



Case report

Chronic migraine with aura as a neurologic manifestation of an atrial myxoma - A case report

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ABSTRACT

Introduction and importance: Atrial myxomas account for more than half of all cardiac tumors. While the symptoms of these are many, the most prominent among them being migraines, heart failure, dyspnea, and chest pain thereby making a diagnosis all the more difficult.

Case presentation: A 53-year-old woman presented with a recent onset of headaches with aura. The latter was triggered by exercise and physical exertion. Taking Ibuprofen 800 mg three times daily provided relief to the patient. Headaches were associated with photophobia and nausea.

Clinical discussion: The patient had the typical triad of symptoms, namely (i) obstructive (light headedness, near syncope, dyspnea, chest pain), (ii) embolic (transient ischemic attacks – TIA, peripheral arterial claudication), and (iii) constitutional (fever, malaise, weight loss). Cerebral infarction is the most frequent complication. The patient had multiple embolic acute and sub-acute infarcts. The aura and headaches were resolved following resection of the myxoma.

Conclusion: Atrial myxomas must enter the differential diagnosis in the case of a patient presenting with migraines associated with aura. In particular, those whose headaches increase with physical exertion require further investigation.

1. Introduction

While primary cardiac tumors are exceedingly rare, atrial myxomas are the most prevalent among them, representing approximately 50% of all cardiac tumors [1–4]. They arise from multipotent stem cells that can differentiate into both neural and epithelial cells [5]. Left atrial myxomas are the most common, outnumbering those on the right by a ratio of about 3:1. That said, they can exist in both atria, each with their own unique pathophysiology. Symptoms of left atrial myxomas include, but are not limited to, mitral valve obstruction, regurgitation, heart failure,

hypertension, dyspnea, chest pain, pedal pain and edema, fever, and emboli [6]. While benign in nature, they pose serious health threats, as their typical morphology, along with the turbulent atrial blood flow, can cause fragmentation of tumor villi, giving rise to cerebral and systemic emboli. Thirty to fifty percent of patients with left atrial myxomas exhibit such a presentation [6]. This gamut of symptoms makes early diagnosis of an atrial myxoma challenging. This case will highlight the unique clinical presentation of an individual presenting to the neurology clinic, her workup and treatment, and current health status.

There are a number of theories that explain the origin of myxomas.

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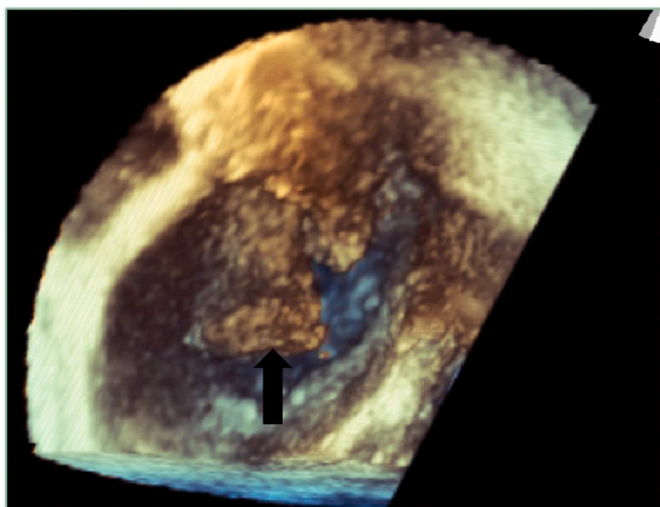


Fig. 1. Trans esophageal echocardiogram (TEE) 3-D view of the myxoma (black arrow) adherent to the atrial wall.

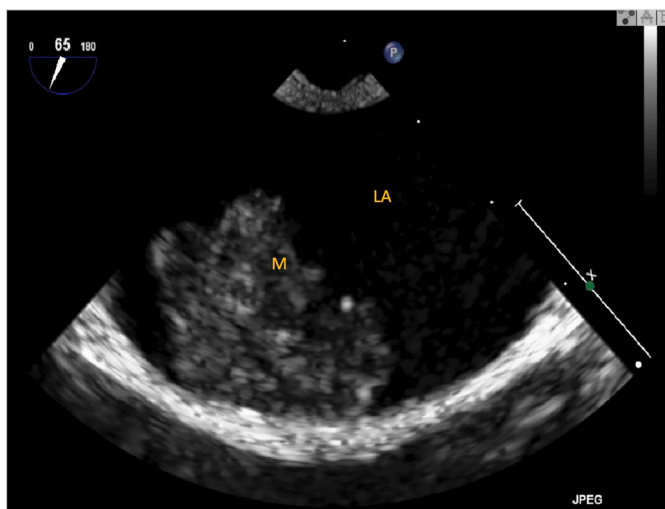


Fig. 2. Left atrial myxoma. Myxoma (M), left atrium (LA).

