Second recurrence of familial atrial myxomas: mother and daughter simultaneously
Zehra Bayramoglu, Kerem Oral, Mehmet Ezelsoy, Belhhan Akpinar

Abstract
Sporadic cardiac myxomas rarely recur, however recurrence rates are higher in patients with a familial aggregation or Carney complex. Carney complex is characterised by multiple mucocutaneous lesions and accounts for up to two-thirds of familial cardiac myxomas. A second recurrence is very rare, even in the case of Carney complex. We report on two cases of recurrent cardiac myxoma, a mother and daughter, who concurrently presented with a second recurrence of atrial myxomas. The time interval between the first and second recurrence following surgery was four years in both. The possibility of repeat recurrence of cardiac myxomas demonstrates the importance of regular echocardiography to detect recurrence and to prevent the potential complications associated with cardiac myxomas. Family screening should be recommended for familial myxomas.

Keywords: cardiac myxoma, Carney complex, familial cardiac myxoma, atrial myxoma

Myxomas that are mesenchymal tumours are typically sporadic and isolated. This disease occurs as a familial form in only around 7% of all cases. This group of patients is younger and they frequently have multifocal tumours; some suffer from additional neoplasms called complex myxoma or Carney complex.

It is important to manage cardiac tumours in patients with Carney complex because the most common cause of death in these patients is heart-related problems; 57% of all-cause deaths include cardiac myxoma, emboli, heart surgery complications and cardiac arrhythmia.1 Treatment is surgical excision and should be performed on detection due to embolic complications.

The relapse risk for sporadically occurring myxomas varies between one and 3% and it is increased significantly, at a rate of 10–21%, for patients with familial aggregation or Carney complex.2 We present two cases, a mother and daughter, with a second recurrence of atrial myxomas within four years of surgical resection.

Case report
A 23-year-old daughter and 50-year-old mother presented in November 2016 with fatigue and exertional dyspnoea. The family history revealed that both women had a history of left atrial myxomas and two concurrent cardiac surgeries that were four years apart. Transthoracic echocardiography (TTE) in 2016 indicated the second recurrent myxomas in the left atrium and they were both referred to our hospital.

The mother and daughter had similar symptoms. Both patients revealed tachycardia with a regular heart rate at about 115 beats per minute, pedal oedema and hepatomegaly. They had hyperpigmentation and nevi on their bodies, similar to Carney syndrome.

Case 1: The daughter had a history of cardiac operations for left atrial myxoma in 2008 and 2012. The history of the young woman revealed that she was in the first trimester of pregnancy at the first recurrence and she had a second cardiac operation. At the time of the second recurrence she was 16 weeks’ pregnant.

TTE of the young woman revealed a stable mass (40 × 25 mm) near the left superior pulmonary vein orifice and a pediculated mass (60 × 45 mm) in the left atrium, which was attached to the septum foramen ovale. The tumour prolapsed from the left atrium into the left ventricle through the mitral valve orifice, causing mitral valve obstruction and moderate regurgitation (Fig. 1).

Following the decision for surgery for the cardiac mass, a medical abortion was performed after getting ethical and legal approval from her family. Five days later, she had a third cardiac operation with a minimal invasive technique (port access). Surgical excision of the intra-cardiac myxoma was performed through a right anterolateral mini-thoracotomy under the breast. Cardiopulmonary bypass was performed via the internal jugular vein, femoral vein and femoral arterial cannulation.

The patient was cooled to 26°C and an incision was made in the left atrium with a ventricular fibrillation technique. A large jelly-like left atrial mass (60 × 45 mm) was seen with attachment to the inter-atrial septum near the anterior leaflet

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The myxoma was obstructing the outflow of the pulmonary veins to the left atrium. It was also prolapsing onto the left ventricle through the mitral valve in diastole. An additional myxoma (40 × 25 mm) was found near the left inferior pulmonary vein (Fig. 2).

The small myxoma with surrounding normal tissue was completely excised. The large one was removed with approximately 1 cm of the inter-atrial septum and the atrial septal defect was closed with a bovine pericardial patch. After irrigation of the atria and ventricle with saline solution to eliminate any tumour fragments, the left atrium was closed. Cardiopulmonary bypass was stopped with sinus rhythm following defibrillation. The duration of cardiopulmonary bypass was 100 minutes.

