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Rare disease

Recurrent non-aneurysmal, metastatic intraparenchymal haemorrhages following resection of atrial myxoma – case report and literature review

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Summary

Atrial myxomas are the commonest cardiac neoplasms. The most common extra-cardiac manifestations are embolic infarcts from tumour embolisation. Infrequently, aneurysm formation and intracranial haemorrhages also occur. Incredibly rare are space-occupying lesions and malignant transformation. The authors report a case of a previously healthy middle-aged lady who developed recurrent and expanding intraparenchymal haemorrhages following resection of a left atrial myxoma without any primary disease recurrence. The case described is completely different from the described literature in that her intracranial vasculature was free of aneurysms on angiography despite central nervous system haemorrhage and no myxomatous or malignant features were seen on histology of the resected symptomatic occipital lesion. The authors compare this case to the available literature and also provide a literature review.

BACKGROUND

Tumours originating from the heart are a rarity with a reported incidence between 0.0017 and 2.8% in various autopsy series. Most are true neoplasms, albeit benign, with myxomas accounting for more than half of these. Myxomas are usually solitary and the most frequent site for a myxoma is the left atrium. Systemic embolisation is a common complication with the brain harbouring majority of these metastases. The intracranial manifestations observed include embolic infarcts, aneurysms, central nervous system (CNS) lesions and haemorrhage. Complete surgical resection is often curative in those with intracardiac disease alone. Although recurrence is rare, it is usually seen after embolisation of primary tumour, after an incomplete resection or in familial cases.

We report a case of a middle-aged female who developed non-aneurysmal, non-myxomatous intraparenchymal haemorrhagic sequelae following successful resection of her atrial myxoma.

We feel this is important to report for the following reasons: the patient did not have aneurysms and yet developed multi-focal CNS haemorrhage. Additionally, no malignant myxomatous features were reported on the histopathology of her CNS lesion after resection and yet she demonstrated repeated worsening of intracranial haemorrhage (ICH) in a naturally malignant course (figure 1).

CASE PRESENTATION

A 47-year-old previously healthy lady first presented to the emergency room in October 2010 with a new-onset chest pain along with dyspnoea and associated with off and on low-grade fever for the last 4 weeks. On examination, she was a middle-aged lady with average height and built, afebrile but with a mild tachypnoea. She was neurologically intact.

On initial presentation, the erythrocyte sedimentation rate was 38. Her arterial blood gases, urea and electrolytes, coagulation profile and liver function tests were unremarkable. Her chest x-ray did not reveal any abnormality. No neuroimaging was done at this stage as it was unwarranted.

A transthoracic echocardiogram (TTE) revealed a mobile, pedunculated, echogenic mass in the left atrium attached to the intra-atrial septum, 6×3×4 cm in size and causing mitral inflow obstruction. She then underwent surgical resection of the mass. She went home 5 days later in a stable condition. A postoperative TTE showed no residual mass. The final histopathology report revealed the mass to be a benign atrial myxoma.

Four months after this surgery, the patient presented in the emergency department in generalised tonic-clonic status epilepticus. A MRI of her brain revealed multiple hyper-intense lesions with surrounding oedema in the cerebellar and cerebral hemispheres bilaterally with no postcontrast enhancement. However, her repeat echocardiogram showed no new or residual atrial mass. A cerebral CT angiography was negative for presence of arterial aneurysms.

She was conservatively managed with phenytoin for her seizures and discharged. Two months later, she was again admitted through emergency for breakthrough seizures and drowsiness of 1 day. A cranial MRI done this time demonstrated multiple hyper-intense lesions with surrounding oedema in the cerebellar and cerebral hemispheres bilaterally with no postcontrast enhancement. However, her repeat echocardiogram showed no new or residual atrial mass. A cerebral CT angiography was negative for presence of arterial aneurysms.

