Ticking Time Bomb: Embolic Risks and Complex Management of an Exceptionally Large Papillary Fibroelastoma

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INTRODUCTION

Papillary fibroelastomas (PFEs) are now believed to be the most common benign primary cardiac tumors, with increasing incidence due to improved detection by echocardiography.[1] They occur predominantly within the aortic or mitral valves but may occasionally originate from both left- and right-sided cardiac valves and chambers.[1-4] Due to the relatively small mean size (6.5-10.4 mm), PFEs are sometimes only identifiable by transesophageal echocardiogram (TEE), often ordered after a neurologic event or prior to cardiac surgery.[1] Papillary fibroelastomas carry a high risk of embolization and are associated with significantly increased incidence of stroke.[1,2,5] This was shown to be particularly true among patients in whom diagnosed PFEs were not surgically resected.[1,2,4] Once PFE is suspected, surgery provides definitive management, with the goal of preventing embolic phenomena. Diagnosis is confirmed by tissue pathology. Histologically, PFEs are avascular and composed of fibroelastic tissue lined by a layer of endothelium.[2]

We present a fascinating case of a 69-year-old woman in whom a large, hypermobile cardiac mass within the left atrium (LA) caused significant mitral stenosis (MS) and mitral regurgitation (MR). Mass size, localization, and behavior were suspicious for atrial myxoma. The diagnosis and management of the large mass proved challenging and complex. Despite a plan for expedited surgical excision, the patient experienced embolic strokes shortly after hospital admission. After stabilization surgery was completed, pathology identified the mass as an extremely large PFE. In light of such an unusual finding and the underrecognized risks of embolic phenomena with PFE, we review existing evidence to support decisive surgical management and highlight areas in which further study is needed.

VIDEO HIGHLIGHTS

Video 1: Two-dimensional TTE, parasternal long-axis view, demonstrates mildly reduced left ventricular systolic function and a large, mobile, heterogeneous, hyperechoic 5.8 × 2.8 cm mass possibly attached to the interatrial septum protruding into the mitral inflow during diastole.

Video 2: Two-dimensional TTE, apical 3-chamber view after the administration of an UEA, demonstrates mildly reduced left ventricular systolic function and a large mass that is partially enhanced.

Video 3: Two-dimensional TTE, apical 4-chamber view with color-flow Doppler (and lowered Nyquist baseline), demonstrates turbulent diastolic flow consistent with hemodynamically significant MS and mild MR.

Video 4: Intraoperative two-dimensional TEE, midesophageal 4-chamber (0°) view, rightward rotated, demonstrates a large, mobile mass that is likely originating from the interatrial septum.

Video 5: Intraoperative two-dimensional TEE, midesophageal mitral commissural (55°) view *(left)* and long-axis (145°) view *(right)*, demonstrates a large hypermobile, heterogeneous mass protruding through the mitral valve during diastole.

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CASE PRESENTATION

A 69-year-old woman with a medical history of hypertension presented to the emergency department with fatigue, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and chills progressing over the last month. On examination, blood pressure was 160/84 mm Hg, heart rate 77 beats/minute, respiratory rate 22 breaths/minute, oxygen saturation 99%, and temperature 36.9°C. The patient demonstrated mildly labored breathing, and breath sounds were mildly decreased in the bilateral bases with expiratory rales. Cardiac auscultation was notable for late systolic 2/6 murmur loudest at the left lower sternal border with mid-diastolic opening snap. The abdomen was nontender, and there was no evidence of ascites. Lower extremities showed bilateral palpable dorsalis pedis pulses without peripheral edema. Neurological exam was within normal limits.

