Angiosarcoma – a rare fatal cause of recurrent pericardial effusions

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SUMMARY

A 40-year-old man presented to the Hospital Sultanah Bahiyah, Alor Setar, Kedah, with constitutional and respiratory symptoms. Physical examination and echocardiogram demonstrated massive pericardial effusion. Patient required multiple attempts of pericardiocentesis due to recurrent pericardial effusion. Initial workup including pericardial fluids examination and computed tomography imaging did not reveal any apparent cause. Magnetic resonance imaging showed a suspicious mass infiltrating into the right atrium. Autoimmune screening was negative. Patient was subsequently treated as having tuberculous pericarditis. However, his disease progressed rapidly and he eventually passed away due to right atrial rupture. Post-mortem revealed a ruptured right atrial tumour leading to massive haemothorax. Histopathological examination confirmed the diagnosis of primary pericardial angiosarcoma.

INTRODUCTION

Pericardial effusions (PE) are relatively common clinical findings, which occur due to either inflammatory or non-inflammatory causes. Recurrent PE without apparent etiology warrant further investigation and may pose clinical dilemma. Primary pericardial angiosarcoma is an extremely rare entity that can give rise to recurrent PE.[1] Unfortunately, the diagnosis of primary pericardial angiosarcoma still remains elusive to most clinicians. This fact was well demonstrated in our patient who was a healthy young man prior to the onset of his disease. He eventually succumbed to a devastating complication of primary pericardial angiosarcoma. The authors review herein the clinical challenges faced while managing this patient as well as the reports available.

CASE REPORT

A previously healthy 40-year-old man presented to the Hospital Sultanah Bahiyah, Alor Setar, Kedah, with one-month history of dry cough, breathlessness, loss of appetite and significant loss of weight. Otherwise, he had neither symptom of connective tissue disorder nor family history for malignancy. During the first encounter, his heart sounds were muffled on auscultation. Otherwise, physical examination revealed no peripheral lymphadenopathy nor organomegaly. Transthoracic echocardiogram showed a massive global pericardial effusion with thickness of 6.92cm, for which he immediately underwent emergency pericardiocentesis and drained 1.5litres of haemorrhagic pericardial fluids. Biochemical analysis of the pericardial fluids revealed 32.94g/L of albumin, 1207U/L of lactose dehydrogenase and 69.73g/L of protein. Cytological examination of the pericardial fluid demonstrated haemorrhagic smears with scattered haemosiderin-laden macrophages but no malignant cells were detected. Culture from pericardial fluids also yielded negative results for bacterial, fungal as well as tuberculous infections. Inflammatory markers were markedly raised with C-reactive protein at 26.28mg/L and erythrocyte sedimentation rate at 61mm/hour. First computed tomography (CT) scan of his thorax, abdomen and pelvis offered little clues in an effort to search for the cause of PE. No pericardial mass was demonstrated on this first CT scan. The scan however showed bilateral pleural effusion, a few paratracheal nodes and thrombosis in the right internal jugular vein as well as right brachiocephalic vein. The patient was then commenced on warfarin therapy. Autoimmune screening was negative. Tumour markers were all normal except for CA125 which was exceptionally raised at 567.3U/mL. Peripheral blood film showed no presence of blast cells or any evidence of haematological disorders. Retroviral screening was negative.

Throughout his follow up, the patient was subjected to pericardiocentesis again as serial echocardiogram showed that the PE recurred 2 weeks after the first episode. Repeated analysis of the pericardial fluid again did not reveal any obvious cause. The patient was also readmitted a few weeks later for acute breathlessness episode, during which he developed massive right pleural effusion that required emergency pleural drainage. Positron Emission Tomography (PET) scan was scheduled at another health centre in Penang as the service was not available locally in Alor Setar, Kedah. The plan didn't materialize due to admission and his frail condition. Follow up computed tomography scans did pick up an irregular filling defect within the right atrial chamber with worsening pericardial thickening, which initially was thought to be right atrial thrombosis. Eventually, cardiac

