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# Severe functional mitral stenosis due to a left atrial myxoma masquerading as asthma

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**SUMMARY**

While cardiac myxomas are the most common primary cardiac tumours, their overall incidence remains rare. Most cases (90%) are sporadic and occur in the third–sixth decades of life with a female predominance and have a specific predilection for the left atrium (75%). While often asymptomatic, clinical presentations depend on the tumour size, architecture and location. Echocardiography remains the mainstay for diagnostic evaluation. Tumour resection is the only definitive treatment. Histopathology using H&E and immunohistochemical stains, such as calretinin and CD34, confirms the diagnosis. We present a case of a patient with reported history of asthma who presented with recurrent acute on chronic shortness of breath refractory to inhaler therapy, multiple outpatient visits and hospitalisations for ‘asthma exacerbations’. After further evaluation, she was diagnosed with a left atrial myxoma attached to the inferior aspect of the intra-atrial septum complicated by severe functional mitral stenosis.

**BACKGROUND**

The diagnosis of atrial myxoma remains a clinical challenge due to non-specific findings at initial presentation; as such, myxoma is only suspected in 5.7% patients, and thus a high index of suspicion is needed.<sup>1 2</sup> In this case, we presented an ‘asthmatic’ patient whose course was complicated by failure of inpatient and outpatient therapy for ‘asthma exacerbations’ without improvement and instead was found to have subtle signs of heart failure, highlighting the pitfalls of diagnostic anchoring.

**CASE PRESENTATION**

A 45-year-old woman with history of obesity, deep vein thrombosis, pulmonary embolism (PE) and reported asthma presented with recurrent acute on chronic shortness of breath and associated fatigue that were refractory to her usual asthma treatment. Further inquiry highlighted history of chronic dry cough, palpitations, orthopnoea, paroxysmal nocturnal dyspnoea and marked dyspnoea on exertion that significantly limited her functional capacity, with progression over the past year. She denied lower extremity swelling, pleuritic chest pain, sick contacts, fevers, night sweats, significant weight loss or specific triggers for her exacerbations. Physical examination was notable for mild sinus tachycardia and ambulatory desaturation. Pulmonary evaluation demonstrated symmetric chest rise, bibasilar fine crackles, without wheezing. Cardiac evaluation revealed no parasternal heave or displaced maximal impulse, a normal S1 and S2,

a third heart sound initially thought to be a ‘fixed split S2’ and later considered as the ‘tumour plop’, and a low-grade diastolic murmur.

**INVESTIGATIONS**

Prior pulmonary function tests (PFTs) demonstrated a restrictive pattern with pre-bronchodilator and post-bronchodilator forced expiratory volume in one second (FEV1) of 63%, FEV1/forced vital capacity of 76% and 80%, respectively, and diffusing capacity for lung carbon monoxide (DLCO) of 69%. There were no prior imaging studies. Complete blood count (CBC) and comprehensive metabolic panel (CMP) were unremarkable except for an elevated creatinine (1.3 mg/dL). N-terminal (NT)-pro hormone BNP (NT-proBNP) was mildly elevated (955 pg/mL).

Electrocardiography showed sinus tachycardia and left atrial enlargement. Given the lack of diagnostic criteria for asthma, CT angiography (CTA) was performed to evaluate for PE, which was negative but demonstrated an intracardiac, left atrial filling deficit and bibasilar mild patchy densities (figure 1). Transthoracic echocardiogram (TTE) revealed a left atrial mass attached to the inferior aspect of the intra-atrial septum complicated by severe functional mitral stenosis and severely elevated pulmonary artery systolic pressure (figure 2, videos 1 and 2). Mild mitral and tricuspid regurgitations were also present. Left ventricular ejection fraction remained preserved (60%–65%) with no evidence of diastolic dysfunction. There was no evidence of patent foramen ovale or septal defect.