Chest x-ray showed mild prominence of the pulmonary interstitium suggestive of mild pulmonary edema. Comprehensive metabolic profile was within normal limits. Complete blood count showed

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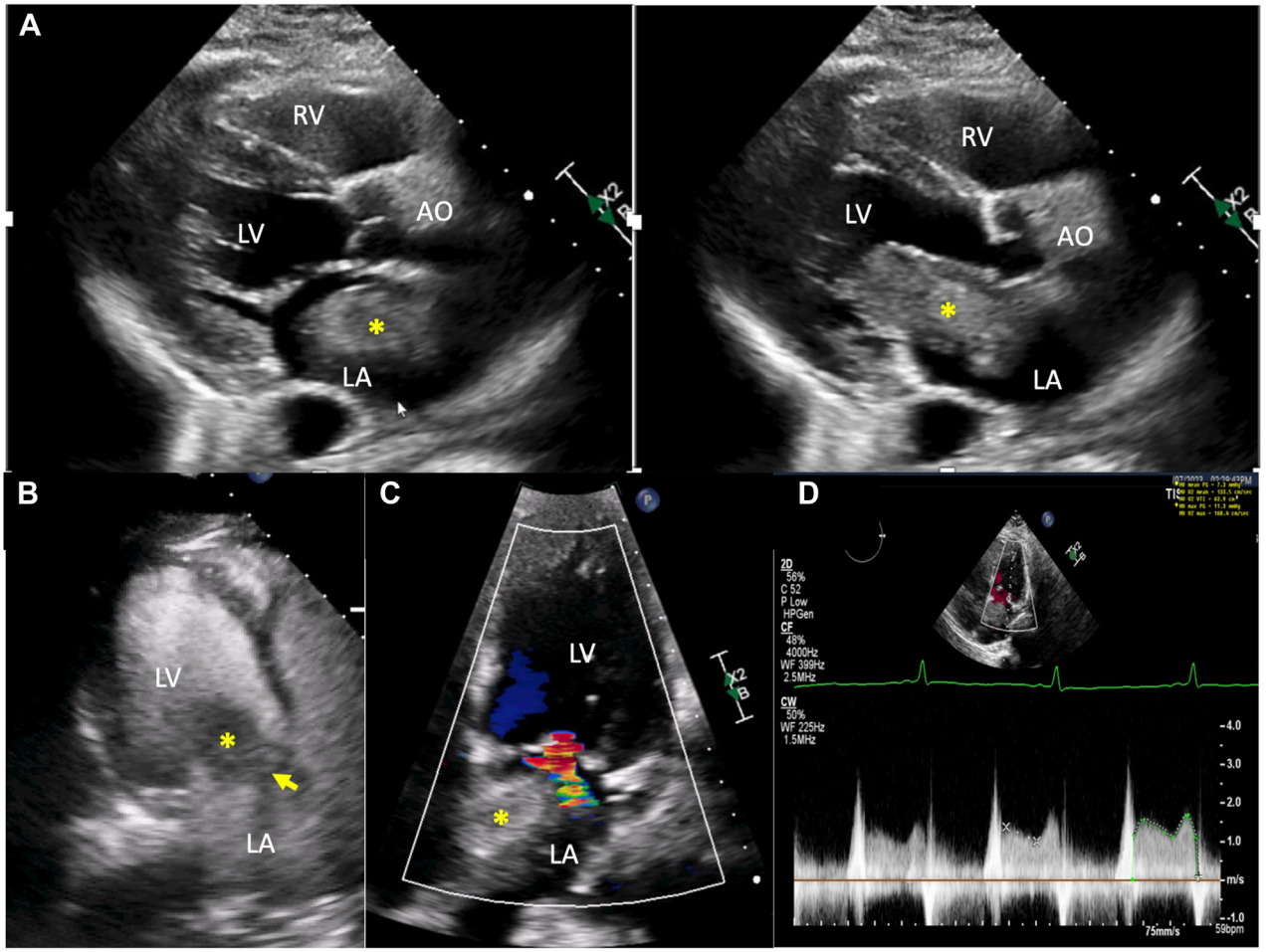