Currently, they are thought to emerge from the “entrapped embryonic foregut”, deriving from multipotent mesenchymal cells with the ability to differentiate in both neural and epithelial cell lines. As tumors, myxomas present histologically as scattered cells within a mucopolysaccharide stroma, as seen in this case presentation [7]. Angiogenesis is common among the early developmental stages of a myxoma, as these cell lines produce vascular endothelial growth factor (VEGF) [8,9]. Macroscopically, common myxomal surfaces may appear to be smooth, villous, or friable. They are pedunculated and gelatinous in consistency [7]. These tumors range in diameter from 1 to 15 cm and weigh between 15 and 180 g. Large tumors tend to have a smooth surface and are commonly associated with cardiovascular symptoms. Myxomas associated with emboli present as friable or villous, which constitute about 35% of all cases.

Approximately 17% of patients with an atrial myxoma present with neurological manifestations [10]. However, clinical manifestations can vary considerably. Typically, patients present with arrhythmias, intracardiac flow obstruction, embolic phenomena and constitutional symptoms. Among the neurologic complications associated with an atrial myxoma, ischemic cerebral infarction is the most commonly encountered neurologic complication [11]. Cerebral infarction might

recur for patients with an untreated myxoma. Delayed neurologic presentation of a myxoma includes myxomatous metastasis and oncotic aneurysms [12]. Tumors with an irregular shape and surface are more prone to embolism. The fracturing of small fragments is considered to be responsible for embolic events leading to neurologic manifestations [13].

Studies of atrial myxomas and secondary brain infarction presenting as migraine aura are extremely limited in the current literature. Migraine with aura is a relatively uncommon presentation of an atrial myxoma [14]. In this report, we present a case of a left atrial myxoma triggering migraine with aura and provide hypotheses regarding this phenomenon.

2. Case presentation

This work is been reported in line with the Surgical CAse REport (SCARE 2020) guidelines [15]. Written informed consent was obtained from the patient's next of kin for the publication of this case report and accompanying images. A 53-year-old female presented to the Neurology Clinic, at the Center for Brain and Neurological Care in Fulton, Maryland, with intermittent headaches lasting from a few hours to a day or two in duration. Initially, the headaches were of a low frequency (about two per month), described as throbbing, associated with an aura triggered by exercise or physical exertion. She elaborated this psychedellic pattern aura as “zig zag squiggly lines” highlighted with bright colors of “pink and blue.” At the onset of the aura, the patient would lie down in a dark room and take ibuprofen 800 mg for relief of symptoms. The aura typically lasted about 20 min. Headaches were associated with photophobia and nausea. With the passage of time, symptoms progressed to the point that the headaches were exacerbated with even the slightest exertion. Lasting for at least 4 h, her migraines fulfilled International Headache Society's (IHS) criteria for the diagnosis of migraine. However, the event that precipitated the visit to the clinic was an increase in the frequency of her aura, coming on about 4–5 times per week, now consistently associated with physical exertion. Further precipitating the consult was the onset of new symptoms associated with a transient ischemic attack (TIA), including severe tingling of the right side of the face, arm, and leg, again precipitated by physical exertion. The duration of these symptoms was more prolonged, often lasting up to 8 h and causing difficulty with ambulation and upper extremity motor function. Additionally, she reported an overall feeling of malaise, complaining of diffuse arthralgia, jaw and hip pain, fatigue, unintentional weight loss (seven pounds in four weeks), and a low-grade fever of 100.1 °F.

