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A case of metastatic primary cardiac angiosarcoma

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Abstract

We report a 49-year-old Southeast Asian woman diagnosed with metastatic primary right atrial angiosarcoma (PCA) and the difficulties encountered in this diagnosis and its subsequent management. Diagnosis of PCA is often delayed due to non-specific clinical presentation of patients. These tumours often present once metastatic spread has occurred, restricting treatment options and leading to very poor prognosis. Patients undergo a multidisciplinary team (MDT) approach involving chemotherapy, radiotherapy and, if eligible, surgery, but evidence-based treatment guidelines have yet to be established due to the rarity of the tumour.

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Introduction

Angiosarcomas are rare aggressive malignancies formed from the inner lining of blood vessels. Primary malignant tumours of the heart are extremely rare, of which angiosarcomas are the most common in adults.[1] Diagnosis of PCA is often delayed due to non-specific clinical presentation, and can sometimes be missed altogether, only being diagnosed at autopsy.[2] At the time of diagnosis, up to 75% of patients have systemic metastases, restricting treatment options and leading to very poor prognosis with a median survival of three to six months.[3] Therefore a high degree of clinical suspicion and sensitive investigations are crucial for diagnosis.[4]

Current management of patients with PCA is an MDT approach involving a combination of chemotherapy, radiotherapy and, if the disease is localised, radical surgery. However, specific evidence-based treatment guidelines have yet to be established due to the rarity of the tumour.[4]

In this paper we report the case of a 49-year-old Southeast Asian woman with a delayed diagnosis of metastatic primary right atrial angiosarcoma and the difficulties encountered in this diagnosis and its subsequent management. Patient survival from the initial presentation to death was seven months. Literature surrounding PCAs is then critically reviewed.

Case presentation

A 49-year-old woman from China presented with new pleuritic chest pain, one month of exertional dyspnoea and three months of cough, poor appetite and night sweats. Prior to that, she was fit and well. On examination the patient was tachypnoeic and tachycardic, and there were bi-basal crackles and a pericardial rub on the chest and precordial auscultation. Blood tests showed normocytic anaemia (haemoglobin 92 g/l), raised C-reactive protein (199 mg/l) and alkaline phosphatase (291 u/l). Troponin-T was marginally elevated (12 ng/l). An electrocardiogram demonstrated sinus tachycardia and a chest X-ray showed a globular heart. A transthoracic echocardiogram showed a small volume pericardial effusion and echodense mass adjacent to the right atrium (RA) and right ventricle (RV) free wall (Figure 1). Left ventricular function was normal with an ejection fraction over 55%. The suspected diagnosis was pericarditis, treated with ibuprofen, although its cause was still undetermined.

Due to patient symptoms, previous travel to China and pericardial mass, it was felt the patient was at high risk of pericardial tuberculosis and she was admitted to the infectious diseases ward. Sputum for acid-fast bacilli and a QuantiFERON-TB Gold blood test were sent, which were both negative. A computerised tomography (CT) scan of the chest, abdomen and pelvis showed extensive bilateral miliary pulmonary lesions, a large right renal mass, multiple liver lesions and pericardial enhancement. A hypervascular

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Figure 1 Transthoracic echocardiography, subcostal view. Subcostal view of conventional two-dimensional transthoracic echocardiogram at initial presentation shows a small volume pericardial effusion (1.3 cm) and an echodense cardiac mass adjacent to the right atrium/right ventricle free wall. RA: right atrium, RV: right ventricle, LA: left atrium, LV: left ventricle, red arrows: pericardial mass

