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CASE REPORT

Primary undifferentiated pleomorphic cardiac sarcoma with *MDM2* amplification presenting as acute left-sided heart failure

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SUMMARY

Primary cardiac tumours are a rare clinical entity that can present with myriad of non-specific cardiopulmonary symptoms. We describe a case of a 61-year-old previously healthy woman who presented with progressive dyspnoea and lower extremity swelling, suggestive of acute left-sided heart failure. Transthoracic echocardiogram revealed a large, 3.7×3.2 cm intracardiac mass resulting in severe mitral valvular dysfunction. The patient underwent surgical resection of the mass, however, negative margins were not obtained, and the tumour quickly returned. Histological and molecular analysis was consistent with the diagnosis of undifferentiated pleomorphic sarcoma with murine double minute 2 (*MDM2*) amplification. Given the overall grim prognosis, the patient chose to pursue comfort-based care. She died at home 9 months after the initial diagnosis. Here, we provide an updated review of the literature for the classification of undifferentiated pleomorphic cardiac sarcoma and potential treatment modalities.

BACKGROUND

Primary cardiac tumours are a rare clinical entity. Depending on the exact location, they can present with a variety of cardiopulmonary symptoms, such as left- or right-sided heart failure, embolic phenomena or conduction abnormalities. The majority of cardiac tumours, approximately 75%, are benign myxomas. These typically arise from the left atrium causing mitral valve dysfunction and subsequent left-sided heart failure.[1–3] If the tumour is localised and non-invasive, resection is often curative. Cardiac sarcomas, however, are high grade, clinically aggressive neoplasms associated with a poor clinical prognosis. These tumours account for only 10%–20% of all primary cardiac neoplasms and can be further subdivided according to histological features.[4]

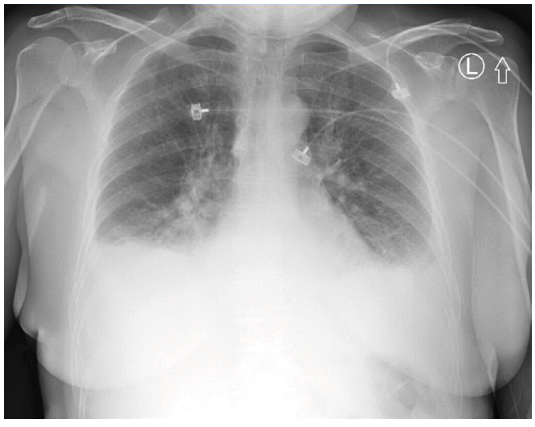

Figure 1 Initial chest X-ray showed moderate-sized bilateral pleural effusions.

