Left Atrial Myxoma as a Neurological Problem: A Case Report and Review

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Abstract:

A puzzling neurological illness in a patient with a clinically normal heart was explained at autopsy by cerebral embolization from a left atrial myxoma (LAM). Constitutional symptoms associated with LAM were present. Cerebral angiography revealed aneurysms and focal areas of abnormal blushing. Cerebral and cardiac pathology is presented.

The surgical follow-up of seven other cases is reported to determine the "curability" of such tumors.

We believe that echocardiography should be performed in any case of suspected cerebral embolization even though cardiac symptoms and signs may be absent.

Additional Key Words: aneurysm, cerebral emboli, echocardiography

Introduction

Primary cardiac tumors are found in only 0.05% of routine autopsies. About half are myxomas, with a majority (75%) present in the left atrium. One-third of left atrial myxomas (LAM) present with neurological symptoms and signs due to cerebral embolization from this friable, supposedly benign tumor. A majority of these tumors occur in adulthood, from the ages of 30 to 60 years, but no age is immune.

Renewed interest in this tumor is mirrored in the cardiac, radiological, and neurological literature for the following reasons:

1. Ultrasound echocardiography has proved highly accurate in detection of left atrial tumor.
2. The angiographical appearance of cerebral vessels affected by myxomatous emboli has been found characteristic, although not diagnostic, of the disorder.
3. Careful pathological examination of the myxoma emboli in cerebral vessels has shown that a disturbing degree of invasiveness is present in what was previously considered a histologically benign tumor.

This paper describes a 48-year-old woman who experienced a complicated neurological illness of insidious onset, culminating in death. Symptoms of cardiac disease were absent during her illness. The systemic manifestations associated with left atrial myxoma were present, but the diagnosis was made only at postmortem examination. We document this case because her clinical presentation did not suggest cerebral embolization, because of the absence of cardiac symptoms, and finally because of the recent sophistication of echocardiography in the detection of this tumor. Complete neurological and detailed neuropathological findings are discussed in reference to early diagnosis, treatment and prognosis. The authors think that when weight loss, intermittent fever, elevated sedimentation rate, and anemia are present in a patient with a progressive puzzling neurological illness, echocardiography should be performed.

Also, we have outlined the clinical presentation and postsurgical follow-up of seven patients with atrial myxomas at Presbyterian Hospital, San Francisco, California. Two of these patients expired shortly after surgery and their autopsy findings are reported.

Case Report

A 48-year-old right-handed Caucasian woman (P250021) presented with weakness of the left arm of six months' duration.

She was in good health until about two years before admission when she had a sudden, brief loss of consciousness, without sequelae. During the year prior to admission she complained of intermittent frontal headaches and gradually became unsteady on her feet and clumsy with her left hand. Six months before admission neurological examination and skull x-rays were reported normal. In the ensuing six months her left arm became progressively weaker and spastic. Twelve days before admission her frontal headaches increased in severity and she developed focal, clonic-tonic activity...
of her left arm which spread to the left leg and then to the right arm and leg lasting three hours and without loss of consciousness. Four days later she entered another hospital with left face, arm and leg weakness. A spinal tap revealed an opening pressure of 210 mm H2O. The cerebrospinal fluid was acellular, the protein was 117 mg %, and the glucose 60 mg %. A second spinal tap two days before admission revealed an opening pressure of 260 mm H2O, cerebrospinal protein of 125 mg %, glucose of 75 mg %, and 20 red blood cells (RBCs). Diagnostic studies, including brain scan and skull x-rays, were reported as normal. Hemoglobin was 14.7 mg %, packed cell volume (PCV) 44%, white blood cell count (WBC) 12,700 with 80% neutrophils, 1 eosinophil, 14 lymphocytes and 5 monocytes. Urinalysis, blood sugar, and electrolytes were normal.

Admission examination revealed a woman with a flat affect whose left arm was clenched against her chest. Blood pressure was 160/90. Pulse, temperature and respirations were normal. Pulmonary and cardiac examinations were normal. Small telangiectases were scattered over her chest and neck. The remainder of the general examination was normal. Neurological examination revealed an impaired mental status. She did not know the year, her birth date, or place of birth. She could remember only one object out of three after ten minutes and interpreted proverbs concretely. There was a marked spasticity in the left arm and leg and normal strength in the right arm and leg. Muscle stretch reflexes were hyperactive on the left. Bilateral Hoffman and Babinski signs were present. A prominent snout reflex and bilateral grasp reflexes were noted. The remainder of the neurological examination was normal. Initial SGOT was 145. Several days later it was 75. Urinalysis revealed a trace of protein and 68 RBCs. PCV was 40.5%, hemoglobin 14.2 mg %, and WBC 11,600 with 68% neutrophils, one band, 1 basophil, 25 lymphocytes and monocytes. The sedimentation rate was 56 mm per hour. LE preps and serology were negative. The total serum protein was 7 gm %. A serum electrophoretic pattern showed an acute inflammatory response with increased gamma globulin.

