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CASE REPORT
Cardiovascular imaging

The challenging approach of a young patient with a primary intimal sarcoma of the heart: a case report

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Background Primary intimal sarcomas of the heart are extremely rare and have a dismal prognosis. Their management represents a complex clinical challenge since complete surgical resection is the only reliable possibility of cure but is only possible in 50% of patients. In non-resectable disease, anthracycline-based therapy is the most effective treatment, but pazopanib may be used in patients unfit to receive anthracyclines.

Case summary A 38-year-old man presented with acute right heart failure symptoms due to a primary intimal sarcoma of the heart. A definite diagnosis was made after cardiac surgery. Multi-modality cardiac imaging showed early recurrence of disease with mitral valve and pulmonary veins' invasion, and the patient was deemed inoperable. Due to chronic kidney disease and previous heart failure symptoms, he was started on first-line pazopanib palliative treatment. After 11 months of chemotherapy, there was good clinical tolerance and no evidence of disease progression, which occurred after 13 months.

Discussion This case highlights the value of a multi-modality imaging approach for cardiac masses. Most importantly, it reports the successful treatment of a young patient with a primary intimal sarcoma of the heart who was started on palliative pazopanib, with a significantly higher progression-free survival than is reported in the literature. This finding may support pazopanib as a good alternative as first-line treatment when there is contraindication for anthracycline-based chemotherapy.

Keywords Case report • Intimal sarcoma • Multi-modality imaging • Pazopanib

ESC curriculum 2.2 Echocardiography • 2.3 Cardiac magnetic resonance • 2.4 Cardiac computed tomography • 6.8 Cardiac tumours • 7.5 Cardiac surgery

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Learning points

- Primary intimal sarcoma of the heart is an extremely rare disease that affects young patients and is associated with a very poor prognosis when complete surgical resection is not achieved.
- A multi-modality imaging approach is essential to establish the diagnosis of cardiac masses and assess organ involvement, to further decide on the best therapeutic strategy.
- Pazopanib may be suitable as a first-line treatment, when anthracycline-based therapy is contraindicated.
- Complete surgical resection of the masses remains the only curative treatment, so heart transplantation and auto-transplantation are increasingly mentioned as possible alternatives.

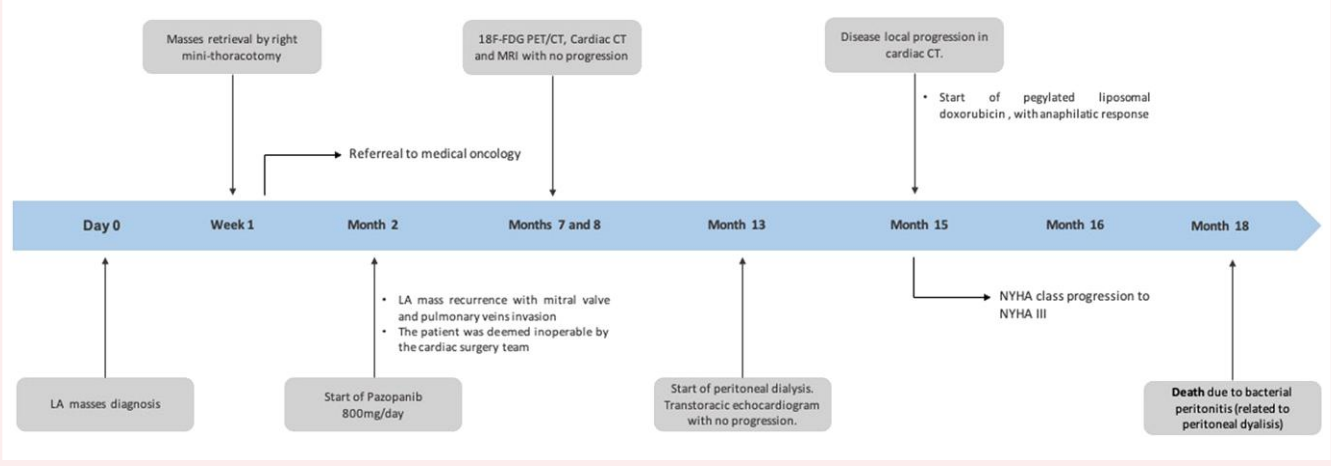
Introduction

Primary cardiac tumours are extremely rare but an important cause of morbidity and mortality.[1] Although only a minority of these neoplasms are malignant,[2] they behave very aggressively and have a poor prognosis.[3] This makes early diagnosis and treatment crucial to improve patients' survival.[3]