Figure 1 **(A)** Two-dimensional TTE, parasternal long-axis view at end systole *(left)* and mid diastole *(right)* demonstrates a large, mobile, heterogeneous, hyperechoic 5.8 × 2.8 cm mass (*) possibly attached to the interatrial septum protruding into the mitral inflow during diastole *(right)*. **(B)** Apical 3-chamber view (mid diastole) after the administration of an UEA demonstrates that the mass (*) is partially enhanced *(arrow)*. **(C)** Apical 4-chamber systolic view with color-flow Doppler (low Nyquist limit) demonstrates the mass (*) and mild MR. **(D)** Apical 4-chamber view with color-flow Doppler-guided continuous-wave spectral Doppler display demonstrates the hemodynamic significance of this large mass with a mean pressure gradient >7.0 mm Hg and calculated mitral valve area <1.0 cm^2 (velocity time integral method) suggestive of moderate-severe mitral stenosis. *Ao*, Aortic root; *LA,* left atrium; *LV*, left ventricle; *RV*, right ventricle.

leukocytosis with white blood cell count of 12.4 (64% neutrophils, 28% leukocytes, 7% monocytes, and 1% eosinophils) and normocytic anemia (hemoglobin, 10.0 g/dL; mean corpuscular volume, 84 fL). Repeat serial troponin-I levels were both <0.012 ng/mL, but pro-BNP was elevated at 4,750 pg/mL. Electrocardiography showed sinus rhythm with symmetric T-wave inversions in inferolateral leads. Transthoracic echocardiogram (TTE) revealed mildly reduced global left ventricular systolic function with a Simpson's biplane ejection fraction of 50.1% with an echodense 5.8 × 2.8 cm mass protruding from the LA into the mitral inflow causing moderate-severe MS (mean pressure gradient, 7.3 mm Hg; mitral valve area, 0.79 cm^2 by velocity-time integral) and mild MR (Figure 1, Videos 1-3). Injection of ultrasound-enhancing agent (UEA) showed partial enhancement.

The right ventricle was dilated (basal diameter 4.2 cm) with preserved systolic function (tricuspid valve S′ velocity, 12.3 cm/sec; tricuspid annular plane systolic excursion, 2.2 cm) and elevated right ventricular systolic pressure 57 mm Hg (tricuspid Vmax, 3.8 cm/sec).

Intravenous (IV) furosemide was started to address pulmonary edema and orthopnea, with concurrent beta blocker initiation for hemodynamically significant MS. An IV heparin continuous infusion was started for embolic stroke prevention, given the high risk of thrombosis. Cardiothoracic surgery was consulted to evaluate for urgent surgical excision. A computed tomography (CT) scan of the chest, abdomen, and pelvis was completed to evaluate for possible extracardiac mass or malignancy. Findings were notable for several small pulmonary nodules and enlarged pulmonary artery. No significant findings were reported within the abdomen or pelvis. A preoperative coronary angiogram was performed and revealed mild nonobstructive coronary artery disease. Right heart catheterization showed moderate pulmonary hypertension believed to be predominantly postcapillary with a large V wave in the pulmonary capillary wedge pressure tracing. Pressure tracings demonstrated the following findings: right atrium, 7 mm Hg; right ventricle, 48/8 mm Hg; pulmonary artery, 57/32 (mean 43) mm Hg; and pulmonary capillary wedge/V wave, 35/31 mm Hg. The cardiac output (4.1 L/min) and index (2.3 L/min/m^2) were normal, and the pulmonary vascular resistance was increased (4.3 Woods units). After multidisciplinary meeting, surgical excision was scheduled 2 days later.