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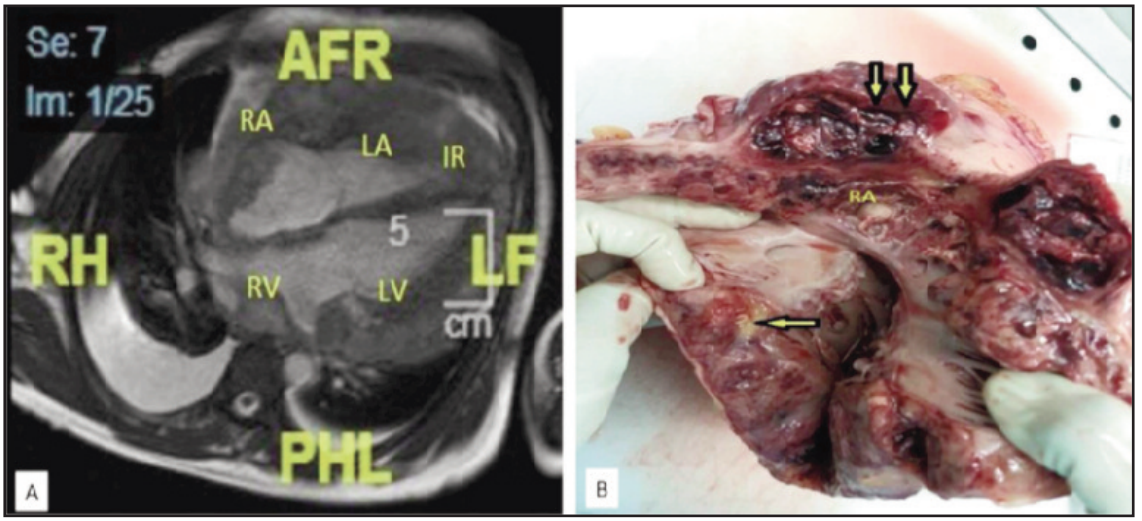

Fig. 1: (A) Magnetic resonance scan showed irregular filling defect (IR) with pericardial thickening. RA: right atrium, LA: left atrium, RV: right ventricle, LV: left ventricle. AFR, RH, PHL and LF refer to directions of magnetic resonance image plane. (B) Examination of heart showed thickened fleshy pericardium with areas of haemorrhage. The right atrial (RA) mass (double arrow) was ruptured. The right coronary artery (single arrow) was patent.

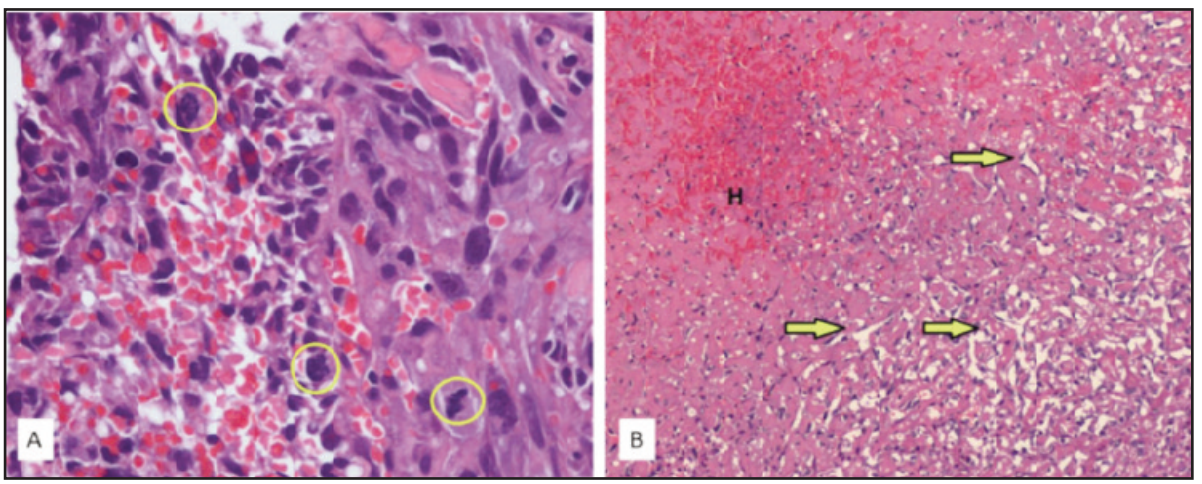

Fig. 2: (A) The tumour cells are pleomorphic, hyperchromatic with eosinophilic cytoplasm and frequent mitoses (circle), including aberrant forms. (B) The tumour cells are spindle and formed vasoformative spaces (single arrow) containing red blood cells. Areas of haemorrhage (H) are also present.

magnetic resonance imaging showed a suspicious mass lesion infiltrating into the right atrium with abnormal thickening of the pericardium with complex PE (Figure 1). Patient was planned for pericardial window in a cardiothoracic centre.

In view of high prevalence of tuberculosis infection in South-East Asia region, a diagnosis of pericardial tuberculosis was first entertained. Patient was then started on anti-tuberculosis treatment as an empirical treatment. Whilst observing clinical response to anti-tuberculosis treatment, the condition of the patient took a turn for the worse when he developed sudden onset of respiratory distress with cardiovascular compromise. Resuscitation was of no avail.

