Unusual Presentation of Atrial Myxoma: A Case Report and Review of the Literature

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Conflict of interest: None declared

Patient: Female, 40-year-old
Final Diagnosis: Atrial myxoma • myocardial infarction
Symptoms: Dry cough • shortness of breath • wheezing
Medication: —
Clinical Procedure: —
Specialty: Cardiology • Pathology • Pulmonology

Objective: Unusual clinical course

Background: Although rare, atrial myxoma is the most common benign cardiac tumor. The recognized triad of presenting symptoms relates to constitutional, embolic, and obstructive effects produced by the tumor. However, the presentation may be non-specific and mimic other diseases, confounding diagnosis.

Case Report: A middle-aged woman presented with wheezing and shortness of breath. With a strong background smoking history, the initial impression was that of acute bronchospasm. She however deteriorated rapidly, with decreased consciousness and cardiac arrest requiring resuscitation. Despite intensive care management, she died within 1 day of admission. Autopsy revealed a previously undiagnosed left atrial myxoma with coronary and systemic embolization.

Conclusions: This case highlights an unusual presentation of atrial myxoma, resulting in fatal simultaneous embolization to the coronary and cerebral arteries. This simultaneous embolic presentation is not common, but the potential consequences are serious. This report also demonstrates that the presentation of a left-sided atrial myxoma with cardiac asthma can mimic respiratory disease and confound diagnosis. In adult patients without a history of chronic respiratory disease, the possibility of cardiac asthma should always be entertained. Furthermore, the importance of considering atrial myxoma as a cause for cardiac asthma is emphasized. The use of trans-thoracic echocardiogram in aiding the rapid diagnosis of atrial myxoma is recommended. Finally, the continued acknowledgement of the important contribution the academic autopsy makes in complementing and improving clinical practice remains imperative.

Keywords: Atrial Myxoma, Familial • Carotid Artery, Common • Case Reports • Coronary Vessels • Neoplastic Cells, Circulating

Abbreviations: COPD – chronic obstructive pulmonary disease; ICU – Intensive Care Unit; FiO₂ – fraction of inspired oxygen; PO₂ – partial pressure of oxygen; PCO₂ – partial pressure of carbon dioxide; TCO₂ – total carbon dioxide; kPa – kilopascal; GCS – Glasgow Coma Scale

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Background

Cardiac myxomas represent the most common benign cardiac tumors in adults [1-3]. The myxoma cell is postulated to arise from resident pluripotent or a multipotent mesenchymal stem cell [1,4,5]. Embryonic rests of the latter persist during septation and differentiate into endothelial cells, smooth muscle cells, and other mesenchymal cells. This explains the prevalence of myxomas in the atrial septum [1]. It may also account for the wide morphologic variation. Cardiac myxomas are most prevalent in adults, especially between the 3rd and 6th decades [1,2,5,6]. They can be sporadic or familial, with sporadic cases being more prevalent in women [4,6]. They are also usually solitary, and most commonly arise in the left atrium, near the fossa ovalis [6,7]. Familial cases are characterized by an autosomal dominant mutation of the PRKAR1A gene located on chromosome 17q2 [3,6]. Myxomas in these patients are more likely to be multiple, located outside the left atrium, and to recur [4,6]. In addition, they may present with cutaneous and mammary myxomas, spotty mucocutaneous pigmentation, malignant melanotic nerve sheath tumors, testicular tumors, and endocrinopathies (Carney’s complex) [4,6].

The clinical presentation of patients with cardiac myxomas consists of one or more features of a classic triad of symptoms due to embolism, intracardiac obstruction, and constitutional manifestations [1-3,8-11]. These are related to tumor size, location, and mobility [1,10,11]. Patients may be asymptomatic, especially those with small tumors [1,12]. Features may even be non-specific, or mimic cardiovascular or systemic diseases [11,13].

We report on a patient with an undiagnosed left atrial myxoma with an unusual presentation, resulting in multiple fatal embolic phenomena.

Case Report

Clinical

The deceased was a middle-aged woman referred to the medical intensive care unit (ICU) of Tygerberg Academic Hospital with the diagnosis of respiratory failure secondary to acute bronchospasm, requiring invasive mechanical ventilation. She had presented to the referring hospital the preceding night with a 2-day history of a dry cough, wheezing, and acute onset of shortness of breath. A similar episode of chest tightness and wheezing was reported 3 years ago, which had resolved with a short course of inhaled beta-2 agonists. Aside from a 2-week history of night sweats, she reported no other symptoms. She was a smoker of approximately 15 pack years and consumed alcohol infrequently. There was no significant occupational or exposure history of note. Despite appropriate medical management of bronchospasm, she had collapsed at the referral hospital, necessitating intubation and ventilation.