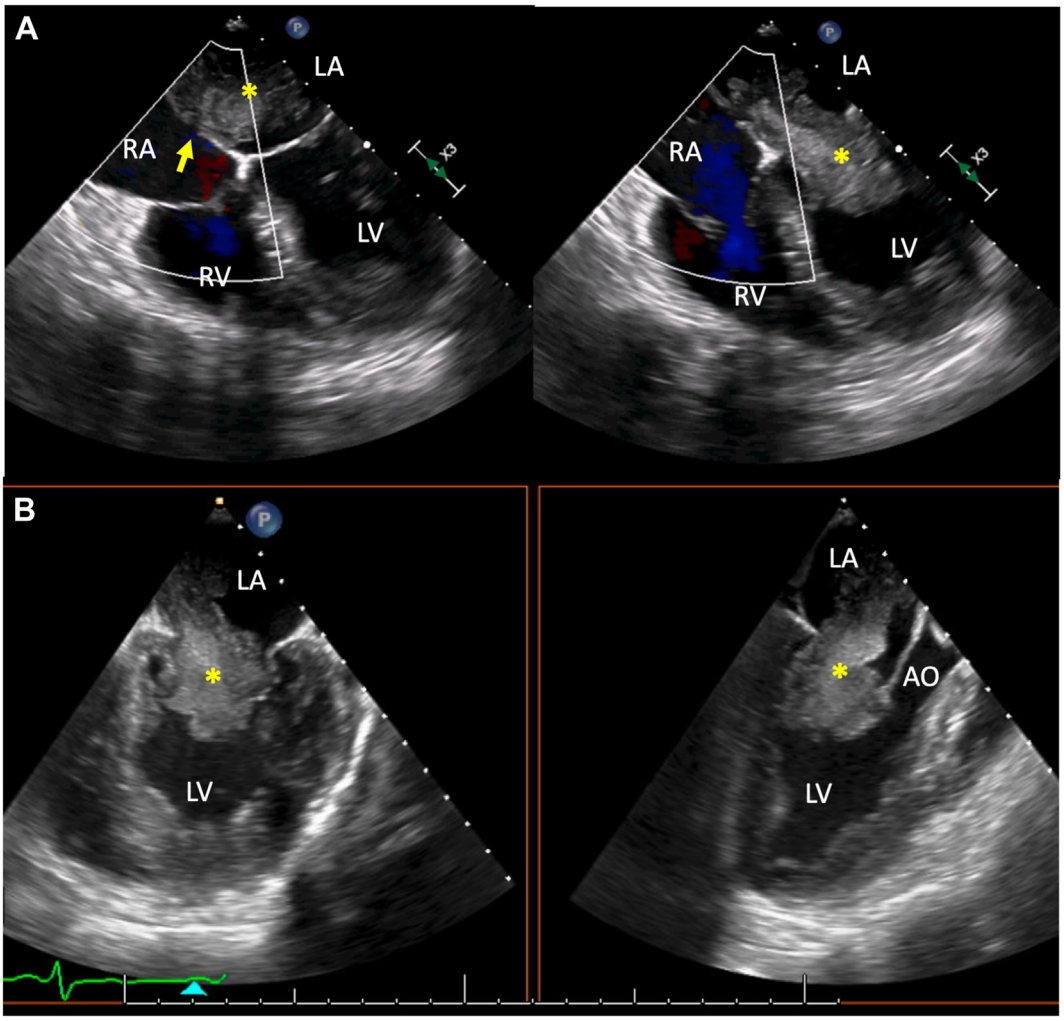

Figure 2 **(A)** Intraoperative two-dimensional TEE, midesophageal 4-chamber (0°) view, rightward rotated in systole *(left)* and diastole *(right)* with color-flow Doppler, demonstrates a large, mobile mass (*) that is likely originating from the interatrial septum *(arrow)* and protruding across the mitral inflow in diastole. **(B)** Mitral commissural (55°) view *(left)* and long-axis (145°) view *(right)* demonstrates a large hypermobile, heterogeneous mass protruding through the mitral valve during diastole. *AO*: Aortic valve; *LV*, left ventricle; *RV*, right ventricle.

One day prior to scheduled surgery the patient developed an acute left-sided facial droop and left arm weakness. Stroke alert was called, and anticoagulation was temporarily held. Brain CT did not demonstrate any clear evidence of stroke or intracranial hemorrhage. A CT angiography of the head and neck did not show any large vessel occlusion or dissection. A magnetic resonance imaging scan of the brain revealed numerous acute multifocal infarcts in the bilateral parietal lobes, right thalamus, and right occipital lobe. There was no evidence of hemorrhagic conversion, and IV heparin was restarted. After 2 additional days of observation, surgical excision was completed. Intraoperative TEE (Figure 2, Videos 4 and 5) visualized a large echodense mass originating from the anterior interatrial septum. After incision at the foramen ovale, the mass was identified and circumferentially excised. Only trivial MR remained by visual assessment. There was no significant postoperative atrial septal defect.

