infiltrate via subintimal growth, leading to weakening of the arterial wall and subsequent aneurysm formation.21,26 This complication can be delayed, and pathologically proven intracranial aneurysms have been reported 5 years after successful left atrial myxoma resection.27

Aneurysm formation associated with embolized atrial myxoma is not caused by blood-flow dynamics but by myxomatous tumor invasion into the vessel wall. Thus, cerebral aneurysm associated with atrial myxoma has been described as having angiographic features similar to those of septic emboli, including multiplicity, peripheral location, and fusiform appearance.27-30 In case 7, a cerebral angiogram demonstrated focal dilatations in 2 distal branches of the left middle cerebral artery consistent with myxoma-related aneurysms and a 3-mm aneurysm in the distal cavernous left internal carotid artery of uncertain significance.

Case 7 also illustrated the second rare complication of myxomatous tumor emboli known as metastatic myxoma. Metastatic cardiac myxoma has been documented in the lung, bones, and soft tissue.31 Metastatic myxoma is infrequent, and intracranial metastatic cardiac myxoma is even less common, limited to single case reports in the literature.31-33 As illustrated by case 7, surgery may not preclude delayed neurologic sequelae and metastatic myxoma is a complication that can present long after cardiac myxoma resection. Rarely, these masslike lesions may precede the diagnosis of the cardiac myxoma by as long as 22 months.34 There is no definitive treatment for metastatic cardiac myxoma, although there is an isolated case report of treatment with irradiation and chemotherapy (doxorubicin hydrochloride and ifosfamide) with a 10-year remission.31

Atrial myxoma is a rare but potentially curable cause of stroke. Neurologic complications associated with atrial myxoma most frequently include cerebral infarct due to thrombus. Rarely, neurologic complications may be due to embolized tumor fragments. Patients with embolized myxomatous tumor represent a minority of patients with cardiac myxoma and appear to be at increased risk for peripheral systemic embolization and delayed neurologic com-

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Myxoma Attachment Description</th>
<th>Prolapse Into MV</th>
<th>Ejection Fraction, %</th>
<th>Size, cm</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Posterior wall of left atrium</td>
<td>Multilobulated, highly mobile</td>
<td>Yes</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>Junction of LAA and pulmonary veins</td>
<td>Highly mobile</td>
<td>No</td>
<td>60</td>
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<tr>
<td>3</td>
<td>Atrial septum (fossa ovalis)</td>
<td>Small stalk, mobile</td>
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<td>65</td>
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<td>4</td>
<td>Atrial septum</td>
<td>Large, mobile</td>
<td>Yes</td>
<td>53</td>
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<tr>
<td>5</td>
<td>Multiple chambers (left atrium)</td>
<td>Multiple masses, mobile</td>
<td>. . .</td>
<td>65</td>
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<td>sessile mass with frondlike mobile projections</td>
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<td>9</td>
<td>Atrial septum (fossa ovalis)</td>
<td>Large, highly mobile</td>
<td>Yes</td>
<td>40-45</td>
</tr>
</tbody>
</table>

Abbreviations: LAA, left atrial appendage; MV, mitral valve (during diastole); ellipses, data not available.

Table 2. Transesophageal Echocardiography Features
lications. Potential neurologic sequelae relevant to patients with tumor embolization include myxoma-induced aneurysmal formation and myxomatous metastasis. Cerebral angiography should be considered in patients with embolic cerebral infarction associated with atrial myxoma, especially in the setting of pathologically confirmed myxomatous emboli elsewhere. In addition to being evaluated for myxomatous intracranial aneurysms, this subset of patients should be monitored for the potential development of metastatic myxoma.

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REFERENCES