On ICU admission, the patient was noted to be heavily sedated, limiting a comprehensive neurological examination (GCS 6T). Her pupils were equal and reactive to light, and she was hemodynamically stable. Mechanical ventilation was necessitated on the sole basis of a decreased level of consciousness. The clinical examination did not reveal overt pathology.

Her admission chest radiograph showed bilateral interstitial infiltrates with fluid in the horizontal fissure. The cardiac silhouette was not enlarged (Figure 1).

Laboratory studies revealed an elevated white cell count (16.8x10^9/L), lactate dehydrogenase (570 U/L), creatinine kinase (1380 U/L), aspartate transaminase (142 U/L), and alkaline phosphatase (131 U/L). Blood cultures were subsequently negative for growth. Other laboratory test results were within normal limits.

The referral diagnosis of severe asthma was revised to resolved acute pulmonary edema of uncertain cause. Further investigations to determine the cause of the pulmonary edema were requested and a review of her neurological state was planned once sedation had worn off.

However, shortly after her initial assessment, and preceding further investigations, she suffered an unexpected cardiorespiratory arrest. A brief period of ST segment elevation was noted on the cardiac monitor prior to arrest, with no other immediately
remediable cause evident. Although return of spontaneous circulation was achieved after 8 minutes, the patient did not regain consciousness after resuscitation (GCS 2T). A significant intracranial event was suspected. An urgent computerized tomography brain scan revealed generalized cerebral edema, cerebellar tonsillar herniation, and a possible thrombosis of the dural venous sinuses, right middle cerebral artery, and right internal carotid artery. The patient died later that evening. An academic autopsy was requested in light of her acute deterioration and uncertain cause of death.

Autopsy

The body mass index was 23.4 kg/m². The calves were symmetrical, and no pedal edema was elicited.

Examination of the cardiovascular system demonstrated a left atrial 50×30×30 mm gelatinous, pedunculated mass attached within proximity of the fossa ovalis, and partially prolapsing through the mitral valve. The tumor had a relatively smooth contour, except for a focal ragged area. Surface thrombus was present. The cut surface appeared variegated (Figure 2A, 2B). Serial transverse sections of the myocardium revealed light-brown mottled areas, involving the left ventricle and interventricular septum (Figure 3A). No scar was seen. The pericardial cavity, pulmonary trunk and branches, and coronary arteries were unremarkable.

A non-occlusive thrombo-embolus was found in the proximal right common carotid artery, with a saddle embolus impacted at its bifurcation (Figure 4A).

Histology of the atrial tumor showed a bland paucicellular neoplasm comprising spindled and stellate cells embedded in a myxoid matrix, with accentuation around abnormal, thin-walled vessels. Old and recent stromal hemorrhage was present, as well as surface antemortem thrombus. The tumor-atrial interface was characterized by chronic mononuclear inflammation

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Figure 2. (A) Superior view of opened left atrium showing myxoma. (B) Formalin-fixed atrial myxoma with overlying thrombus (top), myxoid variegated areas (right), and attachment to atrial septum (bottom). (C) Myocardial-atrial myxoma interface showing tumor cells within a myxoid matrix (bottom) (H&E, ×40). (D) Sparse spindled myxoma cells in a loose eosinophilic matrix, chronic mononuclear inflammation, and hemosiderin in macrophages (H&E, ×200). Inset: Calretinin immunohistochemistry demonstrating positive tumor cells with perivascular accentuation (×100).
and fibrosis. Calretinin staining was positive in tumor cells, confirming the diagnosis of an atrial myxoma (Figure 2C, 2D).

One of the coronary arteries showed non-critical stenosis by fibrointimal hyperplasia. The rest were unremarkable. Sections of the myocardium showed prominent neutrophilic infiltration with loss of myocyte nuclei and contraction band necrosis, consistent with an acute myocardial infarction in the first week of evolution. Hemorrhage was not seen. Some intramural vessels in the left anterior descending coronary artery territory contained fibrin thrombi with spindle cells suspicious for tumor emboli. Calretinin staining confirmed an atrial myxoma origin (Figure 3B-3D). Sections of the impacted carotid embolus showed predominantly antemortem thrombus with a fragment of atrial myxoma (Figure 4B-4D).

The external surface of the brain was dusky and edematous with congested cortical vessels. No signs of herniation were present at examination and the dural sinuses were free of thrombus. Serial coronal sectioning was unremarkable.

Histology showed thrombo-emboli in superficial cortical vessels, with fragments of atrial myxoma confirmed on immunohistochemistry. Features of hypoxic ischemic encephalopathy were absent (Figure 5A-5D).

Examination of the respiratory system revealed a mild elevation in lung weights. No hyperinflation, pleural effusions, or arterial thrombi were seen.

Histology of the lungs showed pulmonary edema fluid and numerous pigmented macrophages. A Perls’ Prussian blue stain confirmed the presence of hemosiderin in some of the macrophages.