Intimal sarcomas are rare, poorly differentiated mesenchymal neoplasms that commonly arise in large arterial blood vessels or in the pulmonary veins but less frequently involve the heart.[4] They are differentiated from other sarcomas by the characteristic pathological feature of MDM2 gene amplification in immunohistochemistry.[5,6] They usually present between the third and fifth decade of life and have an estimated median survival rate of only 3–13 months due to rapid growth and early metastasis.[2,6–8] Hence, their management represents a complex clinical challenge. Although possible in less than 50% of patients due to vital structures' involvement, complete surgical resection with microscopically negative margins (R0) is the only reliable possibility of cure because of poor response to chemotherapy, whether adjuvant after incomplete surgical resection or alone.[7–9] However, in non-resectable disease, anthracycline-based therapy is the most effective treatment for intimal sarcoma (as monotherapy or combined with ifosfamide).[5,10,11] Although pazopanib (a second-generation tyrosine kinase inhibitor that targets the angiogenesis pathway) does not have enough evidence to be recommended as first-line treatment, it can be used in second-line treatment or in those unfit to receive anthracyclines.[5]

With this clinical case, the authors intend to show a very challenging approach of a young patient with a rare, highly aggressive disease. Prompt thorough investigation based on a multi-modality imaging approach and early management by a multi-disciplinary team are essential to perform the diagnosis and guide therapeutic decisions.

Summary figure



Case presentation

A 38-year-old Caucasian man, with chronic kidney disease (CKD) due to IgA nephropathy under systemic glucocorticoid therapy (glomerular filtration rate of 30 mL/min/1.72 m^2), was admitted to the Cardiology Department with right heart failure (HF) symptoms. The patient reported a few months of history of progressive worsening effort-related breathlessness and fatigue (New York Heart Association class II). There was no history of consumptive symptoms, such as weight loss, fever, or night sweating. On admission, he was haemodynamically stable (arterial pressure 116/89 mmHg), had sinus tachycardia (102 b.p.m.), and had a peripheral oxygen saturation of 99% on room air.

Transthoracic and transoesophageal echocardiograms were compatible with three hyperechogenic left atrial (LA) masses, the largest one (42 × 29 × 26 mm) protruding to the left ventricle in diastole, causing severe mitral stenosis, moderate mitral regurgitation, and a high probability of pulmonary hypertension with right ventricular (RV) dysfunction (estimated pulmonary artery systolic pressure of 67 mmHg) (*Figure 1*; Supplementary material online, *Videos S1* and *S2*). N-terminal pro b-type natriuretic peptide (NT-pro-BNP) was 22 397 ng/L. Due to the clinical presentation and imaging characteristics, there was a very high suspicion of obstructive atrial myxoma, and in addition to intravenous furosemide, the patient was urgently referred to surgical resection of the masses without performing any further imaging methods.