Pathology of the 6.0 × 4.3 × 3.5 cm light brown cardiac mass with myxoid and hemorrhagic aspects identified arborizing fronds of paucicellular, avascular, fibroelastic tissue and a diagnostic single layer lining of endocardial cells (Figure 3). The large cardiac mass was a PFE, contrary to preoperative expectations.

Our patient recovered well postoperatively. Eight days after surgery, the patient was discharged home. Two weeks after discharge, the patient was seen in outpatient cardiothoracic surgery clinic and noted to have well-healed surgical incisions. Repeat echocardiogram showed trace MR, no MS and no interatrial shunting. Follow-up in the cardiology clinic was recommended to monitor for PFE recurrence with plan to repeat surveillance TEE in 5 years.

DISCUSSION

Large size, localization to the LA, partial enhancement with UEA, and obstructive mass effect of the mitral valve together made myxoma the most suspected diagnosis of this primary cardiac tumor. However, this case presents a uniquely large PFE and highlights the risk of embolization along with the importance of early surgical evaluation and postoperative surveillance. The management of suspected PFE remains complex and requires multidisciplinary evaluation.

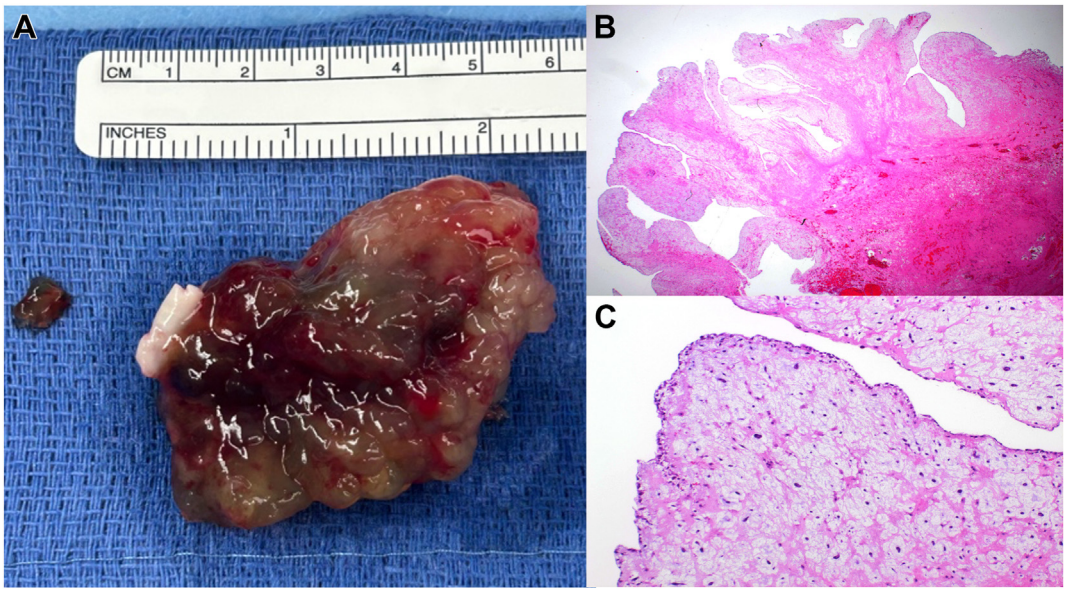

Figure 3 **(A)** Gross pathologic specimen measuring 6.0 × 4.3 × 3.5 cm was heterogenous with light and dark brown color, an irregular surface border with myxoid aspect, and focal hemorrhage. **(B)** Low-power image (12.5× magnification) demonstrates multiple arborizing fronds of paucicellular, avascular, fibroelastic tissue. **(C)** High-power image (100× magnification) demonstrates fronds lined by a single layer of endocardial cells, which are considered diagnostic features of PFE.