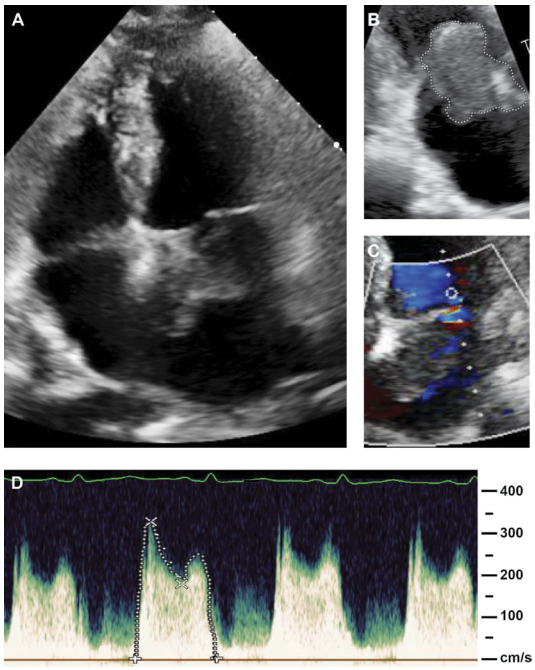

Figure 2 (A)–(C) Initial transthoracic echocardiogram demonstrated a 3.7×3.2 cm lobulated mass attached to the right trigone causing mitral stenosis and mitral regurgitation. (D) This was quantified using Doppler waveform. Severe mitral stenosis was defined by mitral valve area by pressure half time (P1/2T) of 1.7 cm^2. Moderate mitral regurgitation was defined by peak and mean transmitral pressure gradient of 43 and 21 mm Hg, respectively. Severe pulmonary hypertension (pulmonary artery (PA) pressure of 77 mm Hg) and severe tricuspid regurgitation right ventricle/right atrium (RV/RA pressure gradient of 69 mm Hg) were also noted (data not shown).

CASE PRESENTATION

A 61-year-old previously healthy woman presented with a 2-week history of progressive shortness of breath, non-productive cough and lower extremity swelling. On initial evaluation, she was found to be

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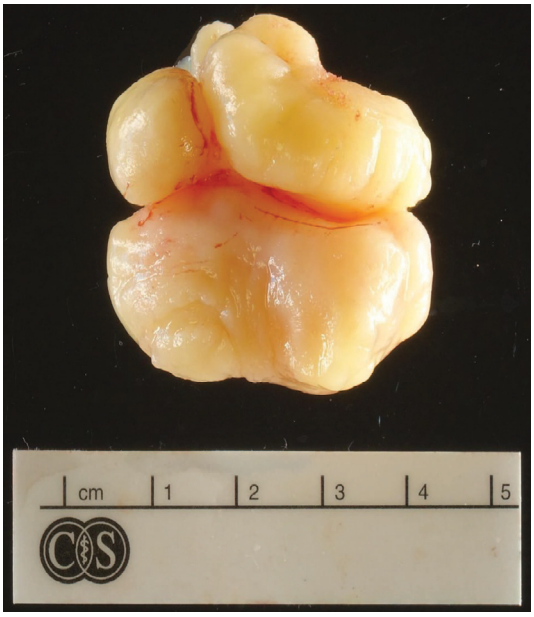
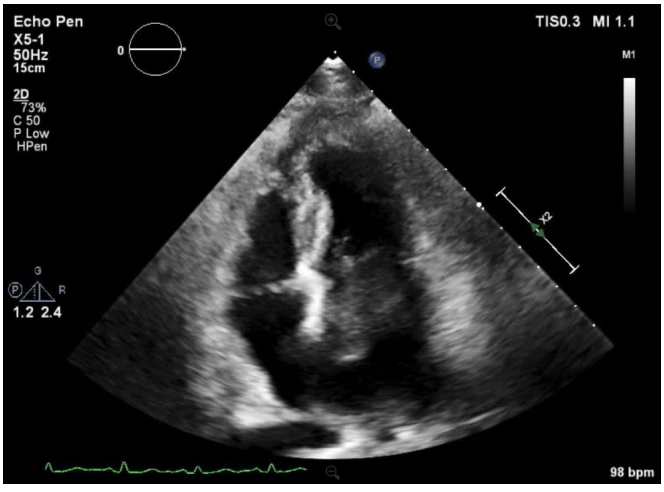


Figure 3 Gross photograph highlighting a 4.5×4.0×2.2 cm left atrial mass overlying right fibrous trigone of mitral valve.