Chest x-rays, EKG, and skull x-rays were normal. A brain scan revealed uptake of isotope in the right cerebral hemisphere with labeling of a small area in the right superior parietal lobe. An electroencephalogram was markedly abnormal with a large area of slowed over the right posterior parieto-occipital lobe and diffuse slowing over the remainder of both hemispheres. Cerebral angiography revealed several capillary blushes with the most prominent in the right posterior parietal region during the arterial phase with fading during the early venous phase (fig. 1). Vascular changes consisting of focal narrowing and dilatation were present in cortical vessels in both cerebral hemispheres (fig. 1). The ventricles were normal in size.

On the fourth day after admission she experienced sudden difficulty in the use of her right arm and headaches which persisted throughout her hospitalization. At no time was her neck rigid. On the sixth hospital day a right parietal craniotomy was performed. The dura was tense and bulging. The brain showed multiple areas of old hemorrhagic discoloration. Frozen sections revealed old and recent hemorrhage with fibrous and vascular proliferations and an atypical

![FIGURE 1](Right carotid angiogram. Subtraction film showing abnormal blushes (vertical arrows) and focal narrowing and dilatations (horizontal arrows).)
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vascular pattern. After discharge to a nursing home she continued to deteriorate. She died suddenly two months later.

General Pathology

GROSS PATHOLOGY
The heart weighed 220 gm. In the left atrium, arising from the superior remnant of the fossa ovalis, there was a pedunculated irregular, friable tumor measuring 3.5 X 2 X 1 cm (fig. 2). The point of attachment to the rim of the fossa ovalis was delicate and measured approximately 8 mm in width. Plaques of thickened endocardium were present on the aortic aspect of the mitral valve. Small areas of gray scarring were present at the apex of the myocardium. The coronary arteries were without arteriosclerosis. The remainder of the general gross pathology was normal.

MICROSCOPIC PATHOLOGY
The myxoma consisted of round and polygonal cells with abundant cytoplasm and indistinct margins. No mitotic activity was seen. Myxoma-engorged and myxoma-distorted small vessels were found in the myocardium (fig. 3).

Neuropathological Findings

GROSS PATHOLOGY
The brain weighed 1,085 gm. External examination revealed numerous scattered areas of brownish subarachnoid and cortical pigmentation ranging from 0.5 cm to 3 cm in diameter and located mainly in the parieto-occipital lobes. The underlying cortical tissue was softened and in some areas sunken below the neighboring cortical surface. Narrowing of the sulci and fullness of the gyri were present in the right parietal lobe where there was evidence of previous superficial surgical excision. One small punctate 0.5 cm area of softened hemorrhage was present in the left lateral lobe of the cerebellum. There was minimal arteriosclerosis; the left anterior cerebral artery was occluded by a fleshy-colored, firm embolus about 1.5 cm from its origin with the anterior communicating artery.

Coronal sectioning demonstrated many areas of small and large hemorrhagic infarctions of varying age in both hemispheres (fig. 4) coinciding with the external brownish discolorations. The largest cortico-medullary junction infarction was located in the right parietal lobe. The head of the right caudate nucleus was destroyed by a punctate, soft hemorrhagic infarction which extended down into the internal capsule, putamen and globus pallidus. An old, firm, nonhemorrhagic linear yellowish infarction measuring 2.5 X 0.5 cm was present in the right superior frontal gyrus. The ventricles were slightly dilated but symmetrical. The right cerebral peduncle was only two-thirds the size of the left cerebral peduncle.

MICROSCOPIC FINDINGS
Representative sections of the cerebrum, brain stem, cerebellum, meninges, choroid plexus and the left cerebral artery thrombus were stained with hematoxylin and eosin, alcian blue, and Masson's trichrome stains. Microscopically there was diffuse infiltration by lymphocytes and macrophages, with many proliferated

FIGURE 2
Left atrium of heart exposed to reveal friable papillary myxoma attached to interatrial septum.
FIGURE 3

Myxoma tumor in myocardial vessel. Hematoxylin and eosin X 100.

Microglia and abundant gitter cell formation in the infarcted areas with extension into the leptomeninges and subarachnoid space. Hemosiderin-laden macrophages were present in the cortex and subarachnoid spaces.

In sections adjacent to infarctions in the frontal and occipital cortex, meningeal vessels contained myxomatous cells and eosinophilic myxoid stroma similar to those seen in the heart. No mitoses or pleomorphism were present. Tumor cells occluded the lumen of numerous vessels; in some instances the internal elastic lamina and media of the vessel appeared invaded by these cells (fig. 5).