Table 1 Diagnostic features and management of cardiac myxoma versus PFE

Parameter	Myxoma	PFE
Epidemiology	Mean age: 50 years Gender predominance: 70% female	Mean age: 63 years Gender predominance: 63% female
Location	Left atrium: 75-85% Right atrium: 9-20% Left ventricle: 1-3% Right ventricle: 1-3% Valvular: <1%	Aortic valve: 59-63% Left atrium or left ventricle: 10-16% Mitral valve: 9-13% Right atrium or right ventricle: 5-7% Tricuspid valve: 4-6% Pulmonic valve: 1-2%
Size	1-15 cm	<1– 4 cm
Characterization	Large polypoidal or papillary mass, heterogeneous, often mobile; pedunculated stalk attachment often to interatrial septum. Presenting symptoms: mechanical effects on AV valves, embolization, or constitutional symptoms.	Smaller size, shimmering borders due to vibration of finger-like projections at blood-tissue interface; predominantly downstream of valve, often with thin mobile stalk. Presenting symptom: most frequently embolization event.
Contrast Perfusion	Often partially enhancing	Generally avascular, without enhancement
Pathology	Stellate, ovoid, or spindle-shaped cells in myxoid stroma	Avascular fibroelastic tissue with endothelial layering
Management	Complete resection recommended to prevent embolic complications	Resection recommended in large left-sided masses (>1 cm) to prevent embolic complications; consider resection of all left-sided masses
Estimated recurrence rate	13.0% in first 10 years	15.8% in first 10 years
Postresection surveillance	Annual TTE for a minimum of 4 years	Consider TEE every 5 years

Many features of this cardiac mass supported the diagnosis of cardiac myxoma over PFE. Indeed, myxomas are the second most common benign cardiac tumors in adults with predilection for the LA, often arising from the interatrial septum with stalk. Myxomas have also been previously reported to reach very large sizes, with maximal dimensions ranging between 1 and 15 cm.[5] Furthermore, a majority of patients presenting with myxomas demonstrate obstructive symptoms or embolic events. Nonetheless, pathology revealed the diagnosis of PFE. A number of important differences in the diagnosis, echocardiographic features, and management of PFE versus myxoma

are highlighted (Table 1). To gain better perspective of the anomalous size of this reported PFE, the majority of PFEs are <1 cm, with the largest cohorts reporting sizes of 8 to 9 mm ± 4 to 5 mm.[3,4] The largest single dimension ever previously reported for a PFE was 70 mm, in fact referring to the thin stalk of a 15 × 15 mm round mobile tumor within the LA originating from the left atrial appendage.[6] However, several other very large pathology-confirmed PFEs have been reported in recent years, the largest measuring 34 to 40 mm in diameter.[7,8] Both originated from the right atrium, which has previously been reported to be the site of the largest PFEs.[1] It is important to note that origin from the interatrial septum or left ventricular endocardium does not rule out PFE. Indeed, Gowda *et al.*[2] reported a small number of resected PFEs attached to the interatrial septum (1.3%) or left ventricle (9%), while Tamin *et al.*[1] grouped together masses within the LA or left ventricle (16%). Conversely, myxomas may rarely involve cardiac valves (more often mitral or tricuspid valves and less frequently the aortic or pulmonic valves).[9,10] The remarkable size of this PFE suggests that the mass had been growing for many years, as PFEs grow at a rate of 0.5 ± 0.9 mm/year.[11] The development of pulmonary hypertension with pulmonary artery enlargement is also suggestive of elevated pulmonary capillary wedge pressures for a prolonged period. The astonishing size of the PFE carried a very important embolic risk.

In addition to the consideration of size and localization, the use of UEAs with TTE serves as an important tool in assessing intracardiac masses. Partial enhancement with UEA is often seen in myxoma. Conversely, PFEs are typically avascular and do not show contrast uptake.[12] However, PFEs with partial contrast uptake have been previously reported.[13] The authors of that study attributed this phenomenon to the spreading of microbubbles between PFE fronds or left ventricular bleeding effect from mass motility. The American Society of Echocardiography acknowledges potential shortcomings of contrast enhancement and recommends perfusion imaging of microbubble replenishment following high mechanical index impulses, ideally in near-field view.[12] Interestingly, in another case of PFE in the more typical aortic position, transillumination echocardiography has also been suggested as an adjunct tool to better define the mobility of elastic fibrils and irregular borders of mass margins.[14] With ongoing advancements in echocardiography, early identification of PFE may help to reduce morbidity and mortality.

