Systemic embolisation as presentation and recurrence of cardiac myxoma two years after surgery

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Primary cardiac tumours are rare when compared with metastatic involvement. The majority of primary cardiac tumours are benign and in adults the majority of these masses are myxomas. The treatment is surgical removal because of the risk of embolisation and/or cardiovascular complications. We describe a female presenting with systemic embolisation and recurrence of cardiac myxoma after surgery. Recurrence of myxoma is rare after surgery in case of solitary tumours but more frequent in patients with familial myxomas in association with the Carney complex. Genetic analysis revealed a mutation in the *PRKARIA* gene that has never been described before. (Neth Heart J 2010;18:499-502.)

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PPrimary cardiac tumours are extremely rare when compared with metastatic involvement of the heart.^{1,2} The majority of primary cardiac tumours are benign and in adults the majority of these masses are myxomas.¹ The treatment of myxomas is surgical removal because of the risk of embolisation and/or cardiovascular complications. In this report, we describe a young female presenting with systemic embolisation and recurrence of cardiac myxoma after surgery. Recurrence of myxoma is rare after surgery in case of solitary tumours but more frequent in patients with familial myxomas in

association with the Carney complex. Subsequent genetic analysis in our patient revealed a mutation in the *PRKARIA* gene which has never been described before. However, it is not known whether this mutation is responsible for the production of an aberrant protein. We present this case because of the peculiar patient characteristics and the genetic rarity.

Case report

In 2005, a 21-year-old female patient was referred to the outpatient cardiology clinic with a six-month history of fatigue, arthralgia, exertional breathlessness and pain in the left leg during walking and cycling. The patient's medical history was uneventful.

Physical examination revealed that the patient's temperature was 38 °C, blood pressure was 120/70 mmHg, there was a loud first heart sound, an opening snap and an apical mid-diastolic murmur; no signs of heart failure were found. Bilateral palpation and auscultation of the carotid, brachial, radial and femoral arteries did not reveal any aberrations; however, the left-sided dorsalis pedis and posterior tibial artery were not palpable. Laboratory tests were normal except for mild anaemia (6.6 mmol/l, normal 7.5 to 10.0 mmol/l) and a raise in the erythrocyte sedimentation rate (ESR) (72 mm/h, normal <10 mm/h) and C-reactive protein (70 mg/l, normal 0 to 10 mg/l). The ECG showed sinus rhythm, an incomplete right bundle branch block and signs of left atrial enlargement. Apart from confirmation of the left atrial enlargement the chest X-ray was normal. The right and left ankle/brachial index (ABI) were 1.0 and 0.62, respectively. Magnetic resonance angiography disclosed a completely normal aspect of the abdominal aorta, bilateral iliofemoral arteries and arterial system in the right lower leg. However, the left popliteal artery was completely occluded with filling of the dorsalis pedis and posterior tibial artery by collaterals. Transthoracic echocardiography revealed a giant, left atrial, highly mobile mass attached to the interatrial septum (figure 1). In diastole,

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Figure 1. Transthoracic echocardiography before the first operation: systolic still frame (parasternal long-axis view) showing Ao (aorta), LA (left atrium), LV (left ventricle), RV (right ventricle) and the myxoma (asterisk).

the tumour prolapsed across the mitral valve into the left ventricle causing obstruction of the mitral valve (figure 2). We supposed the peripheral arterial occlusion was due to embolisation of the atrial mass.

With respect to the peripheral arterial occlusion the consulted vascular surgeon advised a conservative approach. The patient was then referred to the thoracic surgeon for removal of the tumour. At surgery, the left atrium was moderately dilated and was filled with a large, gray-white mass with the pedicle of the mass attached to the upper rim of the fossa ovalis. The tumour was removed completely and the subsequent atrial defect was closed by di-

Figure 2. Transthoracic echocardiography before the first operation: diastolic still frame (apical four-chamber view) showing LA (left atrium), LV (left ventricle), RA (right atrium), RV (right ventricle) and the prolapsing myxoma (asterisk) across the mitral valve.

rect suturing. The patient's postoperative recovery was uneventful. Histopathological evaluation disclosed the tumour to be a myxoma.

In 2006, the patient was seen in the outpatient clinic for a routine check-up. All the symptoms present before surgery had disappeared. On transthoracic echocardiography the left atrium was mildly dilated but was otherwise normal. The left-sided ABI had increased from 0.62 to 0.80.