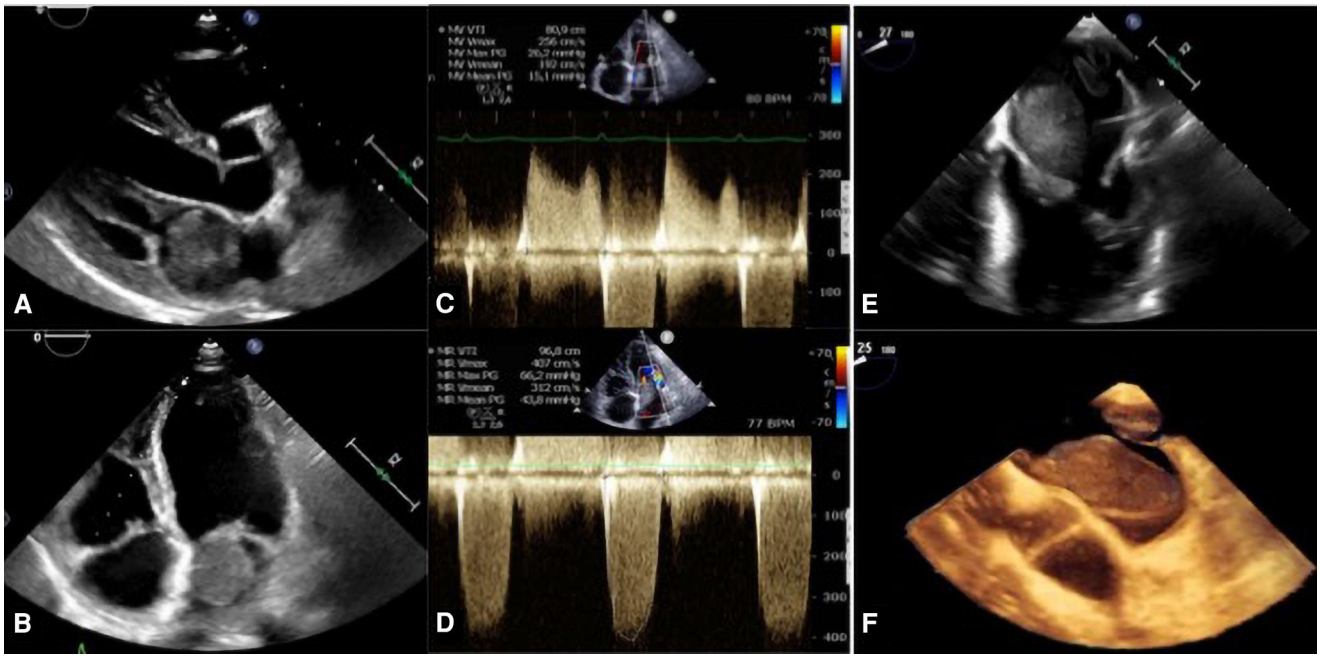


Figure 1 Pre-surgery transthoracic echocardiogram (*A*–*D*) and transoesophagic echocardiogram (*E* and *F*) showing three iso-echogenic regular shaped left atrial masses, the larger with 42 × 29 × 26 mm apparently attached to the inferior portion of the inter-atrial septum and protruding into the left ventricle in diastole. This mass causes severe obstruction to the left ventricular filling (*C*) with mean gradient of 15 mmHg and mitral valve area by pressure half-time of 0.83 cm^2 and also impaired mitral leaflets coaptation with at least moderate mitral regurgitation around the mass (lateral vena contracta of 6.6 mm) (*D*). There was also high probability of pulmonary hypertension and right ventricular dysfunction: peak tricuspid regurgitation velocity of 4.0 m/s (mean right ventricle/right atrium gradient of 64 mmHg), pulmonary artery dilation (diameter of 33 mm), right ventricular outflow tract acceleration time of 84 ms, systolic and diastolic D shape of left ventricular and right ventricular dilation (basal diameter of 41.2 mm), hypertrophy (free wall of 6.5 mm), and dysfunction (fractional area change 14%, tricuspid annular plane systolic excursion 16 mm).