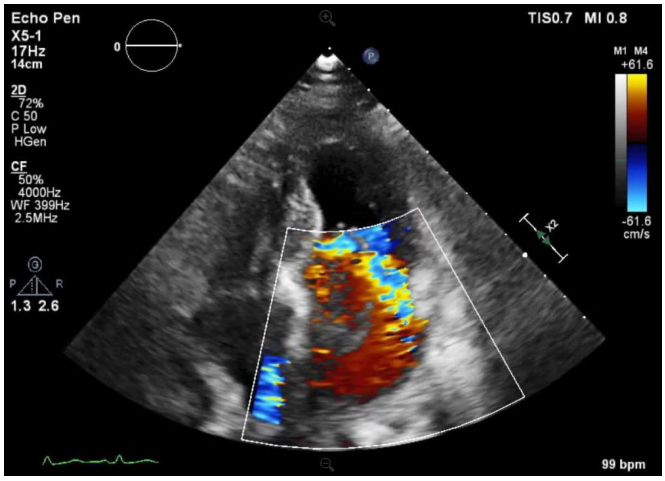
tachycardic (114 beats per min), tachypneic (28 breaths per min) and hypoxaemic on room air (88% SaO_2). Physical examination was notable for jugular venous distention, bibasilar crackles, bilateral lower extremity pitting oedema and an apical holosystolic murmur with a mid-diastolic click.

INVESTIGATIONS

Full laboratory analysis, including cardiac biomarkers, was notable only for a mildly elevated B-type natriuretic peptide (179 pg/mL, reference <100 pg/mL) and an elevated D-dimer (1.9 µg/mL fibrinogen equivalent units (FEU), reference <0.70 µg/mL FEU). ECG showed sinus tachycardia without ischaemic changes. Chest X-ray revealed moderate-sized bilateral pleural effusions (figure 1). Given the high D-dimer, a CT angiogram was obtained. This revealed a right middle lobe subsegmental pulmonary embolism and a large, amorphous filling defect in the left atrium, initially thought to be an atrial



Video 1 Transthoracic echocardiogram apical four-chamber view demonstrating a large mass attached to interatrial septum obstructing flow through the mitral valve.



Video 2 Transthoracic echocardiogram apical four-chamber view with two-dimensional colour Doppler showing severe mitral stenosis and moderate mitral regurgitation resulting from large intracardiac mass.

thrombus. Subsequently, transthoracic echocardiogram (TTE) demonstrated a 3.7×3.2 cm lobulated mass attached to the interatrial wall, causing severe mitral valve dysfunction. A normal left ventricular ejection fraction (67%), severe pulmonary hypertension (pulmonary artery pressure 77 mm Hg) and severe tricuspid regurgitation were also noted (figure 2, videos 1,2).

TREATMENT

The patient was diuresed and underwent bilateral thoracenteses, with prompt symptomatic improvement. She was taken for urgent surgical resection. Intraoperatively, the mass was found to extend from the left atrium, through the interatrial septum, into the right atrium and tricuspid valve. The tumour was debulked, but it was not possible to obtain negative surgical margins due to the extent of invasion into multiple chambers of the heart (figure 3). Histological analysis revealed a high-grade, undifferentiated sarcoma with areas of myxoid differentiation and epithelioid appearing cells. Varying amounts of spindle formation, nuclear atypia, pleomorphism and mitotic figures were also noted (figure 4A–C). Immunohistochemical (IHC) analysis demonstrated desmin positivity, however, other myocyte markers including α-smooth muscle actin, h-caldesmon, myogenin and myoD1 were negative (figure 4D, E). Furthermore, fluorescence in situ hybridisation (FISH) molecular analysis demonstrated amplification of the murine double minute 2 (*MDM2*) oncogene, supporting the diagnosis of undifferentiated sarcoma (figure 5).

After surgical debulking, the patient's symptoms were greatly improved. Repeat TTE showed only residual mild mitral regurgitation without mitral stenosis or elevated pulmonary pressures. After extensive discussions with oncology, the patient deferred adjuvant chemotherapy and radiation.