Additionally, advanced cardiac imaging modalities play an important role in the workup of cardiac masses. Cardiovascular magnetic resonance imaging can prove useful in determining localization, size, infiltration into surrounding tissue, and signal characteristics that may help to differentiate histopathology.[15] Alternatively, cardiac CT is now increasingly used to assess cardiac masses and may be helpful in surgical planning to delineate lesion margins and relationship to tissue planes.[15] Concurrently, evaluation of the coronary arteries to exclude obstructive disease offers unique advantages. For example, in this case coronary cardiac CT may have obviated the need for invasive coronary angiography.

Overall, this case serves as an important reminder of the potentially urgent risk of embolization of cardiac masses. A number of studies support that embolic risk with PFE is best mitigated by surgical excision. Follow-up of a cohort of 511 patients with PFE within the Mayo Clinic demonstrated that surgical excision was associated with significant survival benefit and a nearly 2-fold risk reduction for neurological events at 5-year follow-up.[1] To date, the Mayo Clinic has studied the largest postoperative cohort of 294 patients with PFE having undergone resection. Surgical outcomes were very favorable, with low reported risk of valvular damage or perioperative mortality (1.4%). Risk of operative morbidity and mortality was significantly higher among patients undergoing PFE removal as a secondary surgical indication.[16] The large majority of patients underwent valve-sparing shave excisions. Traditionally, only large left-sided PFEs >1 cm were recommended for excision.[15] However, given the increasing evidence of heightened embolic risk among patients with PFE, regardless of size, early surgical evaluation at experienced comprehensive centers is essential. Many institutions recommend that all patients with left-sided PFE deemed to be surgical candidates be evaluated for surgical excision. The evaluation is recommended independently of mass size or mobility as the potential clinical benefit of reducing cerebrovascular events may outweigh operative risks.

Last, it is worth highlighting that PFEs may recur at higher rates than previously anticipated. Indeed, PFE recurrence rates upon 10-year follow-up assessment were considerable at 15.8%.[16] This is significantly higher than previously estimated, and all recurrences occurred within the aortic position. The significance of the aortic position as a risk factor for recurrence, along with other patient characteristics, will require further study. It has been suggested that recurrence rates may even still be underestimated, due to lack of follow-up or serial surveillance imaging.[16] There are no current clinical guidelines for surveillance imaging after PFE excision. Sorour *et al.*[17] and authors from the Mayo Clinic have recommended that surveillance TEE be completed upon 5-year follow-up after resection. Interestingly, more frequent monitoring with annual TTE (for at least the first 4 years) would have been recommended if this mass had been an atrial myxoma (Table 1).[15] In the future, it is possible that expert opinion may similarly recommend more frequent TTE or TEE monitoring after PFE resection. Overall, based on the reviewed evidence, our team recommended repeat TEE surveillance in 5 years, or sooner, should clinical symptoms warrant.

CONCLUSION

A PFE is the most common benign cardiac tumor in adults and, despite its traditionally small size, carries greatly increased risk of embolic stroke. We present a rare case of an exceptionally large PFE confirmed by pathology, which was heavily favored to represent myxoma. Suspicion of PFE, particularly when left-sided, should prompt multidisciplinary evaluation for surgical excision to reduce the morbidity and mortality associated with embolic events. Our patient unfortunately suffered from multiple embolic strokes just prior to scheduled surgical excision, thus underscoring the importance of early surgical evaluation.

ETHICS STATEMENT

The authors declare that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

CONSENT STATEMENT

Complete written informed consent was obtained from the patient (or appropriate parent, guardian, or power of attorney) for the publication of this study and accompanying images.

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DISCLOSURE STATEMENT

The authors report no conflict of interest.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2024.11.003.

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