**TREATMENT**

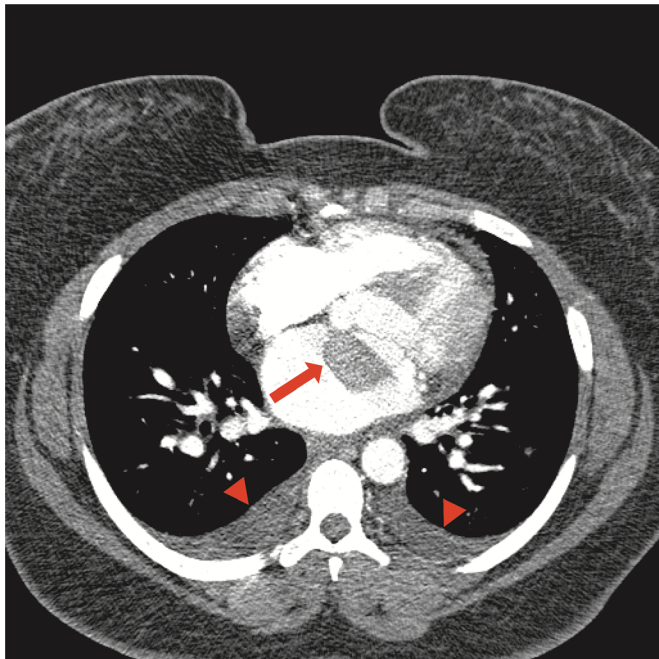
She was referred to a cardiothoracic surgeon. A trans-oesophageal echocardiography (TEE) was performed for surgical planning and to rule out other intracardiac masses. Due to her risk factors, preoperative cardiac catheterisation was performed to rule out coronary artery disease, which was negative. Ventriculography (LV gram) was not performed due to her elevated creatinine.

She subsequently underwent tumour resection via sternotomy with the aid of cardiopulmonary bypass. She was found to have a pedunculated mass adherent to the interatrial septum in close proximity to the anterior mitral valve leaflet and extending into the mitral annulus (figure 3). The mitral valve was tested for competency by directly injecting saline into the left ventricle; there was no regurgitation of fluid back into the left atrium and excellent coaptation of the valve leaflets indicating the valve



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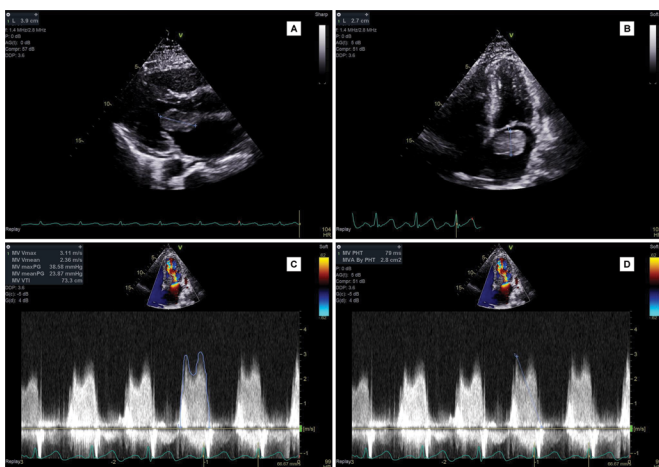


**Figure 1** CT of the chest with contrast. CT angiography without evidence of pulmonary embolism but with intracardiac, left atrial filling deficit (arrow), as well as bilateral mild patchy densities in lower lung fields (arrowheads).

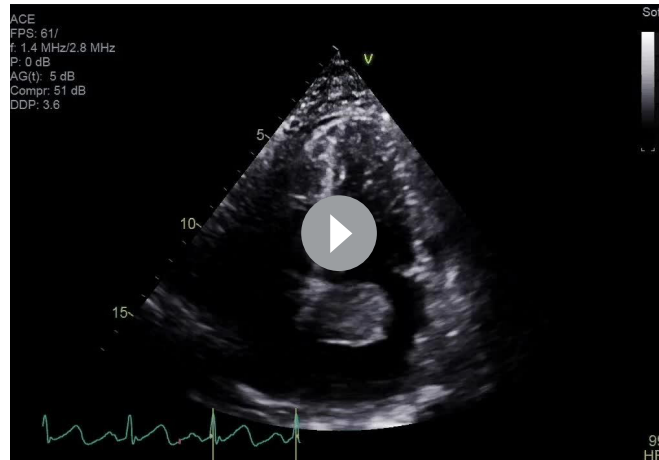
was competent. Postoperative TEE showed normal biventricular function with trace mitral regurgitation and no remaining intracardiac mass. Histopathology using H&E staining showed ‘myxoma cells’ (figure 4A and B). Immunohistochemical staining with calretinin (figure 4C) and CD34 (figure 4D) confirmed the diagnosis.