She was conservatively managed with phenytoin for her seizures and discharged. Two months later, she was again admitted through emergency for breakthrough seizures and drowsiness of 1 day. A cranial MRI done this time demonstrated multiple haemorrhagic lesions in the brain which had increased in number and size. The largest, in the left occipital lobe, measured 22.7×17.1 mm. There was also subtle postcontrast enhancement seen now. A conventional cerebral angiogram done to evaluate the intracranial vasculature again was normal (figure 2). Her echocardiogram was also negative for recurrence. A CAT scan of her chest, abdomen and pelvis revealed no metastatic disease.
She got a neurosurgical evaluation. Lamotrigine was added to her antiepileptic regimen. She was discharged when her serum valproate and phenytoin levels were within desirable range.

Although her seizures were controlled on the new regimen, in 2 months’ time, she was readmitted with progressive right-sided weakness, drowsiness and visual disturbance. Neurological examination revealed a visual field defect, papilloedema and a 4/5 motor power in the right extremities and alexia without agraphia.

To evaluate the status of her brain, an MRI was repeated which showed a growing contrast-enhancing, space-occupying left occipital haemorrhagic lesion, measuring 5.4×2.3 cm and causing a midline shift.

She underwent a craniotomy and excision of this lesion and her status improved subsequently. The histology of the lesion was not consistent with that of atrial myxoma and it was reported as a haemorrhagic infarct. There were no inflammatory cells in the lesion.

She left home stable, with a visual field deficit, subtle memory difficulties and complete recovery of her right hemiparesis.

Three months after her craniotomy, she was brought in with complaints of drowsiness, headache and vomiting. She was unable to walk and had developed central ataxia. A cerebral MRI redemonstrated multiple cerebral and cerebellar haemorrhagic lesions, with the latter having grown considerably since previous imaging. Neurosurgical evaluation was done, however given the size and multiplicity of lesions, she was declared unfit for surgery. As a desperate measure to reduce the intensity of her bleeding, in addition to steroids, a short course of mannitol and symptomatic therapy, she was also given oral tranexamic acid at 500 mg four times a day for 3 days.

Within 24 h of administration, she became better. Her vomiting and drowsiness improved. She became able to walk with assistance and her mannitol was successfully tapered off. At this point, despite no change in her lesion status, she is at home with resumption of her daily activities and remains on a low dose of steroids (dexamethasone 2 mg daily).

**OUTCOME AND FOLLOW-UP**

At this point in writing, the patient remains stable with steroids and is seeking radiotherapy opinion given this review.

**DISCUSSION**

When symptomatic, atrial myxomas have obstructive, metastatic and/or constitutional manifestations and most frequently present with dyspnoea signifying some degree of heart failure. Left atrial myxomas have a propensity to embolise haematogenously and get deposited in the brain, bone, cartilage, skin, abdominal organs and soft tissues. Benign atrial myxomas are usually sporadic with less than one-fifth of the cases being familial as reported in literature. Although rare, these familial cases tend to pose a bigger challenge because they are often multiple, have variable resistance to treatment, a higher risk of recurrence and early age at presentation.
Table 1  Intracranial metastases of cardiac myxomas as reported in literature  