The remaining organ systems were unremarkable.
Intracardiac obstruction is related to large or mobile myxomas interfering with ventricular filling, atrioventricular valve closure, or damage to the valve [1]. The symptoms include dyspnea, cough, recurrent pulmonary edema or features of right-sided heart failure, or features of insufficiency [1,11]. Sudden complete obstruction by a tumor prolapsing into the valve orifice may result in syncope or sudden death [1,10]. We surmise that an antemortem prolapse may have caused the initial collapse at the peripheral facility. Alternatively, the positive chronotropic effect of nebulization with a beta-2 agonist, myocardial infarction, and the obstructive effects of the atrial myxoma may have acted in concert.

Bedside transthoracic echocardiography (TTE) is a rapid, non-invasive, point-of-care assessment that forms an essential adjunct to the hemodynamic evaluation of the critically ill patient. It provides information to guide both therapeutic interventions and/or referral for cardiac or surgical intervention. The utility of TTE has been demonstrated as being comparable to that of transesophageal echocardiography (TOE) in the detection of atrial myxomas [14], and should form part of the initial assessment of suspected cardiac tumors. Although a TTE was included in the immediate management plan of our patient, the short time span before deterioration in the ICU, however, barred its execution.

Embolic phenomena occur in 10-50% of patients with cardiac myxomas [1,7,9]. Embolism is related to breaking off of tumor fragments, or surface thrombi and vegetations [7]. Emboli comprise small fragments or showers, but seldom consist of the entire tumor [15]. Factors associated with an increased risk of embolization include atypical location, an irregular or villous surface, a friable gelatinous consistency, presence of surface thrombus, increased tumor size, increased left atrial diameter, and increased production of matrix metalloproteinases [3,5-7,9,12,15,16]. Some authors have found an inverse or no relationship between embolization risk and tumor size [17,18]. The association of embolization with blunt chest trauma has also been suggested [3,11,19]. In our patient, the possible contribution of cardiopulmonary resuscitation to common
carotid embolization is speculative. Embolization is associated with high morbidity and mortality, with the central nervous system being involved in 50% of embolic cases [2,7]. Right-sided myxomas give rise to pulmonary emboli, while left-sided tumours result in systemic emboli. However, a right-sided atrial myxoma can result in paradoxical systemic embolization in the presence of a patent foramen ovale [1]. The most frequently involved vessels are the cerebral arteries, including the retinal arteries [1,3,7,12]. These emboli can also induce aneurysms and cavernous malformations [10,11,20]. The neurological sequelae include syncope, seizures, stroke, symptoms of cerebellar infarction, and fulminant brain necrosis [2,5]. Women in the fifth decade are at highest risk of an embolic stroke, and in one series, 86.4% of patients with both atrial myxoma and neurological signs had the latter as the initial presenting symptom [5]. Ischemic cerebral infarction is reportedly the most common [16]. The presentation of cerebral embolism is usually that of acute onset [21]. In addition, an acute embolic stroke may be the first presentation of atrial myxoma in a young patient [22]. The history may be that of sudden loss of consciousness following strenuous exercise [22]. Transthoracic echocardiography is a rapid and non-invasive point-of-care assessment, comparable to transesophageal echocardiography in detecting atrial myxomas [14], and should form part of the initial clinical assessment, especially in patients who do not have coronary artery disease risk factors.

Despite numerous reports of cerebral infarction due to left atrial myxomas, we found only 1 case report of common carotid artery occlusion by myxoma, presumed to be of cardiac or primary vascular origin [24]. In a comprehensive review of stroke cases due to cardiac myxoma between 2000 and 2014, only 13% demonstrated involvement of the internal carotid artery, but none involved the common carotid artery [25]. It is possible that in our patient, the large fragment of accompanying tumor surface thrombus predisposed to proximal impaction, compared to emboli comprising solely friable myxomatous fragments, which would impact more distally.

In our patient, failure to regain consciousness after resuscitation suggested an intracerebral insult. The impacted carotid artery tumor embolus and the emboli found in distal cerebral
arterial branches could explain her neurological deterioration. However, the contribution of both acute myocardial infarction and the obstructive myxoma to poor cerebral perfusion cannot be negated. The smaller embolus likely preceded the larger impacted embolus. The absence of frank infarction on CT scan and microscopy can be explained by the time-dependent nature of the evolution of cerebral infarcts. Magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) is highly sensitive in detecting early cerebral ischemia, surpassing both conventional MRI and CT scan in performance [26]. However, its utility in mechanically ventilated patients is reliant on the clinical assessment of the patient and the availability of appropriate resources (including the presence of an MRI-compatible ventilator) among other considerations. In our resource-constrained environment, we elected to perform a CT scan with the aim of determining a potentially reversible cause of the patient’s deterioration. Had she survived longer, infarction may have been histologically demonstrable.