Two years after operation, however, she was admitted to our hospital with complaints of fatigue and pain in the right calf during exertion. At physical examination the only abnormal finding was the absence of pulsations of both dorsalis pedis and posterior tibial arteries. The electrocardiogram was unchanged. The right and left ABI were 0.61 and 0.78 respectively and colour-flow duplex imaging of the lower extremities now showed occlusion of both popliteal arteries. In contrast to transthoracic echocardiography one year before, we could now demonstrate a new tumour attached to the roof of the left atrium (figure 3). Once more, a conservative strategy was advised with respect to the embolic occlusion of the popliteal arteries. The patient was re-operated and at surgery a soft, crumbling tumour with the pedicle of the mass attached to the roof of the left atrium was removed. The defect was closed with a autologous pericardial patch. Myxoma cordis was again confirmed at histopathological examination. The presence of multiple tumours is more frequently seen in familial myxomas in association with the Carney complex. Subsequently, genetic testing was carried out. With sequence analysis the mutation c.423delT was found in the *PRKARIA* gene on chromosome 17q24. This mutation has not been described before and it is unknown whether this mutation will lead to production of an aberrant protein.

Figure 3. Transthoracic echocardiography before the second operation: diastolic still frame (parasternal long-axis view) showing Ao (aorta), LA (left atrium), LV (left ventricle), RV (right ventricle) and the myxoma (asterisk).

Discussion

The incidence of primary cardiac tumours is reported to be between 0.0017 and 0.19% in unselected patients, far less than metastatic tumours to the heart.^{1,2} Three-quarters of the primary tumours are benign and half of them are myxomas. About 75% of cardiac myxomas originate in the left atrium, 15 to 20% in the right atrium and in a minority of patients in one of the ventricles.¹⁻³ Most atrial myxomas arise from the interatrial septum at the border of the fossa ovalis. Approximately 90% of them are sporadic tumours. Myxomas can be diagnosed at all ages; however, 90% of patients are aged between 30 and 60 years with a mean age of 50 years and they are found predominantly in women.^{1,2} Multiple tumours are more commonly seen in familial myxomas.^{2,4} The clinical features of myxomas are determined by their location, size and mobility. Embolism, intracardiac obstruction and constitutional symptoms such as fatigue, erythematous rash, fever, arthralgia and weight loss are the most reported abnormalities.^{1,2,5} Myxomas can cause obstruction of left or right ventricular filling leading to symptoms of dyspnoea due to pulmonary oedema, syncope, sudden death and right-heart failure. Embolic events occur in 30 to 40% of patients and are due to the release of tumour fragments or thrombi from the surface of the myxoma. In the case of left atrial myxomas, emboli affect the cerebral arteries in the majority of cases resulting in stroke.^{1,2} Emboli in peripheral, visceral, renal and coronary arteries can also be found but are less common. Constitutional symptoms most likely result from production of various cytokines (such as interleukin-6) and growth factors by the myxoma.^{6,7}

Echocardiography is the preferred technique for diagnosis.⁸ Surgery is the treatment of choice, showing excellent results with low morbidity and mortality.⁹ Surgical removal should be performed as soon as possible, particularly in patients with embolic events and in cases with multilobular shaped masses since the risk of embolism is also increased in these patients.¹⁰ Recurrence of cardiac myxoma after surgical intervention is rare and is estimated at 0 to 3% in solitary tumours and 12 to 22% in familial forms.^{1,11,12} Familial myxomas may occur as part of the Carney complex, an autosomal dominantly inherited syndrome characterised by spotty skin pigmentation, endocrine tumours (especially adrenocortical disease responsible for Cushing syndrome) and non-endocrine tumours such as myxomas. Incomplete resection is thought to be the main reason for recurrence after surgery for solitary tumours, but intraoperative displacement, embolisation and multifocal tumour precursor cells in the subendocardium are also mentioned as factors for recurrence.^{10,13} In familial myxomas, recurrence after surgery is mostly due to multifocality of aberrant cells. Most of the time recidives are asymptomatic,

they are usually diagnosed during the first four years and in most cases they are detected by echocardiographic follow-up.^{1,12} Echocardiographic studies have calculated the potential tumour growth of myxomas and it is estimated that myxomas can increase 0.15 mm in a month and 18 mm in a year, respectively.¹⁴ Semiannual echocardiographic follow-up studies are therefore indicated after surgical removal of the first tumour.¹