OUTCOME AND FOLLOW-UP

While the patient initially did well, her symptoms eventually returned, and she was readmitted 6 months later. Repeat TTE showed a new mass, measuring 4.3×2.8 cm, attached to the interatrial septum prolapsing through the mitral annulus. She was medically stabilised and discharged with the plan for palliative anthracycline-based outpatient chemotherapy. Over the following 3 months, she was hospitalised three additional times for symptomatic exacerbations. Serial TTEs demonstrated continued enlargement of the left atrial mass, growing

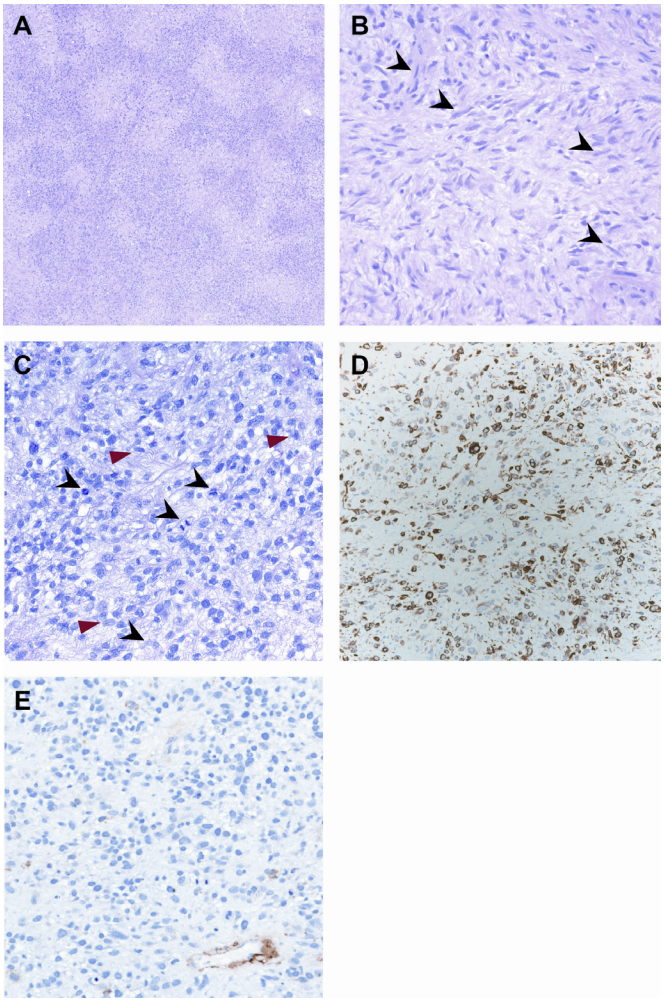


Figure 4 (A) H&E stained sections at low power showed tumour with areas of cellularity and myxoid background. (B) On high power, areas of spindle cell formation can be observed (black arrowheads). (C) Additionally, there are regions of epithelioid appearing cells (red arrowheads) with varying amounts of atypia and pleomorphism. Prominent atypical mitotic figures are also present (black arrowheads). (D) and (E) Immunohistochemical studies depicted strong desmin positivity with a lack of immunoreactivity in other myogenic markers, such as α-smooth muscle actin.

up to 8×3 cm, with the development of a new right atrial mass (2.6×2.1 cm, figure 6). Given the extent of disease, the patient was not a surgical candidate for further procedures. She was discharged with supportive measures, forgoing optional palliative chemotherapy. She died peacefully at home, approximately 9 months after her initial diagnosis.

DISCUSSION

Primary cardiac sarcomas are rare clinical phenomena. The prevalence of primary cardiac tumours has been estimated to be approximately 0.02% (200 tumours per one million people). This is based on a collection of several autopsy series, as the majority of tumours are incidentally found postmortem.[5] Of all primary cardiac tumours, cardiac sarcomas account for only 10%–20% of cases.[4] These malignancies can arise from the mesenchymal cells of the ventricles, atria or pericardium depending on the specific subtype.