**OUTCOME AND FOLLOW-UP**

Following surgery, the patient endorsed significant improvement in her breathing with only mild residual shortness of breath



**Figure 2** Echocardiography demonstrates left atrial myxoma and mitral stenosis with outflow obstruction. Transthoracic echocardiogram shows mobile left atrial mass that is ovoid and pedunculated, measuring 2.7×3.9×2.1 cm, attached to the fossa ovalis/atrial septum, suggestive of myxoma (A and B). There is a significant mean gradient across mitral valve in diastole of 23.9 mm Hg with (C) and a mitral valve area of 2.8 cm<sup>2</sup> (D) consistent with severe functional mitral stenosis.



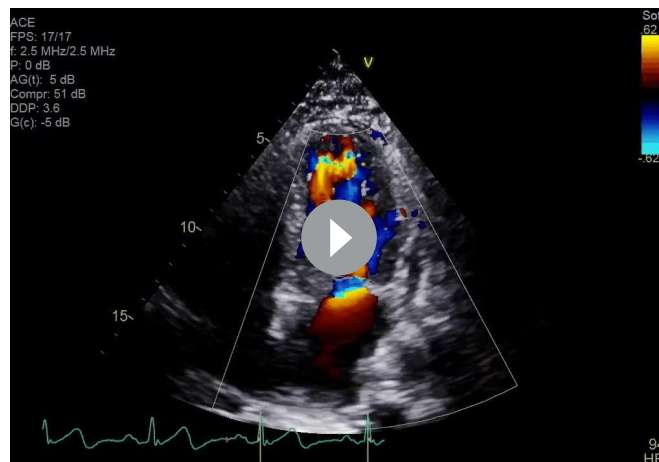
**Video 1** TTE showing a mobile left atrial mass.

while climbing stairs. Six months later, she had complete resolution of all symptomatology with a normal repeat TTE.

**DISCUSSION**

Overall, primary cardiac tumours are rare with myxomas as the most common. Myxomas can be found in left atrium (75%), right atrium (10%–20%), ventricles (2%) and, rarely, within multiple cardiac chambers, which display familial clustering.<sup>1–3</sup> Within the atria, most myxomas are attached to fossa ovalis of the interatrial septum. Myxomas, unlike fibromas and angiosarcomas, are purely endocardial masses that do not infiltrate the underlying tissues.<sup>14</sup>

Most myxomas are sporadic; however, approximately 10% are familial, with two-thirds of familial cases associated with Carney Complex Syndrome, a rare autosomal dominant syndrome characterised by mucocutaneous lesions and endocrine tumours.<sup>5</sup> In sporadic myxomas, women are affected more than men (2–2.7:1), generally in the third–sixth decades of life; the majority of cases are solitary and arise within the left atrium, and the recurrence rate is low (1%–3%) following surgical resection.<sup>3 4</sup> Incomplete excision, intracardiac implantation, malignant transformation and growth from secondary foci are the presumed aetiologies of recurrence.<sup>6</sup> In familial myxomas, women and men are equally affected; median age of detection is



**Video 2** Doppler echocardiography showing haemodynamic consequences of myxoma.

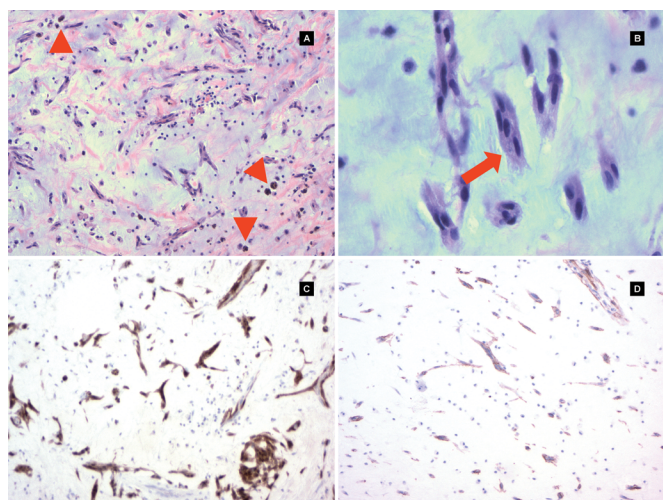




**Figure 3** Gross tumour. Left atrial mass 4.5×4.0×2.2 cm in size, weighing 21.45 g, with a glistening, mottled grey–white to tan–brown, focally haemorrhagic rubbery appearance.