The vessels occluded with tumor were found mostly in the subarachnoid space. Arteries and veins were involved. Microscopic foci of tumor also were found in the superior sagittal sinus. The thrombus in the left anterior cerebral artery showed no evidence of tumor or vessel wall invasion. Nowhere did tumor involve the actual parenchyma of the brain.

Discussion

Malpighi reported on cardiac tumors in the 17th century, but large series have only recently been compiled. Fletcher was able to collect a total of 550 cardiac myxomas in the English literature. Newman et al. collected 312 cases of intracardiac myxoma. The diagnosis remained a pathological curiosity. In life patients were often thought to be suffering from mitral valve disease. Adams et al. found 370 cardiac tumors erroneously diagnosed as mitral stenosis. Goldberg was the first to make the antemortem diagnosis of cardiac myxoma. Successful surgical removal of an intracavitary myxoma did not occur until 1954 when cardiopulmonary bypass was effected. In 1966 survival rate following surgical removal of left atrial myxoma was 83%.

Several questions arise concerning this tumor. What is the typical clinical picture of the LAM? What are the diagnostic procedures employed in making the diagnosis of LAM when the heart is clinically normal? How does cerebral embolization affect the management and prognosis in these patients following surgical removal of their tumor? Finally, is the LAM really a treatable cause of stroke as advocated by Maroon and Campbell?

The LAM presents clinically with obstruction of cardiac flow, systemic embolization and constitutional symptoms, or any combination of the
The obstructive effects of cardiac myxomas result from occlusion and distortion of the mitral valve. Goodwin found that the obstructive cardiac symptoms occurred in about 75% of patients. Pulmonary hypertension and dyspnea were common in his patients. He believed that in the absence of either a mitral valve murmur, pulmonary hypertension or dyspnea, the diagnosis of LAM was improbable but possible. Joynt et al., however, reported 12 patients with LAM who presented with acute neurological episodes without cardiac symptoms, and more recently Maroon and Campbell reported four patients with neurological symptoms and no cardiac signs. It is safe to conclude from these reports that although the majority of patients have cardiac symptoms and signs, their absence does not negate the diagnosis of LAM.

Embolic effects of LAMs (either from platelet thrombi or tumor fragments) have been reported in up to 45% of patients. About half of these emboli were to cerebral vessels. Emboli to small myocardial vessels, present in our patient, were rare in other series. In some cases the diagnosis of LAM was made only after pathological examination of peripheral emboli revealed myxomatous tissue. It has been proposed that any embolic phenomena in a young patient, not clearly related to rheumatic heart disease of subacute bacterial endocarditis, should arouse suspicion of LAM. Our patient was most unusual in that she obviously had experienced multiple cerebral embolic events but a clear clinical history of multiple acute neurological episodes could not be clearly elicited from the patient or her husband.

Constitutional effects of myxoma are the least recognized and most poorly understood, and are often the cause of erroneous diagnosis. These effects include fever, anemia, increased sedimentation rate, loss of weight, abnormal serum and spinal fluid protein. Clubbing has even been described in patients with myxoma. The combination of these systemic manifestations and the obstructive effects of myxoma may point one erroneously toward the diagnosis of subacute bacterial endocarditis. When blood cultures are consistently negative in patients with cardiac signs and symptoms, LAMs should be considered.

The elevated gamma globulin in the spinal fluid has been reported too consistently to be mere coincidence and is thought to be secondary to an immunological response of the body to the polysaccharide component of the tumor. The spinal fluid protein was elevated in our patient; however, protein electrophoresis was not performed. Systemic manifestations of myxoma exemplified by our patient consisted of intermittent fever, leukocytosis,
high sedimentation rate and elevated serum and spinal fluid protein. Kluge et al.\textsuperscript{24} reported 11 patients with cardiac myxomas at our institution, ten of whom displayed one or more of the above constitutional signs or symptoms. The majority of these patients also had evidence of liver disease. He felt that the liver dysfunction was due to immunological mechanisms triggered by the atrial myxoma.

Ideally, the diagnosis of LAM should be made before evidence of peripheral embolization occurs. In view of recent evidence showing that myxoma, once lodged in the cerebral vessels, has the neoplastic propensity to invade and destroy vessel walls, early diagnosis may be life-saving.\textsuperscript{5, 6} Echocardiography has proved successful in the preoperative diagnosis of both right and left atrial myxomas.\textsuperscript{5-7} It is a noninvasive, reasonably accurate method of detecting intracavitary cardiac masses and is a worthwhile screening examination when there is a clinical suspicion of an LAM.