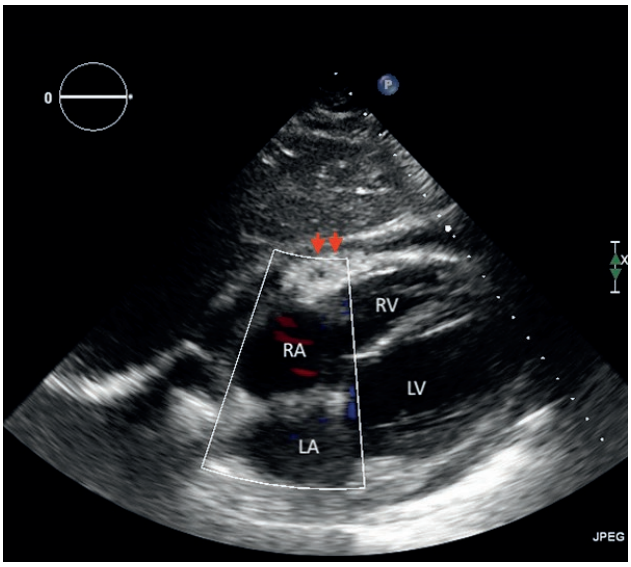
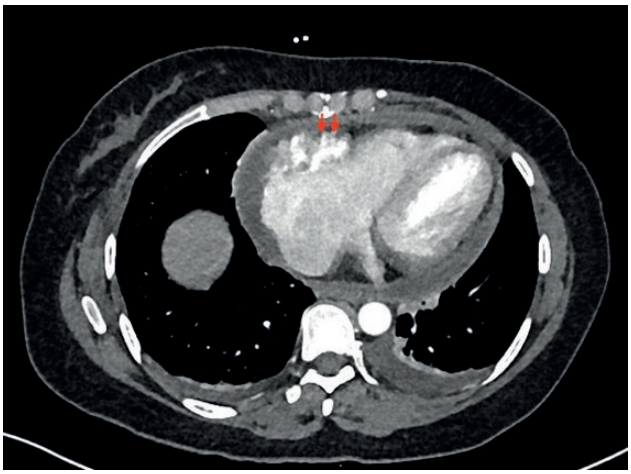


Figure 2 Computerised tomography of chest abdomen pelvis with contrast. Transverse section of chest tomography at initial presentation demonstrates a hypervascular pericardial mass (red arrows) arising from the right atrium and right atrioventricular groove measuring 55 mm × 25 mm with associated pericardial effusion. There are also extensive bilateral miliary pulmonary lesions and small bilateral pleural effusions. No mediastinal or axillary lymphadenopathy was seen. The abdominal images not viewed here showed multiple indeterminate liver lesions and a large right lower pole renal mass consistent with an incidental renal cell carcinoma radiologically (43 × 38 mm). Reported as consistent with extensive tuberculosis and incidental renal cell carcinoma. Red arrows: pericardial mass



pericardial mass of 55×25 mm was noted in the right atrioventricular groove (Figure 2). Due to the CT findings, an initial diagnosis of extensive miliary tuberculosis with an incidental renal cell carcinoma was made. The patient was started on quadruple antituberculous therapy and high-dose steroids.

Due to the pericardial thickening and risk of constrictive pericarditis she also underwent a surgical pericardial biopsy and pericardial window formation. The pericardial biopsy was sent for microbiology culture and sensitivity, and histology. A thick gelatinous pericardial collection was also found at the time of the operation and sent for microbiology. Neither sample grew mycobacteria. It was later noted that the pericardial biopsy was exposed to formalin, making the isolation of mycobacteria suboptimal. Histological examination of the biopsy showed features of fibrinous pericarditis and chronic inflammation of uncertain cause with no granulomas. The patient was discharged on antituberculous treatment with outpatient follow-up. Her symptoms failed to improve and she re-presented to hospital with chest pain and palpitations two weeks later.

Interval CT imaging showed an increase in the number and size of lung nodules and liver lesions, worsening pericardial nodularity and an unchanged pericardial mass with an increased pericardial effusion compressing the RV. An urgent ultrasound-guided biopsy of a liver lesion was performed. Immunohistochemistry detected tumour cells strongly and diffusely positive for CD31 (endothelial marker) and ERG (nuclear vascular marker). Histological appearances were consistent with a high-grade angiosarcoma. A new diagnosis of metastatic PCA was made with lung and liver metastases. Treatment for tuberculosis was discontinued. Needle pericardiocentesis was attempted to avoid impending cardiac tamponade, but the fluid was too thick to drain.