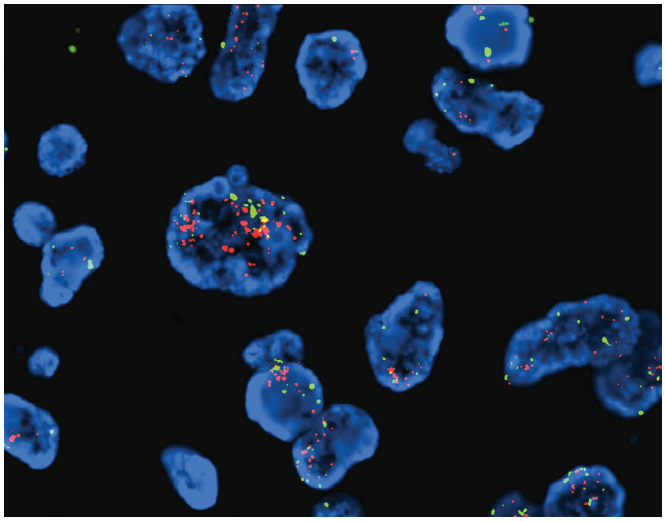


Figure 5 Dual colour fluorescence in situ hybridisation with probes specific for the murine double minute 2 (*MDM2*) locus at 12p15 demonstrating amplification of the orange (3' *MDM2*) signal relative to the control green chromosome enumeration probe (CEP) at a ratio of 2.4 in 20 cells examined.

The WHO has established a universal classification system for cardiac tumours. The 2004 version identified six subtypes of cardiac sarcomas based on histopathological morphology.[6] High-grade myofibroblastic sarcomas with spindle formation were classified as pleomorphic malignant fibrous histiocytoma (MFH); later to be referred to as undifferentiated pleomorphic sarcoma (UPS).[7 8] IHC analysis of MFH/UPS is often negative for specific lineage markers, but these tumours can express desmin, vimentin and α-smooth muscle actin to varying degrees.[7 9] Given the lack of disease-specific markers, the reported frequency of MFH/UPS has varied greatly from less than 10% to over 70% of

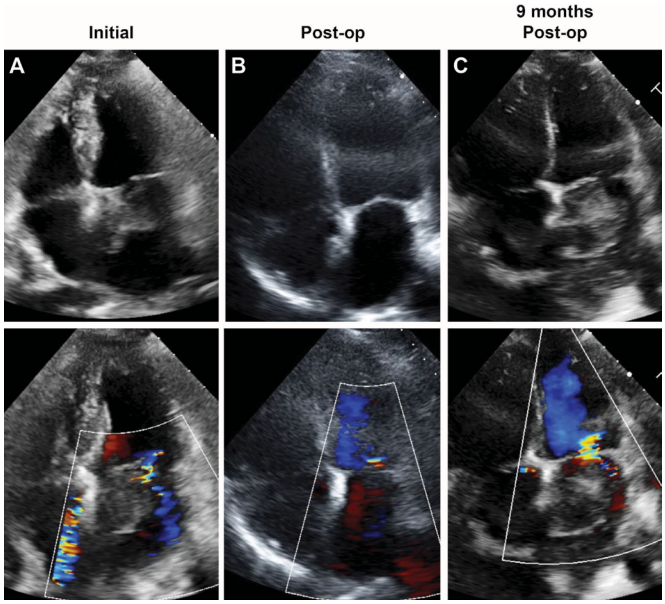


Figure 6 (A) Initial transthoracic echocardiogram (TTE) showed a large left atrial mass (top) with mitral regurgitation (bottom). (B) Postoperative TTE demonstrated resection of mass (top) with significant improvement of mitral regurgitation (bottom). (C) TTE 6 months postoperatively depicted recurrence of left atrial mass (top) and subsequent mitral regurgitation (bottom).

all cardiac sarcomas, depending on the histopathological criteria used for classification.[10 11]

In 2014, Neuville *et al* performed a retrospective analysis of 100 cardiac sarcoma samples in attempt to identify unique molecular markers for the different subtypes.[9] They concluded that the most common type of cardiac sarcoma was intimal sarcoma (42%). Histologically, they described these as high-grade myofibroblastic neoplasms with spindled morphology (similar to the WHO description of MFH/UPS). By molecular analysis, they showed that 100% of these tumours demonstrated amplification of the oncogene *MDM2*, as determined by FISH. *MDM2* protein overexpression was then confirmed using IHC. From this, they classified sarcomas with similar histology, in the absence of *MDM2* amplification, as undifferentiated sarcoma (22%).