Our patient has a combination of characteristics that are not frequently seen in patients with myxoma cordis. First, although emboli are observed in 30 to 40% of patients with myxomas, stroke is the most predominant event. Nevertheless, before the first and second operation our patient was seen with peripheral emboli in the left and right popliteal artery, respectively. Second, it is advised to repeat echocardiography twice a year after surgery for myxoma. In our patient echocardiographic evaluation was done on a yearly basis. Because of the possibility of recurrences, especially in the first four years, and the potential fast tumour growth in case of recidivism, this case underlines the importance of following the guideline to perform echocardiography every six months. Third, it remains unclear whether the patient had a recurrence of myxoma in connection with the Carney complex. In families with the Carney complex the majority have mutations in the *PRKARIA* gene. Indeed, we found a mutation in the *PRKARIA* gene. However, the mutation c.423delT has not been described before and it is unknown whether this mutation is responsible for production of an aberrant protein. Moreover, we found that the mutation was present in a mosaic pattern; this means that in some tissues the mutation is present in a higher percentage of cells than in other tissues. This finding is in agreement with the fact that no other family members are known with myxoma cordis. Apart from the presence of myxoma no other characteristics of the Carney complex were found in our patient. Additional genetic analysis will now be performed to understand the distribution of this mutation in the different tissues of this patient. Fourth, recurrence of myxoma is not frequently observed after surgery and if present incomplete resection is the main reason in case of solitary myxoma. However, the pedicle of the first tumour was attached to the interatrial septum and the pedicle of the second tumour was attached to the roof of the left atrium. Therefore, if the presence of a solitary myxoma is presumed, other mechanisms such as intraoperative displacement, intracardiac implantation of embolic fragments from the original tumour and the growth of pretumoural cells in another part of the myocardium might have contributed to the development of the second myxoma. However, when Carney complex is present, recurrences are more frequent due to multifocality of aberrant cells.

Conclusion

We describe a patient presenting with systemic embolisation and recurrence of cardiac myxoma after surgery. Recurrence of myxoma is rare after surgery in case of a solitary tumour, but more frequent in patients with a mutation in the *PRKARIA* gene. In this patient we found a mutation in the *PRKARIA* gene that has never been described before. It is uncertain whether this mutation will produce an aberrant protein. Further genetic analysis must be performed to unravel the possible genetic origin of the recurrence of myxoma. ■

References

- 1 Reynen K. Cardiac Myxomas. *N Engl J Med*. 1995;333:1610-7.
- 2 Butany J, Nair V, Naseemuddin A, Nair GM, Catton C, Yau T. Cardiac tumours: diagnosis and management. *Lancet Oncol*. 2005;6:219-28.
- 3 Kuon E, Kreplin M, Weiss W, Dahm JB. The Challenge Presented by Right Atrial Myxoma. *Herz*. 2004;29:702.
- 4 Goswami KC, Shrivastava S, Bahl VK, Saxena A, Machanda SC, Wasir HS. Cardiac myxomas: clinical and echocardiographic profile. *Int J Cardiol*. 1998;63:251-9.
- 5 Keeling IM, Oberwalder P, Anelli-Monti M, Schuchlenz H, Demel U, Tilz GP, et al. Cardiac myxomas: 24 years of experience in 49 patients. *Eur J Cardiothorac Surg*. 2002;22:971.
- 6 Sakamoto H, Sakamaki T, Kanda T, Tsuchiya Y, Sato M, Sato H, Oyama Y, et al. Vascular endothelial growth factor is an autocrine growth factor for cardiac myxoma cells. *Circ J*. 2004;68:488.
- 7 Seino Y, Ikeda U, Shinada K. Increased expression of interleukin-6 mRNA in cardiac myxomas. *Br Heart J*. 1993;69:565.
- 8 Bhan A, Mehrotra R, Choudhary SK, Sharma R, Prabhakar D, Airan B, et al. Surgical experience with intracardiac myxomas: Long-term follow-up. *Ann Thorac Surg*. 1998;66:810.
- 9 Kajihara N, Tanoue Y, Eto M, Tomita Y, Masuda M, Morita S. Surgical experience of cardiac tumors: early and late results. *Surg Today*. 2006;36:602-7.
- 10 Yu SH, Lim SH, Hong YS, Yoo KJ, Chang BC, Kang MS. Clinical experiences of cardiac myxoma. *Yonsei Med J*. 2006;47:367-71.
- 11 Centofanti P, Di Rosa E, Deorsola L, Dato GM, Patane F, La Torre M, et al. Primary cardiac tumors: early and late results of surgical treatment in 91 patients. *Ann Thorac Surg*. 1999;68:1236-41.
- 12 Herman K, Jaarsma W, Plokker HWM, Cramer MJM, Morshuis WJ. Four cardiac myxomas diagnosed three times in one patient. *Eur J Echocardiography*. 2003;4:336-8.
- 13 Mendoza C, Bernstein E, Ferreira A. Multiple recurrences of nonfamilial cardiac myxomas: a report of two cases. *Texas Heart Inst J*. 2007;34:236-9.
- 14 Malekzadeh S, Roberts WC. Growth rate of left atrial myxoma. *Am J Cardiol*. 1998;64:1175-6.