The sarcoma MDT concluded that, given the extent of disease and speed of progression, the patient's life expectancy was unlikely to exceed one year. Palliative chemotherapy was the management of choice as pericardial stripping was felt to offer little long-term benefit. The patient was started on a six-cycle chemotherapy regime with doxorubicin and ifosfamide. Follow-up imaging showed a mixed response to treatment with some response of lung, liver and pericardial lesions, but further progression of skeletal metastases. Disease progression remained rapid and five months after diagnosis the pericardial tumour had increased significantly in size, distorting the RA and RV and encasing the aortic root and pulmonary artery. The patient went on to develop bilateral pleural effusions thrombocytopenia and a haemorrhagic stroke. Seven months after the initial presentation, the patient was transferred to a hospice and subsequently died.

Discussion

Primary cardiac tumours are very rare and only 25% are malignant, of which sarcomas are the most common.[5] Angiosarcomas are the most common type of cardiac sarcoma with an incidence of 0.0001% and tend to affect younger patients, with a male preponderence.[5] While most types of sarcoma arise from the left side of the heart, the majority of angiosarcomas arise from the lateral wall of the right atrium, sparing the septum and often infiltrating the

pericardium.[6] PCAs are aggressive and 75% of patients have metastases at diagnosis, mostly affecting the lungs, and occasionally the lymph nodes, bone and liver.[5,6]

Late diagnosis of PCAs can occur due to the rarity of disease and the non-specific nature of its presenting symptoms. Patients tend to present abruptly and symptoms will depend on location of tumour, size and presence or absence of metastases. The most common symptoms include exertional dyspnoea, chest pain, haemoptysis, fatigue and fever.[7] Many patients will re-present to health services several times before being diagnosed. Localising symptoms of PCAs occur later on when there is extensive local infiltration of the tumour. This may cause haemodynamic effects due to cavity obstruction or vessel occlusion leading to right-sided heart failure, superior vena cava obstruction, arrhythmias, recurrent pericardial effusions and cardiac tamponade.[7] Diagnosis of PCAs thus requires a high degree of clinical suspicion, especially in patients with recurrent pericardial effusions, a right-sided cardiac mass and pulmonary lesions.

Early diagnosis may allow more time for optimal management and the mainstay investigation for diagnosing PCAs is imaging. Transthoracic echocardiography (TTE) is non-invasive and most commonly used to detect a right atrial mass or pericardial effusion, raising suspicion of PCA. Further imaging techniques such as CT or cardiac magnetic resonance imaging (cMRI) help to better differentiate tumours, the extent of their local infiltration and metastatic spread.[8,9] Chest X-rays usually show cardiomegaly, a non-specific sign.

Tissue diagnosis is also crucial, especially in cases with diagnostic uncertainty such as ours. PCAs are defined histopathologically as malignant tumour cells that display endothelial differentiation with mitotic figures and areas of necrosis.[1,10] Microscopically they form irregular vascular spaces and are immunohistochemically positive for endothelial markers such as CD31.[10] Cytology from pericardiocentesis, however, rarely yields a conclusive diagnosis, and tissue specimens obtained from myocardial biopsy via thoracoscopy can be non-diagnostic, with a high risk of cardiac rupture.[11] Therefore tissue diagnosis is not always possible, but if metastases are present, these can sometimes be biopsied too.