Case 2: The mother had a history of two cardiac operations for left atrial myxoma in 2008 and 2012, at the same time as her daughter. She had fatigue, exertional dyspnoea and hyperpigmentation on her skin. TTE of the mother revealed a pedunculated mass (23.9 × 20 mm) that was attached to the inter-atrial septum (Fig. 3).

The mother had a third cardiac operation with a median sternotomy accompanied by moderate hypothermia and cardiopulmonary bypass via the internal jugular vein, femoral vein and femoral arterial cannulation. An incision was made in the right atrium and the trans-septal approach was used.

A large jelly-like pedunculated mass (1.96 × 2.39 mm) was found in the left atrium, attached to the inter-atrial septum.
The myxoma was removed with approximately 1 cm of the inter-atrial septum. After the cardiac chambers were inspected and no additional tumours were found, the atrial septal defect was repaired with a bovine pericardial patch. The duration of cardiopulmonary bypass was 70 minutes and aortic clamp time was 45 minutes.

The postoperative course of both patients was uneventful. Histological examination of the masses confirmed myxoma. Postoperative echocardiographic examination showed no abnormalities. Because the mother had postoperative wound infection in the femoral incision and the daughter had had a medical abortion before the operation, they were both discharged after about 15 days.

**Discussion**

Carney complex, which is a syndrome of cardiac myxomas, spotty pigmentation (lentiginosis) and endocrine overactivity, was first described in 1985 by J Aidan Carney. It comprises 7% of all cardiac myxomas and can be found in all ages, especially young women.

A diagnosis of Carney complex is made based on a detailed patient history, thorough clinical evaluation, a variety of specialised tests and identification of the characteristic symptoms. To make a diagnosis of Carney complex, patients must have two major criteria (cardiac myxoma, skin myxoma, lentiginosis, acromegaly, testicular tumour, thyroid tumour or other endocrine abnormalities) or one major plus one supplemental criteria [affected first-degree relative, activating mutation of protein kinase cAMP-activated catalytic subunit-alpha (PRKACA) and protein kinase cAMP-activated catalytic subunit-beta (PRKACB) or inactivating mutation of protein kinase type I-alpha regulatory subunit (PRKAR1A) gene] (Table 1).

These cases were similar to Carney complex; they had cardiac myxoma and lentiginosis. The recurrence interval was four years for both mother and daughter. They each had three cardiac operations for left atrial myxomas at the same time periods. We did not have any genetic or hormonal analysis done.

Cardiac myxomas related to Carney complex more frequently occur in the left ventricle, compared with sporadic myxomas. Edwards et al. reported that 64% of cardiac myxomas related to Carney complex occurred in the left atrium, 44% in the right atrium, 14% in the left ventricle and 12% in the right ventricle. In our cases, the myxomas appeared in the left atrium.

Myxomas usually show signs of obstructed ventricular filling, thereby mimicking a mitral or tricuspid valve stenosis. Production and release of interleukin 6 by the tumour cells gives rise to non-specific symptoms such as fatigue, weight loss, fever and arthralgia. The symptomatology in recurrent myxomas is the same as in general non-recurrent myxomas. These patients had constitutional symptoms at each recurrence; the daughter also had symptoms mimicking mitral valve stenosis.

Gerbode et al. encountered the first recurrence of a myxoma after removal. The mechanism of recurrence can be explained by incomplete resection of the original tumour, leading to regrowth; familial predisposition for recurrence; intra-cardiac tumour seeding of the first one; and due to the existence of a pre-tumoural focus in the myocardium, leading to recurrence. In these two cases, the reason was most probably due to family predisposition.

Predicting recurrence of cardiac myxomas is still an open question. Keeling et al. found significant immunological changes in myxoma patients. In the case of recurrence, serum protein electrophoresis, C-reactive protein, fluorescein-activated cell sorter, interleukin 2 receptor and intracellular adhesion molecule levels may be altered. Immunological and genetic screening of these patients may help to identify patients at risk for additional recurrence. Normally, echocardiographic follow up should be performed each year to detect myxoma recurrences early. Patients with known Carney complex should have this examination every six months if they have already had a surgical resection.