<table>
<thead>
<tr>
<th>S. No</th>
<th>Author</th>
<th>Reported in (year)</th>
<th>Age (years)</th>
<th>Type of brain lesion on radiology</th>
<th>Type of brain lesion on HP</th>
<th>Location of brain lesion</th>
<th>Presence of aneurysms</th>
<th>Sites other than brain</th>
<th>Surgery for cranial lesions</th>
<th>Adjuvant treatment</th>
<th>Outcome as of 2005</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Raza E</td>
<td>2012</td>
<td>47</td>
<td>Haemorrhagic</td>
<td>Haemorrhagic infarct, no myxomatous features</td>
<td>Cerebrum, cerebellum</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
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<tr>
<td>2a</td>
<td>Wolf et al</td>
<td>2008</td>
<td>60</td>
<td>Multiple enhancing nodules</td>
<td>Myxoma invading vascular wall</td>
<td>Cerebrum, cerebellum</td>
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<td>No</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
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<td>2b</td>
<td>Wolf et al</td>
<td>2008</td>
<td>60</td>
<td>Periventricular white matter lesions, multiple nodular lesions</td>
<td>Myxoma invading vascular wall</td>
<td>Cerebrum, cerebellum</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
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<td>3</td>
<td>Moiyadi et al</td>
<td>2007</td>
<td>35</td>
<td>Solid and cystic</td>
<td>Metastatic atrial myxoma: glandular variant</td>
<td>Cerebrum</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
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<td>4</td>
<td>Altundag et al</td>
<td>2005</td>
<td>41</td>
<td>Haemorrhagic</td>
<td>Benign embolic myxoma</td>
<td>Cerebrum, cerebellum</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Radiotherapy</td>
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<tr>
<td>5</td>
<td>Hirudayaraj et al</td>
<td>2004</td>
<td>50</td>
<td>Soft tissue mass</td>
<td>Low-grade myxosarcoma</td>
<td>Cerebrum</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>NK</td>
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<td>6</td>
<td>Acikel et al</td>
<td>2004</td>
<td>58</td>
<td>Embolic infarct</td>
<td>Metastatic atrial myxoma</td>
<td>Cerebrum, cerebellum</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NK</td>
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<td>7</td>
<td>Hou et al</td>
<td>2001</td>
<td>37</td>
<td></td>
<td></td>
<td>Bone</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Dead</td>
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<tr>
<td>8</td>
<td>Bemot et al</td>
<td>1998</td>
<td>31</td>
<td>Metastases</td>
<td>Metastatic atrial myxoma</td>
<td>Cerebrum</td>
<td>NR</td>
<td>No</td>
<td>Lung, muscle</td>
<td>Yes</td>
<td>Radio and chemotherapy</td>
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<td>9</td>
<td>Scarpelli</td>
<td>1997</td>
<td>64</td>
<td>Mass lesion</td>
<td>Metastatic atrial myxoma: glandular variant</td>
<td>Cerebrum</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>NK</td>
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<td>10</td>
<td>Kanda et al</td>
<td>1994</td>
<td>70</td>
<td>Mass lesion</td>
<td>Benign intracerebral myxoma</td>
<td>Cerebrum</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<td>11</td>
<td>Samarantunga et al</td>
<td>1994</td>
<td>60</td>
<td>Enhancing subcortical lesion</td>
<td>Epithelioid haemangiendothelioma with myxoid features</td>
<td>Cerebrum</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Alive</td>
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<tr>
<td>12</td>
<td>Wada et al</td>
<td>1993</td>
<td>70</td>
<td>High density lesions</td>
<td>Benign myxoma</td>
<td>Cerebrum</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>NK</td>
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<td>13</td>
<td>Todo et al</td>
<td>1992</td>
<td>32</td>
<td>Enhancing mass: partly cystic</td>
<td>Sarcoma with myxoid degeneration</td>
<td>Cerebrum</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>14</td>
<td>Chozick et al</td>
<td>1992</td>
<td>61</td>
<td>Enhancing mass</td>
<td>Malignant astrocytoma</td>
<td>Cerebrum</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>15</td>
<td>Kotani et al</td>
<td>1991</td>
<td>48</td>
<td></td>
<td></td>
<td>Aorta, skin</td>
<td>Yes</td>
<td>No</td>
<td>Dead</td>
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<tr>
<td>16</td>
<td>Ng and Poon</td>
<td>1990</td>
<td>54</td>
<td>Solitary lesion</td>
<td>Myxoma tissue, haemosiderin, fibrosis</td>
<td>Cerebrum</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Alive</td>
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<tr>
<td>17</td>
<td>De Morais et al</td>
<td>1988</td>
<td>73</td>
<td></td>
<td>Infiltrative cardiac myxoma</td>
<td>Pancreas, stomach, kidney</td>
<td>No</td>
<td>No</td>
<td>Dead</td>
<td></td>
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<tr>
<td>18</td>
<td>Kadota et al</td>
<td>1987</td>
<td>44</td>
<td>Enhancing mass</td>
<td>Myxomatous tissue</td>
<td>Cerebrum</td>
<td>NR</td>
<td>Skin</td>
<td>Yes</td>
<td>No</td>
<td>NK</td>
</tr>
<tr>
<td>19</td>
<td>Bazin</td>
<td>1987</td>
<td>56</td>
<td>Multiple high density enhancing</td>
<td>Myxomatous features</td>
<td>Cerebrum, cerebellum</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>NK</td>
</tr>
<tr>
<td>20</td>
<td>Markel et al</td>
<td>1986</td>
<td>18</td>
<td>Mycotic aneurysms</td>
<td></td>
<td>Cerebrum, multiple fusiform aneurysms</td>
<td>Bone</td>
<td>No</td>
<td>No</td>
<td>Alive</td>
<td></td>
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<tr>
<td>21</td>
<td>Morimoto</td>
<td>1986</td>
<td>44</td>
<td>Enhancing low density mass</td>
<td>Clusters of spindle and stellate cells</td>
<td>Cerebrum</td>
<td>NR</td>
<td>Skin</td>
<td>Yes</td>
<td>No</td>
<td>Alive</td>
</tr>
<tr>
<td>22</td>
<td>Seo et al</td>
<td>1980</td>
<td>36</td>
<td>Intracranial mass</td>
<td>Myxoid stroma with inflammatory cells</td>
<td>Lateral ventricle</td>
<td>NR</td>
<td>Bone</td>
<td>Yes</td>
<td>No</td>
<td>Dead</td>
</tr>
<tr>
<td>23</td>
<td>Budzilovich et al</td>
<td>1979</td>
<td>52</td>
<td>Mass</td>
<td>Myxoid invasion of neural tissue</td>
<td>Cerebral, cerebellar</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Dead</td>
</tr>
<tr>
<td>24</td>
<td>Rankin and De Souza</td>
<td>1978</td>
<td>44</td>
<td>Mass</td>
<td>Blood sinusoids with myxoid and connective tissue</td>
<td>Choroid plexus</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Alive</td>
</tr>
</tbody>
</table>