20; cases are more often right sided, though all chambers may be involved; and recurrence rate is significantly elevated.<sup>3</sup>

Our patient carried a diagnosis of intermittent asthma since childhood. Her symptoms, while initially relieved with inhaled steroids and intermittent albuterol, had become refractory to her usual regimen over the past year; she experienced worsening dyspnoea, with multiple outpatient, urgent care and hospital visits, where she was managed for asthma exacerbations. Despite recurrent hospitalisations, her symptoms persisted. Her PFTs,



**Figure 4** Histopathology. H&E staining at 100× (A) and 400× (B) shows myxoid (bluish) background with hyperchromatic multinucleated myxoma cells (arrow), haemosiderin deposition (arrowheads) and chronic inflammatory cells. Calretinin (positive brown staining) helps differentiate myxoma from thrombus (C) and CD34 (positive brown granular staining), while variably expressed in atrial myxomas, when positive staining helps confirm the diagnosis (D). Gamma correction has been applied to (C) and (D).

performed at her last admission, demonstrated no improvement of FEV1 with bronchodilator and a restrictive disease pattern— atypical for an asthma diagnosis. Given the lack of diagnostic criteria for asthma, extensive workup—including CTA to rule out PE and TTE with bubble study to rule out underlying valvular abnormalities or intracardiac shunt—were performed. These revealed a left atrial myxoma complicated by severe functional mitral stenosis leading to her recurrent presentations that mimicked a diagnosis of heart failure.

Dyspnoea is the most common presenting symptom of myxomas.<sup>1</sup> While the overwhelming majority of myxomas are asymptomatic and found incidentally on autopsy, they may cause symptoms by virtue of their intracardiac location and mimic other disease states—collagen vascular disease, infective endocarditis, idiopathic paroxysmal atrial fibrillation, amaurosis fugax and myocarditis.<sup>4,5</sup> While asthma is not a common presentation, there are case reports with patients diagnosed and treated as late-onset asthma prior to myxoma diagnosis, suggesting that atrial myxomas can indeed mimic the symptoms commonly seen in asthma.<sup>7</sup> Indeed, our patient was diagnosed with intermittent asthma in childhood who later developed refractory symptoms to traditional asthma therapy. Given the atypical nature of her presentation and lack of congruence of her PFT with her asthma diagnosis, there was high clinical suspicion for an alternative diagnosis.

The clinical presentation of an atrial myxoma depends on the tumour's size, architecture and location, which can lead to insufficiency or obstruction causing aberration in intracardiac blood flow with resultant valvular regurgitation or stenosis (67%), embolisation (29%), constitutional symptoms such as fevers (19%), weight loss or fatigue (17%), immunologic manifestations, including myalgia, weakness and arthralgia (5%), or sudden death. Although more than half of cases have obstructive symptoms, only 10% have severe functional mitral stenosis.<sup>1,2,5</sup> In our patient, the insidious and progressive nature of her symptoms were felt to be atypical for asthma and more likely due to her tumour's growing size and location.

Laboratory studies are generally non-specific and non-diagnostic. Nevertheless, myxomas have been associated with anaemia; thrombocytopenia; and elevated leucocyte, erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and serum gamma globulins, especially in those with systemic symptoms. In these cases, association with elevated serum interleukin-6 (IL-6) has been demonstrated, with higher levels associated with increased tumour burden. Intriguingly, in some cases, IL-6 has also been used as a marker of recurrence. One study suggested that recurrence occurred in those cases of intrinsically aggressive tumours, as characterised by elevated IL-6 levels, irrespective of tumour size. Mechanical haemolysis due to intracardiac turbulent flow has also been suggested to cause anaemia and thrombocytopenia.<sup>8</sup> Except for elevated creatinine, our patient's CBC and CMP were normal. Unfortunately, neither ESR and CRP, nor IL-6 were ordered. Her mildly elevated NT-proBNP is explained by severe obstruction of the mitral valve caused by tumour extension into the annulus during diastole, which caused a severe functional stenosis and heart failure symptomatology.

