Familial Atrial Myxoma: Three Related Cases at an Australian Tertiary Institution

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Carney complex accounts for up to two-thirds of familial cardiac myxoma. It is a rare autosomal dominant syndrome, which is also characterized by multiple mucocutaneous lesions and endocrine tumors. We report on three first-degree relatives who underwent surgical resection at the same Australian tertiary institution. One patient re-presented with a recurrent tumor at an interval of 6 years. In this context, the role of interval surveillance, family screening, and genetic testing is explored. We recommend interval echocardiographic surveillance for affected individuals and first-degree relatives given the high risk of recurrence and the morbidity and mortality associated with cardiac tumors in any location.

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

Methods

Patient medical records were reviewed retrospectively. A family pedigree across three generations was constructed based on personal communications with the patients (Fig. 1). Informed consent was obtained.

Case 1

A 41-year-old female of Maori and English heritage presented with intermittent neurological symptoms over a 2-week period. She experienced several episodes of right hemiparesthesia and expressive dysphasia associated with general malaise, headache and light-headedness over this time period. Constitutionally, she was generally unwell with a non-specific headache and light-headedness over the same time period. A brain computed tomography (CTB) revealed age advanced cerebral atrophy but no acute pathology. She was referred for transthoracic echocardiogram (TTE) with a presumptive diagnosis of transient ischemic attack (TIA). She underwent TTE, which revealed a 1.6 cm left atrial myxoma, with normal ventricular and valvular function. From there, she commenced therapeutic anticoagulation (rivaroxaban) and antiplatelet therapy (aspirin) and was referred for surgery. Previously healthy with no significant medical history, she had undergone multiple resections of a recurrent cutaneous...
myxoma on her right eyelid in the past. The patient
gave a family history of cardiac tumors in her father.
Physical examination on admission revealed a slim,
olive-skinned female with no evidence of mucocutane-
ous pigmented or myxomatous lesions. Given her level
of global skin pigmentation, it was difficult to discern
any distinct macular lesions consistent with lentigines.
Cardiac examination was normal. There were no objec-
tive neurological findings.

The patient proceeded to resection via a median ster-
notomy and right atrial incision, with an incidental find-
ing of a patent foramen ovale. The intra-atrial septum
was excised en bloc with the myxoma and reconstructed
with a bovine pericardial patch. Histopathology con-
firmed cardiac myxoma with typical S-100 and calreti-
nin-positive myxoma cells apparent. The patient had an
uneventful postoperative course and was discharged
4 days after surgery. Inpatient random serum levels of
plasma prolactin (PRL), growth hormone (GH), and
insulin-like growth factor-1 (IGF-1) were within normal
range. No other biochemical or imaging investigations
were performed at this time. The patient has four chil-
dren (age range, 17–22 years) all of whom are currently
healthy (Fig. 1). Follow-up was arranged with their family
doctor, with a recommendation that her children undergo TTE to screen for cardiac myxoma in the first
instance.

Case 2
A 67-year-old English man, father of case 1, presented
with a syncopal episode and associated hypotension with
a right visual field deficit. This was on a background of a
cerebrovascular accident 6 years prior and excision of a
left atrial myxoma detected at this time. In the emer-
gency department, CTB revealed no acute abnormality.
TTE revealed a 5.3 × 3.6 cm left atrial myxoma attached
to the intra-atrial septum via a thick stalk that prol-
lapsed across the mitral orifice with some obstruction to
inflow. Other echocardiographic findings were of mild
left ventricular dilatation with moderate systolic dys-
function and inferior and inferolateral wall akinesis. He
proceeded to coronary angiogram, which revealed a 50%
mid-left anterior descending (LAD) stenosis and no
other significant coronary artery disease. He was referred
for surgical excision as an inpatient and underwent a
redo median sternotomy and excision of myxoma,
including extensive resection of septum and left atrial
roof requiring reconstruction with pericardium.

Case 3
The brother of case 2 (paternal uncle of case 1) under-
went resection of a left atrial myxoma 5 years ago at
73 years of age. He presented with a transient episode of
right eye visual loss and a history of pre-syncopal epi-
sodes over the preceding 1 month. CTB was normal with
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TTE showing an echogenic lesion originating from the intra-atrial septum. Background history included resected colorectal cancer and testicular surgery for an unknown indication. He had previously undergone two excisions of cardiac myxoma. In this presentation, he underwent complete excision of the intra-atrial septum, which included the calcified base of the myxoma. The defect was then repaired with bovine pericardium. Histology showed foci of myxoid matrix containing spindle and stellate cells consistent with features of atrial myxoma.