HP, histopathology; NA, not applicable; NR, not reported; NK, not known; SOL, space-occupying lesion.
Familial syndromes with atrial myxomas include naevi, atrial myxoma, myxoid neurofibromata and ephelides, lentigines, atrial myxoma, mucocutaneous myxoma, and blue naevi and the autosomal dominant Carney’s syndrome. In cases where these are suspected due to presentation, the family can be screened with TTE or genetic testing depending upon availability.

Neurologic manifestations of atrial myxoma are common and include ischaemic events with myxomatous fragments occluding or stenosing the small calibre intracerebral vasculature. This embolisation may occur as part of the natural history or may be iatrogenic when during resection and removal, a fragment dislodges. Moreover, although less common, arterial wall weakness has also been described and is associated with both myxomatous and non-myxomatous aneurysm formation, often years after resection of the primary tumour. Even less often seen are the haemorrhagic sequelae, both intraparenchymal and subarachnoid bleeds subsequent to rupture of these aneurysms. True metastasis and proliferation of extra-arterial myxomatous tissue is a rare phenomenon, at best.

The age, sex, location and initial presentation of atrial myxoma in our patient correspond to that described in literature (table 1). However, she represents a rare case where she had recurrent large cerebral parenchymal haemorrhages mainly in the vertebrobasilar territory but also involving the anterior circulation without any histological evidence of myxomatous features in the lesions or any angiographic evidence of aneurysm in intracranial vessels. There is paucity of data regarding this rare phenomenon.