Stoane et al.\textsuperscript{10} were the first to describe the characteristic cerebral angiograms in two patients with LAMs with no cardiac signs. They found "filling defects of varying size without interruption of flow and focal changes in the arterial wall and perivascular tissues ranging from slight dilatation and irregularity to pseudo-aneurysm formation." Mechanical destruction and scarring were thought to be the basis for these vessel changes. These vessel changes could not be distinguished from those occurring with septic aneurysms and in some forms of arteritis. Burton and Johnston\textsuperscript{25} also emphasized the causal relationship between cerebral aneurysms and atrial myxomas in a 41-year-old woman, even demonstrating myxoma tumor in the aneurysm. They, too, felt the vessel wall was weakened by mechanical forces. New and Price et al. clearly established the neoplastic properties of myxoma to be responsible for these aneurysmal dilatations and vessel irregularities in a clinicopathological and angiographical study of a 21-year-old female.\textsuperscript{8, 6} Our patient did have filling defects and aneurysmal dilatations on cerebral angiography.

The question now arises—if our patient had undergone removal of her myxoma, what would the chance of future intracerebral bleeding have been? Scant data are presently available in the literature to answer this question. Only one patient has been
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found; she, at the time of removal of her LAM, displayed no neurological signs or symptoms, but she returned three years later with acute onset of aphasia, slurring of speech, and characteristic aneurysmal changes on the cerebral angiogram.

It was because of this paucity of information regarding the prognosis of patients following removal of their LAM that we outlined the surgical follow-up of seven such patients (table 1). Six of these patients had atrial myxomas located in the left atrium and one (MJ) had a right atrial myxoma with a patent foramen ovale, a right-to-left shunt, polycythemia, and the possibility of paradoxical embolization of myxoma tumor. This case has been reported previously.

All had cardiac murmurs and abnormal EKGs. The duration of symptoms before surgical removal of their tumor ranged from nine months to five years. Two of the three patients who showed evidence of neurological dysfunction and constitutional symptoms expired within two months of removal of their tumor. Autopsy on one of these patients (SH) revealed evidence of splenic and cerebral infarction and myxoma emboli in a common iliac vessel. An intense myocarditis also was seen in this patient. The neurological symptoms displayed by MJ were possibly related to her polycythemia and not to paradoxical cerebral embolization from her right atrial myxoma. The atrial tumors were all lobulated and large. In no instance did pathological examination reveal mitotic activity or pleomorphism (suggestive of malignant transformation).

Summarizing these data it appears that the deciding factor in regard to survival following tumor removal is the preoperative presence of embolic phenomena. The sedimentation rate was elevated in two patients who displayed no other symptomatology following removal of their tumor. The size of the atrial tumor and the histological appearance of the tumors were similar in all seven patients.

**Summary**

A puzzling neurological illness in a patient with a clinically normal heart was explained at autopsy by cerebral embolization from a left atrial myxoma. In such a patient the systemic symptoms of weight loss, intermittent fever, anemia and an elevated erythrocyte sedimentation rate should lead to the suspicion

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Cardiac symptoms</th>
<th>Embolic symptoms</th>
<th>Constitutional symptoms</th>
<th>Duration of symptoms</th>
<th>Duration of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.O.</td>
<td>51 F</td>
<td>Dyspnea</td>
<td>Orthopnea</td>
<td>Anemia</td>
<td>5 yrs.</td>
<td>8 yrs.</td>
</tr>
<tr>
<td>B.R.</td>
<td>53 M</td>
<td>Dyspnea</td>
<td>Orthopnea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.A.</td>
<td>32 F</td>
<td>Dyspnea</td>
<td>CHF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.P.</td>
<td>43 F</td>
<td>Dyspnea</td>
<td>Orthopnea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.J.</td>
<td>54 F</td>
<td>Dyspnea</td>
<td>Sudden right arm weakness and aphasia, 10-21-70</td>
<td></td>
<td>13 mos.</td>
<td>1 yr.</td>
</tr>
<tr>
<td>S.H.</td>
<td>12 F</td>
<td>Dyspnea</td>
<td>Cyanotic episodes in legs</td>
<td></td>
<td>9 mos.</td>
<td>2 mos.</td>
</tr>
<tr>
<td>V.V.</td>
<td>15 F</td>
<td>Dyspnea</td>
<td>Gross hematuria</td>
<td></td>
<td>2 yrs.</td>
<td>1½ mos.</td>
</tr>
</tbody>
</table>

*Congestive heart failure.
†Erythrocyte sedimentation rate.
of an atrial myxoma and the performance of echocardiography. The cerebral angiograms in this case showed characteristic focal narrowing, dilatation and aneurysms of the blood vessels.

The myxoma emboli, in this case, showed evidence of invasiveness and raise the question of "curability" of such lesions in patients who have already embolized. A review of seven cases suggests that embolization indicates a poor prognosis.

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Stroke. 1973;4:451-458
doi: 10.1161/01.STR.4.3.451
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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