Post-mortem of the patient revealed a massive right haemothorax (2600ml of blood and blood clots) secondary to a ruptured right atrial wall with infiltrating pericardial tumour (Figure 1). The heart was enlarged and globular weighing 1700 grams with diffuse thickening and nodularity of the pericardium. A haemorrhagic fleshy tumour within the pericardium (35-55mm thickness) extending into the atrial myocardium was present. Histologically, the tumour was composed of malignant spindle cells in haphazard fascicles with prominent cleft-like spaces, several blood lakes and in areas forming abortive blood vessels (Figure 2). The malignant cells displayed plump, oval to elongated nuclei, fine chromatin pattern with small nucleoli, and eosinophilic to vacuolated cytoplasm. Areas of coagulative necrosis, haemorrhage and hyalinization were seen. The tumour invaded the myocardium with focal transmural involvement into the right atrial pectinate muscle. A tumour embolus was seen in the right lung parenchyma. The malignant cells were diffusely positive for CD34, CD31, SMA, CD99 and cytoplasmic staining of WT-1. Additional immunostains calretinin, h-caldesmon, CKAE1/AE3, myogenin and S100

were negative. Based on our findings, a diagnosis of pericardial angiosarcoma, spindle cell variant was made. The cause of death of this patient was concluded as massive right haemothorax secondary to ruptured right atrial wall with pericardial angiosarcoma.

DISCUSSION

Sarcomas are the most common pericardial malignancies with mesothelioma accounting for 50% of cases, followed by synovial sarcomas and angiosarcomas.[1] Other uncommon sarcomas include leiomyosarcomas and liposarcomas. Based on histomorphology findings especially the presence of vessels formation with atypical spindle cells and supportive IHC expression: diffuse positivity for CD34, CD31, SMA, CD99 and WT-1(cytoplasmic) with negative calretinin, h-caldesmon, the diagnosis of angiosarcoma, spindle cell variant, grade 2 was made.

Angiosarcomas can have variable histomorphological features composed of epithelioid or spindle cells, ranging from well differentiated tumours forming ramifying channels lined by atypical cells with apical snouts, abortive vascular formation and to the less differentiated ones containing sheets of spindle cells with vascular lakes. Immunohistochemical stains are crucial in differentiating between different types of sarcomas especially in the higher grade poorly differentiated tumours. The tumour cells are positive for CD31, CD34 and WT-1. Cytoplasmic positivity for WT-1 was observed instead of nuclear positivity which is seen in mesothelioma. Mesotheliomas are also calretinin and high molecular weight cytokeratin positive. WT-1 expression can be used in diagnosing vascular neoplasms with a stronger expression usually seen in spindle cell types.[2] Myogenin, h-caldesmon and S100 were negative thus ruling out rhabdomyosarcomas, leiomyosarcomas and liposarcomas or malignant melanomas, respectively.

In spite of all the advancements in the medical field, there is no standardized treatment protocol for pericardial sarcomas. For patients with this disease, a multidisciplinary treatment approach is proven to improve life expectancy but eventually patients succumb due to the progress of the disease. Treatment options include tumour resection but complete resection is rarely achieved. Adjuvant chemotherapy for resectable cases and chemoradiotherapy in unresectable disease is usually the mainstay of treatment.[3,4]

Diagnosing and managing pericardial angiosarcoma pose clinical challenges due to a number of reasons as highlighted in our case. Our patient presented with non-specific symptoms which often mimic other medical conditions. This inevitably leads to delay in the diagnosis and hence definitive treatment. Pericardial mass in our patient was initially misdiagnosed as cardiac thrombus and subsequently also misdiagnosed as pericardial tuberculosis. A more systemic approach should have been adopted when it is clinically difficult to distinguish between different aetiologies for recurrent haemorrhagic pericardial effusion. While antimicrobial therapy can be initiated when there are doubts, extensive investigation for malignancy should not be delayed at the same time. False negative findings in our initial CT imaging should not have dismissed the possibility of malignancy. Retrospectively, this could be due to massive PE masking the presence of any mass there. PET scan would be the ideal imaging modality in identifying cardiac tumour as well as differentiating benign from malignant cardiac tumours, as suggested by recent study by Meng et al.[5] The same study also demonstrated that 18F-FDG PET uptake could give useful prognostic value for cardiac tumour. Unfortunately for our patient, the PET scan was not a viable option due to clinical and logistic reasons.

Aggressive nature of this disease paints a poor prognostic picture even if diagnosis is eventually achieved. Within a short period, our patient's disease progressed rapidly. Initial computed tomography showed no obvious aetiology. Magnetic resonance imaging scan subsequently showed an infiltrating pericardial mass within a short period of time. At this juncture, there is no well-established clinical guideline to help clinician in managing this disease. Systemic approach is highly advocated in managing recurrent PE. Investigation for cardiac malignancy should be prompt. Awareness of the disease is hence of crucial importance so that clinicians have high index of suspicion to make accurate early diagnosis.

CONCLUSION

Clinicians should have a high index of suspicion for a primary cardiac tumour when dealing with recurrent pericardial effusions. Diagnostic work up for possible primary cardiac tumour should be prompt in view of its potential aggressive nature and poor prognosis. Primary cardiac angiosarcoma may mimic other medical conditions and has extremely poor prognosis.

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