While TTE is adequate for diagnosis and is regularly used to assess tumour location, size, shape, attachment, mobility, and valve anatomy and function with sensitivity up to 95%, TEE is considered the gold standard. TEE is nearly 100% sensitive and accurately delineates the attachment sites of the myxoma, as well as the presence of cysts, calcifications and haemorrhage within the myxoma.<sup>9</sup> CT or MRI can be considered when diagnosis is unclear after echocardiographic evaluation but is usually

reserved for cases suspicious of malignancy. On non-contrast CT, myxomas are typically hypodense (approximately +22.5 HU, lower than thrombi or adjacent blood) and may have calcifications.<sup>10–12</sup> In our patient, CTA of the chest, initially performed to rule out PE, incidentally demonstrated a left-atrial filling defect concerning for a mass (figure 1).

Myxoma prolapse through mitral valve in diastole results in partial obstruction of blood flow, causing functional mitral stenosis, or mitral ‘pseudo-stenosis’.<sup>13</sup> Doppler echocardiography can demonstrate valvular dysfunction and associated outflow obstruction by calculating the mean pressure gradient across the valve in apical views. The degree of mitral stenosis is evaluated by mitral gradient ( $\geq 10$  mm Hg), mitral valve area (MVA,  $< 1$  cm<sup>2</sup>) and elevated pulmonary pressures. Our patient’s mitral gradient and MVA, measured by pressure half-time method, were 23.9 mm Hg and 2.8 cm<sup>2</sup>, respectively, which was consistent with severe functional mitral stenosis (figure 2C and D). She also had pulmonary hypertension, bilateral pleural effusions and tricuspid regurgitation as complications of her mitral stenosis.

A large left atrial myxoma may also cause annular dilation with resultant mitral regurgitation. It is important to note that the tumour itself can disturb the regurgitant jet, thus masking the severity of regurgitant flow on a routine echocardiography.<sup>14</sup> In our case, her mitral valve was evaluated by saline injection into the left ventricle and postoperative TEE, which showed a competent valve with trivial mitral regurgitation.

Surgical resection is definitive and curative with excellent early and long-term prognosis; however, recurrence does occur.<sup>3</sup> Biannual follow-up with echocardiography for at least 4 years after resection is recommended, as the risk of recurrence decreases after 4 years.<sup>14</sup>

Histologically, myxomas are comprised of stellate ‘myxoma’ cells, often referred to as ‘lepidic’ cells, which have abundant eosinophilic cytoplasm and oval nuclei with indistinct nucleoli. There is abundant myxoid stroma and often haemorrhage and

mild inflammation. Calretinin staining differentiates myxomas from mural thrombi or papillary fibroelastomas (figure 4C). Myxomas are variably immunoreactive to CD34, S-100, CD31, NSE, actin, desmin, alpha-1 antitrypsin and factor VII, demonstrating its heterogeneous phenotype (figure 4D). Sporadic and familial cases have similar histological appearances.<sup>4 15 16</sup>

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**Contributors** UZ drafted the report, conducted the literature review and formatted the figures and videos. RQ wrote the surgical report and provided related images. EA wrote the histopathology report and provided related images. CH revised and supervised the report. All authors were involved in the patient’s care and approved the final report.

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## Patient’s perspective

This past year was very frustrating, because my symptoms worsened despite using multiple asthma medications. My daily life was severely disrupted. If I had asthma, why were my treatments not working? When I found out that I had tumour in my heart, I was overwhelmed. I cried. I felt relieved to finally get the definitive answer to my symptoms.

## Learning points

- ▶ Consider an alternate diagnosis when patients’ carried diagnosis does not match their current presentation.
- ▶ Rarely, myxoma can present as a severe functional mitral stenosis mimicking signs and symptoms of heart failure.
- ▶ Echocardiography and histopathology confirm the diagnosis.
- ▶ Surgical resection is curative.

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