Surgery was performed through a right anterior mini-thoracotomy and histopathology of the retrieved masses revealed a predominantly hypercellular neoplasm full of spindle, ovoid, and epithelioid cells in a myxoid stroma, as well as nuclear pleomorphism and images of necrosis. There was a high mitotic count with up to 20 mitosis/10 high magnetic fields. Immunohistochemistry and fluorescent *in situ* hybridization detected the MDM2 gene amplification in 77% of the analysed nuclei and were negative for other histological sarcoma types (CKAE1/AE2, CDK4, S100, CD34, smooth muscle actin, desmin, myogenin, caldesmon, ERG, Fli-1, CD31, and CD99). Tumour infiltrated the myocardium and margins were not evaluated due to sample fragmentation. Considering these features, the patient was diagnosed with a primary intra-cardiac intimal sarcoma, pT1G3 according to FNCLCC (Fédération Nationale des Centres de Lutte Contre le Cancer)—pT1 (tumour size—organ confined), G3 (histological Grade 3 according to total differentiation, high mitotic count, and extent of necrosis).

Following the diagnosis of a primary cardiac tumour, the patient was referred to the Medical Oncology Department. Early local recurrence with a large LA mass with mitral valve, LA appendage, and pulmonary veins infiltration was diagnosed only 2 months after surgery on echocardiogram, positron emission tomography (PET)/computed tomography (CT)-18F-fluoro-2-deoxy-D-glucose (18F-FDG), cardiac CT, and cardiac magnetic resonance (CMR) (*Figures 2* and *3*). Staging with thoraco-abdominal-pelvic CT excluded metastatic disease, although PET/CT-18F-FDG showed a hypercaptant site in the right fifth rib.

Despite remaining asymptomatic and with an ECOG performance status 1, the patient was deemed inoperable due to local structures' invasion and was proposed to first-line palliative treatment. Due to CKD and previous HF, chemotherapy with pazopanib was preferred over ifosfamide and doxorubicin. The patient was started on pazopanib 800 mg/day, with good clinical tolerance and stable disease for 13 months (cardiac mass stabilization and reduced captation in follow-up PET/CT). He died 18 months after the diagnosis.

Discussion

This case represents a very rare case of a young patient with primary intimal sarcoma of the heart and highlights several clinical challenges in the management of these patients.

First, diagnosis of cardiac masses is demanding and a thorough multimodality imaging approach is essential to define the best therapeutic strategy. Echocardiography is the first-line imaging technique to diagnose cardiac masses and assess their location and functional impact.[2] Although echocardiography and three-dimensional echocardiography showed some very characteristic features of myxoma, such as the regular-shaped masses and the apparent attachment to the inter-atrial septum, the authors acknowledge the importance of other imaging modalities to further characterize cardiac tumours, namely cardiac CT and CMR, and that in this case, their prior execution before surgery could