Workup through her primary care physician included magnetic resonance imaging (MRI) of the brain without contrast and a referral for a full ophthalmology evaluation through a neuro- ophthalmologist which yielded negative results. Patient was then referred to a neurologist for the treatment of suspected migraine with aura. Her first MRI of the brain without contrast revealed mild scattered hyperintense foci in the bilateral fronto-parietal subcortical white matter. Her past medical history was negative for migraines until a year ago. She was postmenopausal and not on hormone replacement therapy. She was a non-smoker. Significant review of systems included a “weird numb sensation of the tongue,” positive for atypical chest pains, palpitations, lightheadedness upon standing and exertion. An electrocardiogram (EKG) ordered by her PCP revealed normal sinus rhythm with no electrophysiological evidence of atrial fibrillation or other arrhythmias. She also noticed severe calf pain that came on with prolonged, brisk ambulation, which subsided with rest. She frequently felt palpitations after long hikes described as if her heart was “flip-flopping,” associated with pulsatile tinnitus. These episodes lasted a few minutes at a time. She complained of leg pain, particularly in the calf suggestive of intermittent claudication as well as a history of Raynaud's phenomenon with cold painful fingertips on exposure to cold temperatures, two years prior to her presentation to the clinic. Her family history was significant for myocardial infarction (both parents), and migraines (sister).

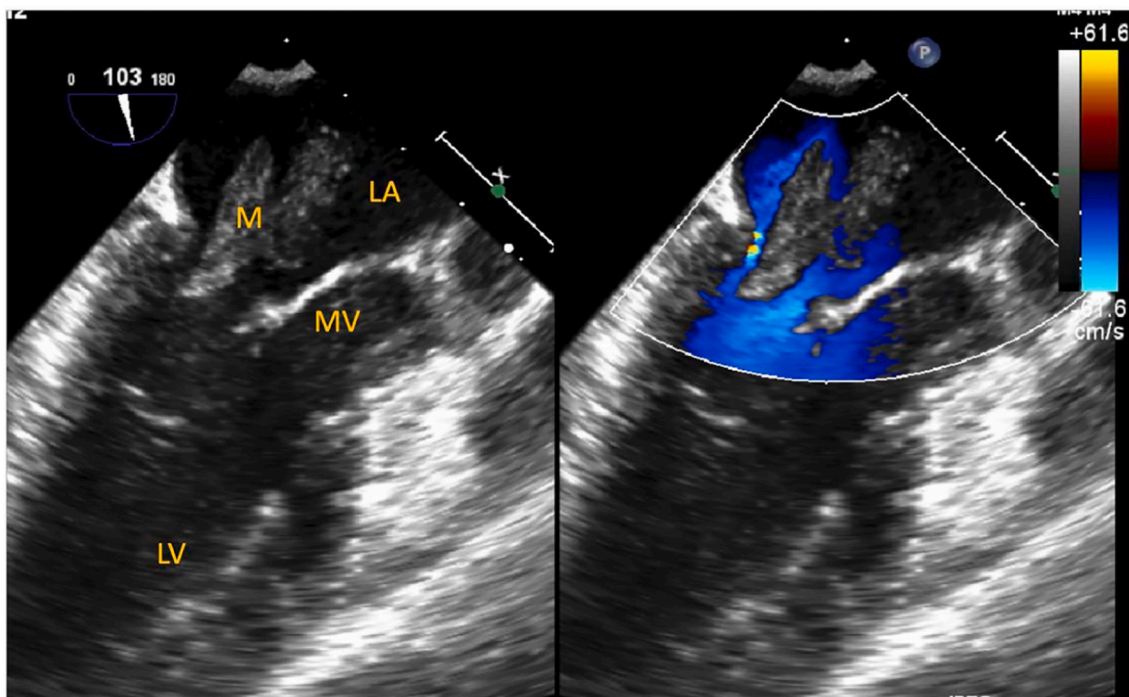


Fig. 3. Myxoma (M) in the left atrium (LA), mitral valve (MV) and the left ventricle (LV) are also seen.