Due to the rarity, complexity and rapidly progressing nature of PCAs, an MDT approach is required. Specific evidence-based algorithms for PCAs are not yet available due to the rarity of cases so management decisions are often extrapolated from extracardiac soft-tissue sarcomas. Surgical resection with adjuvant chemotherapy is possible in local, non-metastatic disease; however, complete resection is difficult since PCAs are large and often involve vital cardiac structures. Some studies show that even incomplete resection may help with tumour control and a prolonged symptom-free period.[12] Radiotherapy is a recognised treatment in localised disease, but it can cause myocardial injury. In advanced metastatic PCAs, anthracycline-ifosfamide regimens have been used providing better overall survival than surgery or radiotherapy.[13,14] Doxorubicin-based regimens are currently gold standard chemotherapy, but they have cardiotoxic effects, which can limit their use.[9,13,14] Recent studies suggest that taxanes such as paclitaxel may be of more benefit, with less cardiotoxic effects.[4] However, due to the poor condition of these patients at presentation, chemotherapy may have limited use and newer therapies still in trials may prove promising, such as tyrosine kinase inhibitors (TKIs) of angiogenesis.[4,13] Approaches offering a combination of surgery, radiotherapy and chemotherapy, or targeted TKIs, may offer hope for increased survival in certain patients.

Conclusion

We presented the case of a 49-year-old Southeast Asian woman of metastatic PCA. It highlights the non-specific clinical presentation of the disease, its diagnostic difficulties and the choice of diagnostic modalities on offer to aid early diagnosis. It also highlights the rapid and aggressive course of PCAs. Although doxorubicin-based chemotherapy is currently the mainstay of treatment for metastatic PCAs, more studies are required to develop evidence-based algorithms for optimal management, including the use of newer more targeted therapies.

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References

1 Burke A, Virmani R, Rosai J et al. *Atlas of Tumor Pathology: Tumors of the Heart and Great Vessels*. 3rd series. Washington DC: American Registry of Pathology; 1995.
2 Lahat G, Dhuka AR, Lahat S, et al. Outcome of locally recurrent and metastatic angiosarcoma. *Ann Surg Oncol* 2009; 16: 2502–9.
3 Lee CH, Chan GS, Chan WM. Unexplained recurrent pericardial effusion: a lethal warning? *Heart* 2003; 89: e11.
4 Penel N, Bui BN, Bay J-O et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. *J Clin Oncol* 2008; 26: 5269–74.
5 Shanmugam G. Primary cardiac sarcoma. *Eur J Cardiothorac Surg* 2006; 29: 925–32.
6 Virmani R. Tumors and tumor-like conditions of the heart. In: Silver MD, Gotlieb AI, Schoen FJ. *Cardiovascular Pathology*. 3rd ed. Churchill Livingstone; 2001; 583–605.
7 Wang H, Shi J, Liu H et al. Clinical and diagnostic features of angiosarcoma with pulmonary metastases: a retrospective observational study. *Medicine (Baltimore)* 2017; 96: e8033.
8 Yang HS, Sengupta S, Umland MM et al. Primary cardiac angiosarcoma evaluated with contrast two-dimensional and real-time three-dimensional echocardiography. *Eur J Echocardiogr* 2008; 9: 733–8.

9 Gaballah AH, Jensen CT, Palmquist S et al. Angiosarcoma: clinical and imaging features from head to toe. *Br J Radiol* 2017; 90:20170039.
10 Nayar S, Nayar PG, Cherian KM. Angiosarcoma presenting as syncope. *Asian Cardiovasc Thorac Ann* 2008; 16: 154–6.
11 Randall MB, Geisinger KR. Angiosarcoma of the heart: pericardial fluid cytology. *Diagn Cytopathol* 1990; 6: 58–62.
12 Bouma W, Lexis CP, Willems TP et al. Successful surgical excision of primary right atrial angiosarcoma. *J Cardiothorac Surg* 2011; 6: 1–6.
13 Cioffi A, Reichert S, Antonescu CR et al. Angiosarcomas and other sarcomas of endothelial origin. *Hematol Oncol Clin North Am* 2013; 27: 975–88.
14 Pervaiz N, Colterjohn N, Farrokhyar F et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. *Cancer* 2008; 113: 573–81.