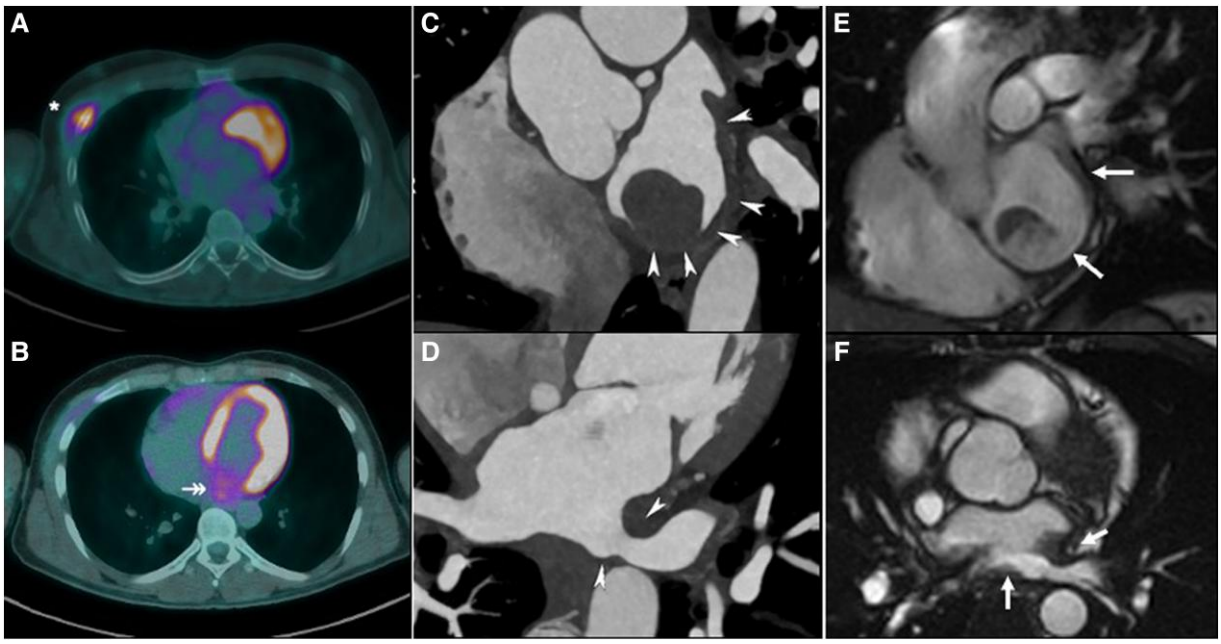


Figure 2 Multi-modality imaging of left atrial mass recurrence. *A* and *B* show hypercaptation in the myocardium, in the left atrial (*B*, double-pointed arrow) and also in the fifth left rib (*A*, asterisk) with soft tissue involvement (SUV_{max} of 5) in positron emission tomography/computed tomography-18F-fluoro-2-deoxy-D-glucose. *C* and *D* correspond to cardiac computed tomography images, revealing posterior left atrial wall and mitral leaflet invasion (*C*, arrowheads) and also contiguity to the pulmonary left veins' ostia (*D*, arrowheads). Cardiac magnetic resonance images are in accordance (*E* and *F*, respectively, arrows).

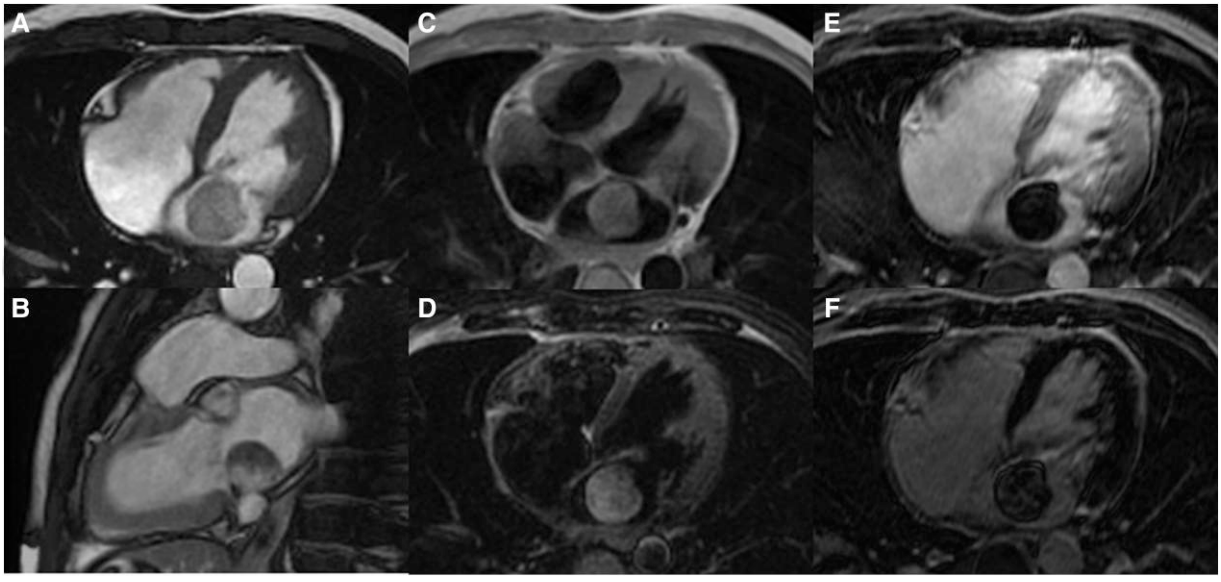


Figure 3 Cardiac magnetic resonance characterization of the mass, showing heterogenicity in most images due to its heterogeneous nature: iso-intense and heterogeneous mass in cine steady-state free-procession (SSFP) images (*A* and *B*); iso-intense in T1-weighted images (*C*); hyper-intense and heterogeneous in T2-weighted images (*D*); hypo-intense signal in early gadolinium enhancement images (*E*); heterogeneously enhanced in late gadolinium enhancement images (*F*).