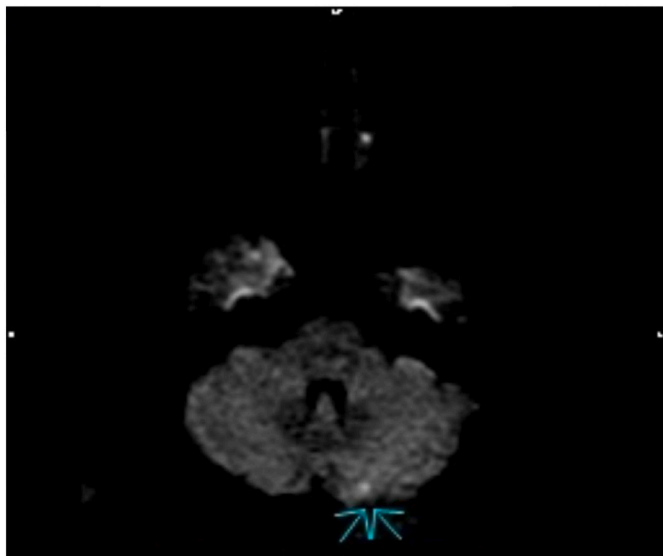


Fig. 4. Axial DWI. Left cerebellar embolic ischemic infarction (arrows).

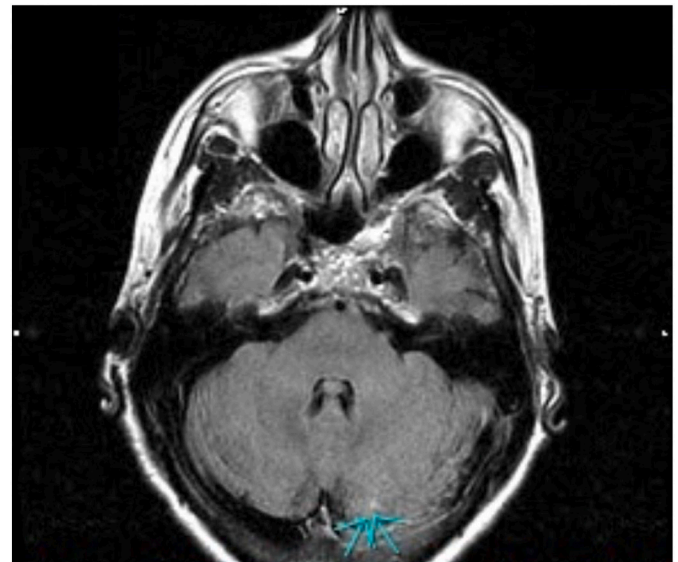


Fig. 5. Axial FLAIR. Left cerebellar acute embolic ischemic infarction.

No abnormal vital signs were observed at presentation (weight 128 lbs.; height 65", BMI 21, blood pressure 101/79 mmHg, pulse 65). Physical examination revealed equally reactive pupils to both light and accommodation. There was no jugular venous distension. Lungs were clear to auscultation and heart sounds were regular in rhythm with no notable murmurs. Abdomen was soft and nontender. Peripheral pulses were intact. Skin examination revealed cold extremities with no skin rashes. Her serology panel yielded the following: CRP 44.9 (elevated); ANA negative; rheumatoid factor: 8.6; WBC 4.0; Hb 12 g/dl; Hct 28%; platelets 272; ESR 25; alkaline phosphatase 130; albumin 4.6; globulin total: 2.9; bilirubin 0.10; BUN 13; creatinine 0.76.

Most concerning was her presentation with symptoms of right hemisensory loss with weakness of the lower extremities and

progressively worsening migraine aura which prompted an urgent TIA work up. Carotid artery Doppler scan was negative for stenosis. MRI of the brain with and without contrast was positive for multiple bilateral foci of acute ischemia, the largest of which was located in the right frontal lobe. Many additional punctate and sub-centimeter foci of acute to sub-acute ischemia were identified in the bilateral frontal and parietal lobes, as well as a small focus of acute ischemia in the left cerebellum. The multiplicity and distribution of foci suggested embolic etiology. Magnetic resonance angiography (MRA) of the intracranial vasculature did not reveal any atherosclerosis or aneurysms (Figs. 1-6).