Intracranial haemorrhages occur secondary to aneurysm formation. If and how often will non-aneurysmal arteries bleed into the parenchyma cannot be predicted. Knepper et al have, in their series, reported one case of subarachnoid haemorrhage where the haemorrhage occurred without angiographic evidence of aneurysms. We postulate that silent tumour embolisation occurred during surgery and then manifested later with seizures and development space occupying lesion. This seems more probable especially due to the fact that there was significant load of lesions in the territory of posterior circulation.

The time from diagnosis of atrial myxoma to the appearance of intracranial aneurysms is also variable.

Figure 2 Four-vessel cerebral angiogram showing absence of aneurysms and vasculitis.
serial cerebral angiography be done for detection is still a matter of debate since the treatment modalities for these aneurysms, whether aneurysmectomy or chemotherapy with doxorubicin, have yielded inconclusive results. The treatment of spontaneous intraparenchymal bleed remains supportive and preventive. There are no guidelines specific for bleeds due to atrial myxomas. In our patient after surgical excision of the largest haemorrhagic lesion, tranexamic acid was started to prevent rebleeding. Although there is literature to support the use of tranexamic acid in patients with berry aneurysms and subarachnoid haemorrhage, we have employed the same in the hope of preventing further episodes of non-aneurysmal intra-parenchymal haemorrhage at least as a temporising measure. It has been 2 months since the initiation of this therapy with no new episode of parenchymal bleed, although it is premature to predict future risk. How long will the antifibrinolytic effect of the 3-day course of tranexamic acid last can also not be predicted. In addition, it cannot be ruled out that the effects of tranexamic acid was due to chance, improving natural history or the use of concurrent medications to lower intracranial pressure.

The possibility of a concomitant disease like vasculitis cannot entirely be ruled out, although the absence of stroke and the expanding nature of each ICH over time, argues against this theory. We were unable to find evidence of inflammatory cells in the resection lesion at biopsy which further refutes this possibility although does not eliminate it entirely.

In patients with intraparenchymal manifestations of atrial myxoma, there are only four reported cases that received brain radiation. Most recently, Moiyadi et al described a patient who received 25Gy focal radiation following craniotomy and excision of lesion with no residual neurological deficit post treatment. Altundag et al have also reported a case where a patient received 30 Gy whole brain radiation for an embolised benign myxoma. Previously, Bernet et al reported a patient who received 5000 Gy whole brain radiation along with chemotherapy for myxomatous metastases with malignant features to the brain and elsewhere; resolution of these lesions was seen following treatment. The earliest report we could find was by Todo et al where a patient received 60Gy of radiation for brain lesion. This patient, however, died of cerebral herniation due to enlarging intracranial masses within a year of treatment. We are now contemplating radiation in our case; however, our patient's histopathology of haemorrhagic infarct taken from the occipital location does not necessarily correlate with the intervention in the literature.

**FUTURE DIRECTIONS**

It has been hypothesised that interleukin-6 may be responsible for the metastasising nature of the otherwise benign cardiac myxomas. This is an area which can be looked at in future. When atrial myxomas are associated with intracranial haemorrhage, further research is needed into haemostatic therapy, safety of surgery and irradiation especially when aneurysms and malignant potential are not found as in this case.

**Learning points**

- Atrial myxomas are the commonest cardiac tumours with neurologic complications being the most frequent extra-cardiac manifestations; familial atrial myxoma syndromes exist.
- The neurological sequelae include embolic infarcts, aneurysms, intracranial bleed and space-occupying lesions; in that order of frequency.
- As in the described case, although rare, there may be large intraparenchymal bleeds requiring excision, without angiographic evidence of aneurysms.
- Whole brain radiation may have a role in preventing rebleeding and reducing the size of existing lesions and the literature describes this for both benign and malignant pathology.

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**Competing interests** None.

**Patient consent** Obtained.

**REFERENCES**

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