have altered the surgical strategy used. In fact, CMR is the modality of choice for the assessment of cardiac masses, since it can be used to predict the likelihood of malignancy by tissue characterization.[1,2] Cardiac CT is very useful to look for calcified masses and analyse other structure involvement, such as mitral valve and pulmonary veins infiltration.[2] Positron emission tomography/CT is the method of choice to detect post-surgery local recurrence or distant metastasis.[2] All these methods are essential for patient follow-up since they significantly increase the sensitivity of detecting disease recurrence or local progression, as was also revealed by our case.[2] Although data on the best follow-up routine after surgery are scarce, in high-grade patients, imaging exams may be done every 3–4 months in localized or every 2–3 months in metastatic disease.[11]

The second main obstacle for the diagnosis of cardiac masses is the difficulty in obtaining a pre-operative histological sample—this is particularly true for left cardiac masses.[9] Hence, surgery often plays both a diagnostic and therapeutic role.[12] However, complete surgical resection is very often impracticable through conventional approaches because of accessibility and anatomic issues, such as the local invasion of vital structures.[9] This raises a particular concern, since complete surgical resection is the most effective treatment and the only proved to significantly improve survival.[6–9] Aggressive neoadjuvant chemotherapy with doxorubicin-based regimens may reduce the mass size and help in the surgical approach, but it does not seem to impact overall survival.[9] Therefore, heart transplantation has been proposed to improve margin-free rates (R0),[6,8] but evidence of clinical benefit is still scarce and controversial. Furthermore, due to the lack of organ availability and the risks of immunosuppression, auto-transplantation has been proposed as an alternative to overcome the technical difficulties of left-sided tumour resection.[9]

Finally, this case also represents the difficulties in the real-world clinical practice for choosing the best medical treatment. Although the first-line chemotherapy is based on anthracyclines, with or without ifosfamide, this regimen was considered unsuitable for several reasons. On one hand, the clinical presentation with HF symptoms, RV dysfunction, and the very early recurrence of a large LA mass significantly increased the inherent risk of irreversible myocardial injury caused by both drugs. Additionally, their cardiotoxic potential included the risk of acute HF and tachyarrhythmias, which was enhanced by the pre- and post-hydration regimen required during drug administration (approximately 3 L of fluid therapy). Also, the anthracycline gastrointestinal toxicity increased the risk of worsening kidney disease and progression to dialysis. Finally, severe CKD is a contraindication for the use of ifosfamide. Hence, considering pazopanib results as a second-line and further treatment in the PALLETE trial for soft tissue sarcomas,[10] it seemed a very reliable alternative with a manageable toxicity profile. After failure of standard first-line chemotherapy with anthracyclines, pazopanib showed a median progression-free and overall survival of 4.6 and 12.5 months, respectively.[10] These times were similar when pazopanib was used as a first-line therapy in elderly patients or in patients who were unfit for anthracyclines.[5,13] Taking this into consideration and against what was expected, this patient showed a significantly higher progression-free survival and overall survival times under pazopanib.

In summary, this case highlights the value of a multi-modality imaging approach for the diagnosis of cardiac masses and especially for the follow-up after surgery. Most importantly, it reports the treatment of a young patient with a primary intimal sarcoma of the heart who was started on palliative treatment with a second-line therapeutic agent, with a good clinical response and a higher progression-free survival than is reported in the literature. This finding may support pazopanib as a good alternative as first-line treatment when there is contraindication for anthracycline-based chemotherapy.

Lead author biography

Mariana Martinho is a cardiology resident in Hospital Garcia de Orta, Almada, Portugal. She has an active research interest in general cardiology and particularly in interventional cardiology.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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