A two-dimensional echocardiogram showed the presence of a large myxoma in the left atrium, freely moving with the blood flow in and out of the mitral apparatus abutting to the left ventricle (Figs. 7-9). At this

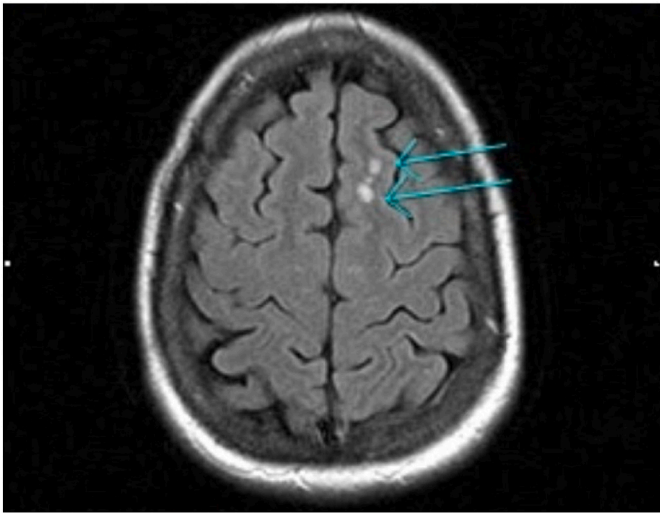


Fig. 6. Axial FLAIR. Left frontal lobe multiple acute embolic ischemic infarctions.

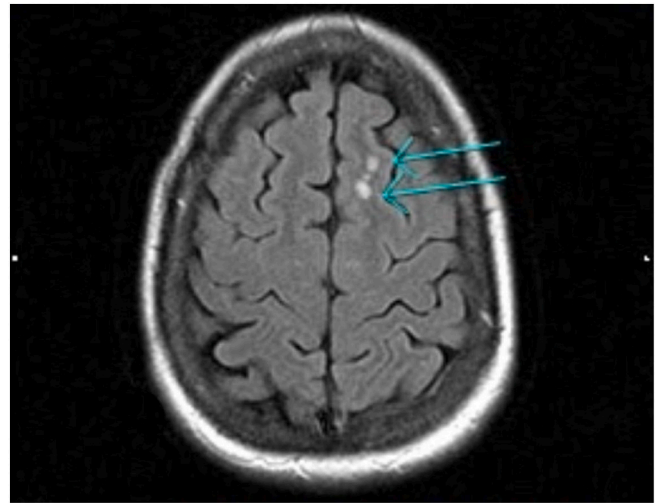


Fig. 8. Axial FLAIR. Frontal lobe multiple acute embolic ischemic infarctions.

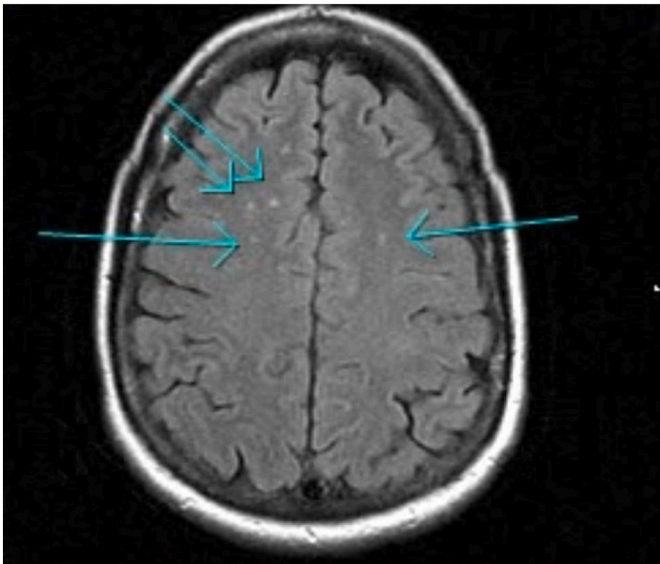


Fig. 7. Axial FLAIR. Bilateral frontal lobe age indeterminate ischemic changes.