Myxomas usually appear as well-defined, smooth, oval or lobular lesions that are commonly pedunculated. Normal intra-cardiac structures and embryological remnants can sometimes be mistaken for atrial myxomas on TTE. Transoesophageal echocardiography (TEE) may demonstrate the site of insertion and other surface features of the myxoma, as well as haemorrhage, necrosis, cysts and calcification. TEE has limitations in viewing the right heart and extra-cardiac structures, and requires sedation.

Cardiac magnetic resonance imaging has become increasingly valuable for determining cardiac tumours. It is very useful to differentiate myxomas from other cardiac masses, thrombus and anatomical abnormalities. Myxomas typically appear hyperintense compared with normal myocardium and hypo-intense compared with the blood pool. Following contrast agent administration, lesions often show more heterogeneous enhancements on late gadolinium enhancement. In difficult cases, both TEE and cardiac magnetic resonance imaging may be helpful for follow up.

Complete surgical removal of the tumour and its cardiac attachment is usually curative. Excision of the underlying atrial septum with shaving off of part of the myocardium (at least 5-mm margin all around) underlying the stalk is necessary during primary myxoma excision for the prevention of recurrence; closure with untreated autologous pericardium is dictum in all atrial myxoma

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**Table 1. Diagnostic criteria for Carney complex.**

A patient with Carney complex must either exhibit two of the manifestations of the diseases listed, or exhibit one of these manifestations and meet one of the supplemental criteria.

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Supplemental criteria</th>
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<tr>
<td>1. Spotty skin pigmentation with typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa)</td>
<td>1. Affected first-degree relative</td>
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<td>2. Myxoma (cutaneous and mucosal)</td>
<td>2. Inactivating mutation of the PRKAR1A gene</td>
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<td>3. Cardiac myxoma</td>
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<td>4. Breast myxomatosis or fat-suppressed magnetic resonance imaging findings suggestive of this diagnosis</td>
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<td>5. Primary pigmented nodular adrenal disease or paradoxical positive response of urinary glucocorticosteroids to dexamethasone administration during Liddle test</td>
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<td>6. Acromegaly due to growth hormone-producing adenoma</td>
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<td>7. Large cell-calcifying Sertoli cell tumour</td>
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<td>8. Thyroid carcinoma or multiple, hypo-echoic nodules on thyroid ultrasonography in a young patient</td>
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<td>9. Phammonomatous melanotic Schwannoma</td>
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<td>10. Blue nevus</td>
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<td>11. Breast ductal adenoma</td>
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<td>12. Osteochondromyxoma</td>
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**Background:**

- **Purpose:** To report the first recurrence of atrial myxomas in a young patient.
- **Method:** Case report.
- **Results:** The mother and daughter both had cardiac myxomas that recurred after resection.
- **Conclusion:** Recurrence of atrial myxomas is rare and can occur after resection. Further studies are needed to understand the mechanisms of recurrence.

**Key Points:**

- Atrial myxomas are rare cardiac tumours that can recur after resection.
- Recurrence of atrial myxomas is associated with incomplete resection and familial predisposition.
- Further research is needed to understand the mechanisms of recurrence.

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**Disclosure:** The authors declare no conflicts of interest.

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**References:**

4. Liddle test: A test used to differentiate mineralocorticoid excess from salt-sensitive hypertension.
5. TTE: Transoesophageal echocardiography.
6. TEE: Transoesophageal echocardiography.
7. Gadolinium enhancement: A type of imaging used in magnetic resonance imaging to enhance the visibility of tissues.
8. Myxoma: A type of cardiac tumour that appears as a soft, gel-like mass.
9. Carney complex: A genetic syndrome characterized by cardiac myxomas, spotty skin pigmentation, and endocrine overactivity.
excision cases.\textsuperscript{12} Also, radical excisional therapy and total cardiac transplantation have been reported.\textsuperscript{13} In our cases, the tumours were excised with wide margins and the atrial septal defects were closed with a bovine pericardial patch to exclude a third recurrence of the tumour due to incomplete resection.

**Conclusion**

The reported cases of repeated recurrent, benign atrial myxomas demonstrate the importance of regular echocardiography after surgical resection in order to detect recurrence and avoid complications. Also, genetic counselling should be offered to affected individuals and their families.

**References**