Discussion

Approximately, 10% of cardiac myxomas are familial with CNC accounting for the majority of these.\(^5,6\) CNC is a rare multiple neoplasia syndrome, first described in 1985 by J Aidan Carney as a “complex of myxomas, spotting pigmentation and endocrine over-reactivity.”\(^7\) It displays autosomal-dominant inheritance with nearly 100% penetrance. CNC can occur sporadically due to de novo germline mutations, but 70% of affected individuals have a parent with the disease.\(^4,5\) To make the diagnosis of CNC, patients must meet two major criteria or one major plus one supplemental criterion (Table 1).\(^5\) Thus, patients with histologically proven cardiac myxoma only require one other major criterion, a recognized gene activation/inactivation or any affected first-degree relative, to meet the diagnostic criteria. More than 80% of affected individuals have cutaneous manifestations, ranging from simple lentigines to atypical naevia and cutaneous myxomas.\(^4\) Typically, lentigines manifest during puberty and fade with age, with a distribution focused on the face, lips, and genitalia. Cutaneous myxomas, usually <1 cm in size and asymptomatic, are seen in up to 55% of patients, typically on the eyelids, external auditory canal, nipples, and genitalia. Case 1 gave a history consistent with resection of multiple eyelid myxomas in the past. Beyond mucocutaneous lesions, the most common lesions in CNC are cardiac myxomas. In contrast to sporadic cardiac myxomas, which are almost exclusively left atrial in origin and predominant in elderly females, familial myxomas affect all heart chambers and have an equal incidence in males and females, with a median age of detection of 20 years.\(^4,6\) However, initial presentation can be late with the reported cases presenting after 40 years of age. Associated endocrine pathology includes pituitary adenoma, adrenocortical tumors, and thyroid nodules.\(^5\) Large cell-calcifying Sertoli cell tumors (LCCSCT) occur in up to 75% of male patients with CNC, having a not insignificant risk of malignant change. Breast and ovarian tumors have been reported in female sufferers.

Genetics

More than two-thirds of patients diagnosed with CNC carry a mutation of the protein kinase type I-alpha regulatory subunit (PRKAR1A) gene on loci 24.1–24.3 of the long arm of chromosome 17.\(^5\) Dysfunction of the downstream regulatory unit leads to cyclic adenosine monophosphate (cAMP) over-activity and unrestrained cell

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<tr>
<th>Table 1 Carney complex: diagnostic criteria*</th>
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<td>Major criteria</td>
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<td>Spotty skin pigmentation in typical distribution</td>
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<td>Breast myxomatosis</td>
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<td>PPNAD or paradoxically positive Liddle’s test</td>
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<td>Acromegaly secondary to GH adenoma</td>
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<td>LCCSCT</td>
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<td>Thyroid carcinoma</td>
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<td>PMS (psammomatous melanotic schwannomas)</td>
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<td>Multiple epithelioid blue naevi</td>
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<td>Breast ductal adenoma</td>
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<td>Supplemental criteria</td>
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<td>Activating mutations of PRKACA and PRKACB</td>
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<td>Inactivating mutation of PRKAR1A gene</td>
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*Two major criteria (confirmed on histology, imaging, or biochemistry) or one major and one supplemental criterion make the diagnosis of Carney complex. Adapted from Correa et al. (2015).\(^5\) GH: growth hormone; PPNAD: primary pigmented nodular adrenocortical disease; LCCSCT: large cell-calcifying sertoli cell tumors; PRKAR1A: protein kinase type I-alpha regulatory subunit; PRKACA: protein kinase CAMP-activated catalytic subunit alpha; PRKACB: protein kinase cAMP-activated catalytic subunit beta.
proliferation and tumor formation in affected tissues. More than 125 different mutations have been documented across 400 kindreds, with the vast majority of mutations unique and present in only a single pedigree. For patients without a recognized mutation, the genetic cause remains unclear, and importantly the absence of a detectable mutation in this gene does not preclude a diagnosis of CNC. Thus, work-up for possible CNC is recommended for any patient presenting with familial cardiac myxoma. Genetic testing may be indicated for patients meeting diagnostic criteria and their first-degree relatives. None of the cases in our series underwent genetic testing. However, some members of the family in the United Kingdom had undergone genetic screening (Fig. 1).

Management

The standard of care treatment for cardiac myxoma is earliest possible complete surgical resection via median sternotomy, as was performed in all reported cases. For simple, isolated myxomas, a right atrial incision provides adequate access in 85% of cases. If suboptimal exposure is obtained, then a biatrial approach can be used. At our institution, atrial myxomas are excised with full thickness of the left atrium with 0.5 cm margin around the stalk. Autologous or bovine pericardium can be used to reconstruct the intraatrial septum where primary closure is inadequate. In this group of patients, where multiple and recurrent lesions are often seen, a thorough inspection of the interior of the chambers is essential at the time of surgery. A more radical excision is sometimes necessary. Previously, cardiac auto-transplantation and bi-atrial resection have been described for multiple recurrences. Concomitant coronary artery and/or valve surgery is often undertaken; however, no significant disease was seen in this familial cohort.

Surveillance

Patients with cardiac myxoma associated with CNC experience recurrence in up to 30% of cases, whereas in total population of cardiac myxomas reported rates vary 3%–6%. Cases of up to four and seven recurrences in single patients have been reported in the literature. Two of the three patients in our series had tumor recurrence, in both cases at the same location as the first tumor. Recommended clinical surveillance for patients with CNC or any patient with resected cardiac myxoma includes annual TTE. Once a CNC patient is diagnosed with cardiac myxoma, this should be performed biannually, as these patients have an increased risk of recurrence. A complete physical examination including skin evaluation and thyroid exam is recommended at diagnosis and at regular intervals. Annual testicular ultrasound in males for detection/surveillance of LCCSCT is highly recommended. Recommended biochemical screening investigations include serum GH, PRL, and IGF1 and urinary free cortisol as appropriate.

Conclusion

We reported on three first-degree relatives with familial cardiac myxoma who underwent complete surgical resection at our tertiary institution. One patient had a late recurrence at 6 years. Another patient presented with his third recurrence. Clinicians should consider a possible diagnosis of CNC in cases of familial cardiac myxoma. Long-term interval echocardiographic surveillance is recommended for affected individuals and first-degree relatives given the high and sustained risk of recurrence.

Disclosure Statement

The authors have no disclosures or conflicts of interest.

References

1) Roberts WC. Primary and secondary neoplasms of the heart. Am J Cardiol 1997; 80: 671-82.