Fig. 9. Saggital FLAIR. Right frontal lobe acute embolic ischemic infarctions.

point, the patient was transferred to Johns Hopkins University Hospital. A Transesophageal echocardiogram confirmed the diagnosis of left atrial myxoma. An open-heart surgery via cardio-pulmonary bypass was performed. The mass was attached to the left atrial septum and was large enough to abut through the mitral valve and into the left ventricle. The mass was described as “gelatinous” and broke apart easily. Post-surgical pathology examination reported a left atrial mass with focal aberrant glands measuring $3.0 \times 2.5 \times 1.1$ cm in aggregate. The histologic evaluation was consistent with a myxoma (Figs. 10-12). Her hospital stay was uneventful, and she was discharged on day four post-operatively. She has been followed for four years following surgery. Her symptoms have not returned during this time. She denies any recurrent visual disturbances, Raynaud's symptoms, claudication pain, TIA symptoms, tongue paresthesia, palpitations, or arthralgia.

3. Discussion

This patient presented with the triad of symptoms typical of an atrial myxoma, namely, obstructive, embolic, and constitutional. First,

Obstructive symptoms included lightheadedness, near syncope, dyspnea and chest pain, possibly due to obstruction from cardiac output which was seen during surgery and ECHO. Second, embolic phenomena included TIA, Raynaud's phenomenon, peripheral arterial claudication, acute / subacute strokes, and migraine aura [16]. Third, constitutional symptoms were fever, malaise, weight loss, and arthralgia. Patient's experience is possibly due to the release of cytokine IL-6, which play a major role in the proliferation of myxoma cells and the release of acute-phase reactants which is highly associated with systemic manifestations [16]. Our patient presented with each of the aforementioned symptoms. Atrial Myxomas present with a smooth, villous, or friable surface [17]. The latter two tend to be associated with embolic events while the smooth myxomas are usually large and present more with an obstructive picture. This patient presented with a friable myxoma, leading to embolic events that caused a secondary neurologic presentation which included migraine aura.

Cerebral infarction is known to be the most frequent and critical

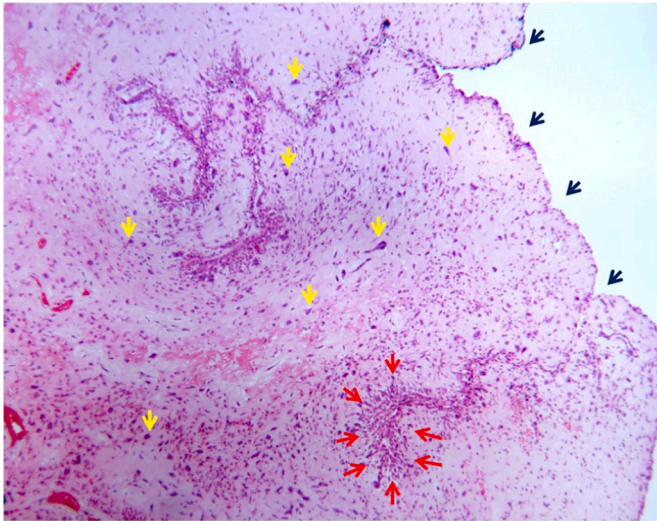


Fig. 10. On low power, this tumor shows an irregular, papillary/villous surface architecture (black arrows), which can be associated with an increased risk for shedding tumor emboli. The tumor itself is comprised of abundant, hypocellular myxoid stroma with hemorrhage and degenerative changes with scattered spindled- to-stellate tumor cells (yellow arrows). Note the presence increased tumor cells surrounding the vessels (red arrows), a phenomenon known as perivascular cuffing [H&E stain, low magnification]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

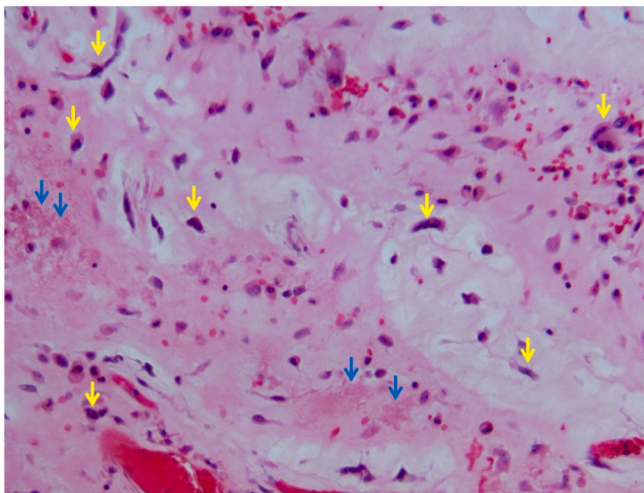


Fig. 11. On higher magnification, spindled-to-stellate tumors cells (yellow arrows) with eosinophilic cytoplasm and hyperchromatic nuclei, including scattered multinucleated cells, are embedded within an edematous and myxoid stroma with red blood cells and admixed fibrin (blue arrows) [H&E stain, high magnification]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