Pulmonary embolism of a right atrial myxoma is not usually clinically evident, although cases of fulminant pulmonary embolism or pulmonary hypertension can occur [1,2].

Coronary artery embolism is rare [15,27]. Wenger and Bauer found that only 11 of 17 469 autopsies at Mount Sinai Hospital from 1929 to 1957 revealed coronary artery emboli. In a review of autopsy studies, they found 74 cases of coronary embolism, with none due to cardiac myxoma embolization [27]. The coronaries are thought to be relatively resistant to embolization due to several factors: they arise from the ascending aorta at relatively right angles in contrast to vessels such as the carotids which arise in a more linear trajectory; they fill during diastole, at which time emboli are already in the systemic circulation; their calibers are small; and the aortic valve leaflets have a protective effect during systole [28-31]. Coronary artery emboli from myxomas are usually to the right coronary artery, and this is postulated to be due to the position of the right coronary ostium [15,31,32]. Coronary artery embolization by myxoma fragments can result in atrial fibrillation [23]. This was not observed in our patient.

Forty cases of myocardial infarction due to cardiac myxomas were reviewed by Braun et al [15]. A third of patients who had documented coronary angiography, had extensive myocardial infarction, and raised creatinine kinase, despite normal coronaries on angiography [15]. Of 17 cases reviewed by Al Zahrani et al. 59% had normal coronary angiograms [28]. Several authors have suggested that this phenomenon may be due to recanalization of the myxomatous embolus, as control angiograms demonstrated complete recanalization within a few days [29,33,34]. Tumor lysis and fragmentation of the gelatinous fragments are also thought to play a role [15]. The stroma of myxomas consists of glycosaminoglycans, of which chondroitin-6-sulphate is the major disaccharide unit. Chondroitin-6-sulphate has an inhibitory action on fibrosis [35]. High serum creatinine kinase levels despite normal angiographic findings were indicative of extensive infarction and reperfusion being too late to preserve the myocardium [15]. Our patient’s elevated creatinine kinase levels and subsequent autopsy findings substantiate that at the time of admission, the myocardial infarct was already unsalvageable. A discrepancy between the large territory of a myocardial infarction and distal location of a tumor embolus within a coronary has been ascribed to embolus migration [36]. It is plausible in our patient that the embolus may have lysed, leaving only fragments in distal intramural arteries.

Other less common vessels potentially affected by thromboemboli include the coronary arteries, abdominal aorta, and visceral and peripheral arteries, but multiple vessel embolism is rare [1,3,7,10,37]. To our knowledge, this is the first report of embolic atrial myxoma resulting in a saddle embolus at the bifurcation of the common carotid artery, concurrently with coronary and cerebral artery tumor emboli.

Our patient presented with undiagnosed left atrial myxoma masquerading as respiratory disease. It is acknowledged that the unusual presenting features of atrial myxomas may lead to delayed diagnosis and poor outcome [8]. We found only 1 case report wherein a patient with a left atrial myxoma presented with recurrent wheeze, and another where the symptoms mimicked chronic obstructive pulmonary disease (COPD) [38,39]. Resection of the tumor resulted in complete resolution of respiratory symptoms [39]. The wheeze in patients with atrial myxomas has been attributed to increased production of interleukin-6, which is directly proportional to tumor size [38]. Wheezing may also result from pulmonary edema due to myxoma obstruction of the mitral valve with diastolic filling defect and increased pulmonary venous pressures (cardiac asthma). The presence of hemosiderin-laden macrophages within alveoli supports the existence of previous pulmonary venous congestion. In addition, the episodic nature of wheezing suggests the transient nature of this cardiac asthma. Interestingly, dyspnea has also been documented as a presenting symptom in neoplastic embolization to coronary and cerebral arteries [37].

**Conclusions**

Atrial myxoma can have a non-specific presentation resulting in a missed diagnosis. Atrial myxoma mimicking respiratory disease is a reminder that not all wheeze is due to bronchial asthma or COPD, and that cardiac asthma should always be excluded by a thorough cardiovascular examination. Transthoracic echocardiography offers a rapid, non-invasive means of diagnosis. Embolic phenomena may be the initial and only presenting...
features of an atrial myxoma. For the pathologist, the finding of an atrial neoplasm should prompt a careful search for tumor emboli. In addition, the finding of an unexplained gross myocardial infarction, with macroscopically patent coronary arteries, warrants the consideration of rare coronary embolism. Lastly, academic autopsies remain critical to accurate death certification, answering clinical questions in cases of unexpected death, improving clinical practice, and guiding counseling of bereaved families.

References:

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Ethics Approval

This case report was approved by the Stellenbosch University Health Research Ethics Committee (Project ID: 16945 HREC reference No: C20/06/021).

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Conflicts of interest

None.