The term cardiac intimal sarcoma was used in reference to previous studies that showed the majority of pulmonary artery intimal sarcomas displayed *MDM2* amplification.[12 13] Traditionally, the term intimal sarcoma refers specifically to tumours arising from the inner endothelial lining of the great vessels; intima meaning innermost. Clinically, these tumours invade the vascular lumen and present with embolic phenomena, compared with cardiac sarcomas which invade the atria and ventricles, resulting in heart failure.[14] Given this, the updated 2015 WHO guidelines eliminated the term intimal sarcoma in reference to cardiac tumours.[15] It was concluded that due to the lack of specificity for molecular testing (such as *MDM2* amplification), the classification of cardiac sarcomas should be based on histological morphology alone. Thus, the title of UPS with or without *MDM2* amplification is more suitable for these types of tumours.[16]

The prognosis of cardiac sarcomas is overall very poor; median survival is less than 1 year.[17] Surgical resection followed by adjuvant chemotherapy, with or without radiation, is the current standard of care. A recent retrospective review of 124 cases showed that complete resection increased median survival by 7 months (11.2 vs 18.2 months), compared with non-resected patients.[18] However, given the highly invasive nature of these tumours, clear surgical margins are difficult to obtain, and the tumours can easily recur. Due to the rarity of cardiac sarcomas, no randomised clinical trial has been performed to identify an optimal chemotherapy regimen. Current treatment modalities are extrapolative, based on protocols for extracardiac sarcomas, including doxorubicin with ifosfamide and gemcitabine with or without docetaxel.[19–21]

The advent of molecular analysis and targeted therapy may offer some promise. On the molecular level, *MDM2* regulates the cell cycle by inhibiting the tumour suppressor p53, through ubiquitin-mediated degradation and transcriptional suppression. When upregulated, *MDM2* results in aberrant cellular proliferation.[22] In recent years, a number of small molecule inhibitors of *MDM2* have been developed which function to stabilise p53 activity. One such *MDM2* inhibitor, nutlin-3a, has been shown to be efficacious in haematological malignancies, such as B-cell chronic lymphocytic leukaemia and acute myeloid leukaemia.[23 24] Another compound, RG7112, has been proven beneficial in dedifferentiated liposarcoma.[25] Finally, due to the central role of p53 in tumourigenesis, there are a number of novel strategies targeting this critical signalling pathway, such as tumour vaccination, microRNAs, oncolytic viruses and immunotherapy.[22]

Learning points

- Primary cardiac tumours are a rare clinical entity. Depending on the exact location, they can present with a variety of cardiopulmonary symptoms, such as left- or right-sided heart failure, embolic phenomena or conduction abnormalities.
- The majority of primary cardiac tumours, approximately 75%, are benign myxomas, for which surgical resection can be curative.
- Cardiac sarcomas account for only 10%–20% of all primary cardiac tumours. These are characterised as aggressive, highly invasive malignancies that carry a poor clinical prognosis, with median survival of less than 1 year.
- There are multiple subtypes of cardiac sarcomas classified by unique histopathological features. Additional genetic and molecular testing, such as immunohistochemical and fluorescence in situ hybridisation, can help further to guide diagnosis.
- Undifferentiated pleomorphic sarcoma (UPS) is histologically characterised as a high-grade myofibroblastic sarcoma with variable degrees of spindle formation, nuclear pleomorphism, atypia and mitotic figures. On a molecular level, UPS can be seen with or without murine double minute 2 amplification.

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