neurological complication of a left atrial myxoma [18]. This patient had multiple embolic (acute and subacute) infarcts at the time of presentation. Her migraine aura was associated with physical exertion and was resolved following resection of the myxoma. An association between migraine aura and left atrial myxoma is strongly suggested in this case due to the disappearance of migraine aura post-surgery. This coincides with the symptomatology of myxomas with an increase in cardiac output and resultant embolic dislodgement. Micro emboli can trigger cortical spreading depression as a pathophysiological correlation with migraine aura [18].

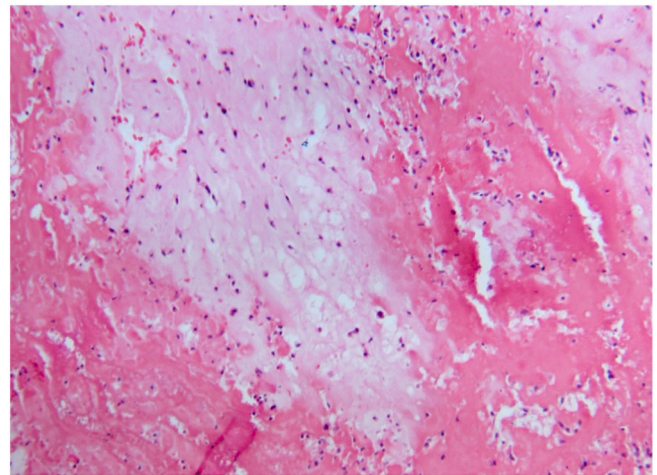


Fig. 12. Representative image of an area of tumor surrounded by a fibrin thrombus, indicating the disruptive and friable nature of the tumor [H&E stain, medium magnification].

Another possibility is a causal relationship between vasoactive intestinal Polypeptide (VIP) secreted by the myxoma and migraine with aura. VIP induces migraine syndrome through glutamatergic neurotransmission [19]. However, our patient was not tested for VIP. In patients with myxomas, there is a 1–3% probability of tumor recurrence following removal [7]. Since tumor removal, this patient has completed an annual ECHO to monitor for such recurrence. Computed tomography angiography (CTA) of the head was negative for aneurysm or stenosis since the resection of the atrial myxoma. Myxomatous production of vascular endothelial growth factor (VEGF) stimulates angiogenesis as well as various cytokines and growth factors, making it increasingly important to monitor for late complications of tumor invasion [20].

The patient is back to full time work at this time and is able to complete her aerobic exercise regimens. Overall, her quality of life has returned to baseline without any recurrence of symptoms. The diagnosis of cardiac myxoma is rare and can be challenging due to its unusual presentation. Delayed diagnosis can result in a poor prognosis and can lead to life threatening conditions including death [21]. To facilitate an early diagnosis, we have implemented a cardiac work up, including two-dimensional ECHO for young patients with prolonged or high frequency migraine aura. With meticulous examination and prompt cardiac work up, we were able to diagnose her condition and remove the myxoma prior to a fatal embolic attack.

4. Conclusion

Due to the plethora of symptoms that an atrial myxoma can present with, migraine aura must not be dismissed from the disease pathology. As in this case, it may well be the initial presenting symptom. Going forward, when dealing with migraine aura patients with an increase in frequency of episodes, one must consider atrial myxoma in the differential diagnosis.

Ethical approval

Yes. Written consent received.

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Author contribution

Shivanthi P. Gunawardane, Michael E. Kramer, Jonathan M. Bearden

- Literature search and data analysis; Jon R. Resar, Jennifer S. Lawton, Derek B. Allison - Data Analysis and first draft Randy M. Becker - Data analysis and critical review; Wayne W. Zhang - Critical Review; Shyamal Premaratne - Final article submission and critical review.

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Guarantor

N/A.

Declaration of competing interest

The authors state that there are no conflicts of interest of any kind.

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