

Case of Primary Pericardial Mesothelioma

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ABSTRACT

Primary malignant pericardial mesothelioma is extremely rare, with a reported prevalence of 0.0022% at autopsy series. It is, however, the most common primary malignancy of the pericardium. To date, only few hundred cases have been reported in the literature. Unlike peritoneal and pleural mesothelioma, there has been no definite correlation between asbestos exposure and pericardial disease. Malignant pericardial mesothelioma carries a poor prognosis with no successful treatment strategies and little benefit from radiation and chemotherapy. We report a 28 year-old man with no medical history who presented with two weeks of worsening dyspnea on exertion to minimal efforts and severe orthopnea. We discuss the diagnostic approach and therapy in our patient and provide a review of the literature pertaining to the epidemiology, clinical features of pericardial mesothelioma and its diagnosis and treatment.

Key-words: Cardiac neoplasm; Pericardium; Mesothelioma; Constrictive pericarditis;

Key Message: Malignant mesothelioma of the pericardium is a very rare neoplasm. Clinical presentation is insidious and invariably followed by progression to tamponade, heart failure or pericardial constriction. Cross sectional imaging followed by biopsy are necessary for a conclusive diagnosis. Successful treatment strategies for this malignancy are lacking so prognosis remains poor.

INTRODUCTION

Primary malignant pericardial mesothelioma (PMPM) is extremely rare, with a reported prevalence of 0.0022% at autopsy series.¹ Pericardial mesotheliomas account for 0.7% of all malignant mesotheliomas.² It is, however, the most common primary malignancy of the pericardium. Clinical presentation may be insidious at first, with malaise, weight loss, dyspnea and chest pain. Pericardial effusion and tumor infiltration ultimately lead to tamponade, effusive-constrictive pericarditis or heart failure. We present a case of primary pericardial mesothelioma in a young male

without any history of asbestos exposure and then review the literature relevant to this devastating but fortunately rare malignancy.

CASE HISTORY

A 28 year-old man with no prior medical problems presented with two weeks of worsening dyspnea on exertion to minimal efforts and severe orthopnea. The patient reported a 20 pounds unintentional weight loss over the past two months. He denied any medication use or toxic exposure. On exam, there was tachycardia and significant jugular distension, which did not decrease with inspiration. Pulsus paradoxus was not present. Heart sounds were muffled but no murmurs, rubs or pericardial knock were heard. No significant edema was noted. An electrocardiogram revealed sinus tachycardia and low voltage QRS complexes. Initial blood analyses were unremarkable and the chest radiograph revealed an

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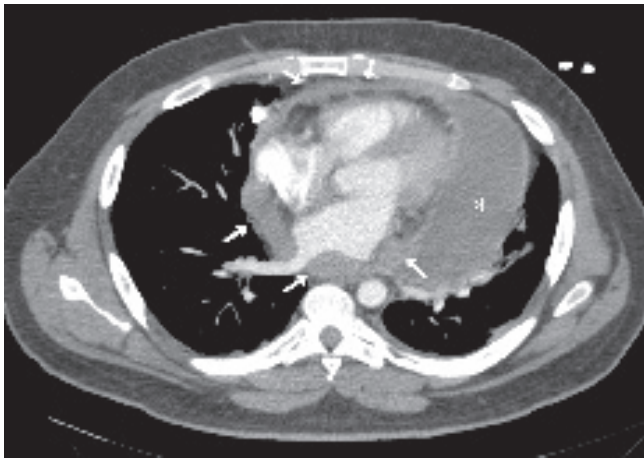


Figure 1: A: Axial contrast-enhanced CT image acquired after pericardial window demonstrates a large localized pericardial effusion (asterisk), pericardial enhancement with pericardial nodules (arrows).

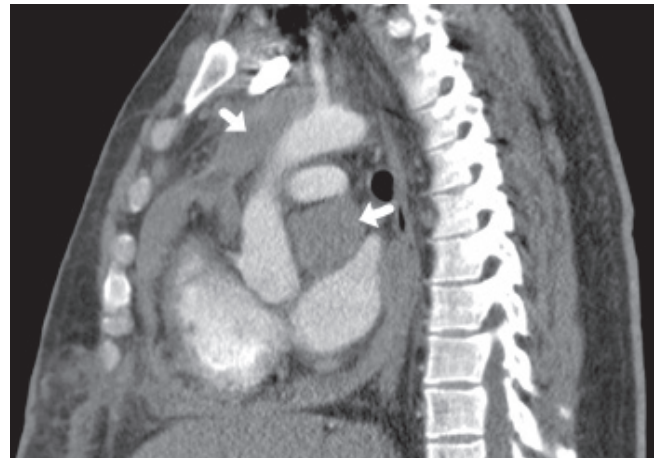


Figure 2: Sagittal image showing mediastinal lymphadenopathy encasing the great vessels (arrows).

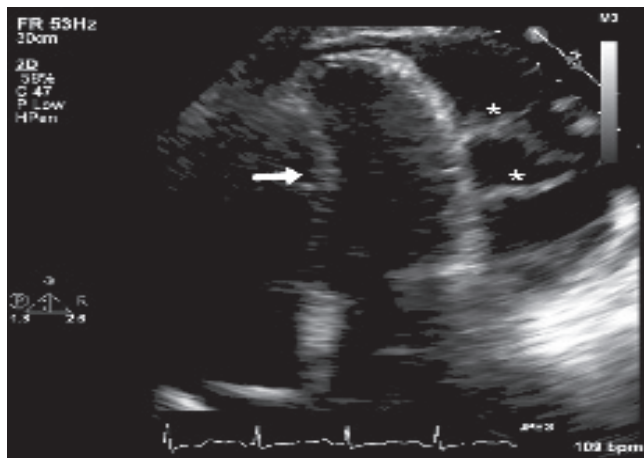


Figure 3: 2-D echocardiography in the apical 4-chamber view after pericardial window showing a large localized pericardial effusion with fibrinous strands (asterisks). The extent of pericardial thickening is not appreciated. Note the diastolic septal bounce suggestive of pericardial constriction (arrow).

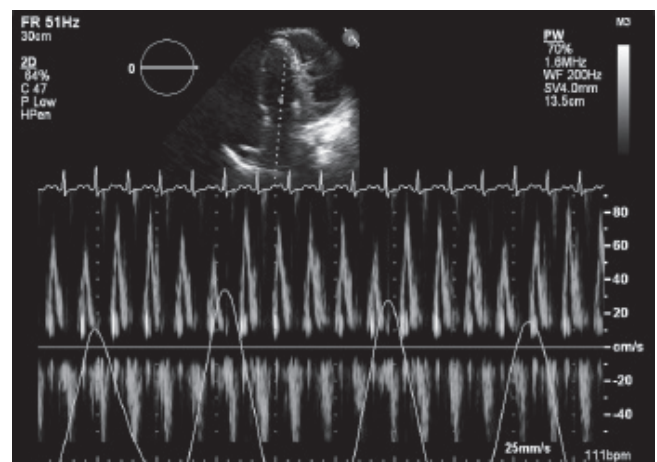


Figure 4: Transmitral pulse Doppler showing significant respiratory variation typical for effusive-constrictive pericarditis.

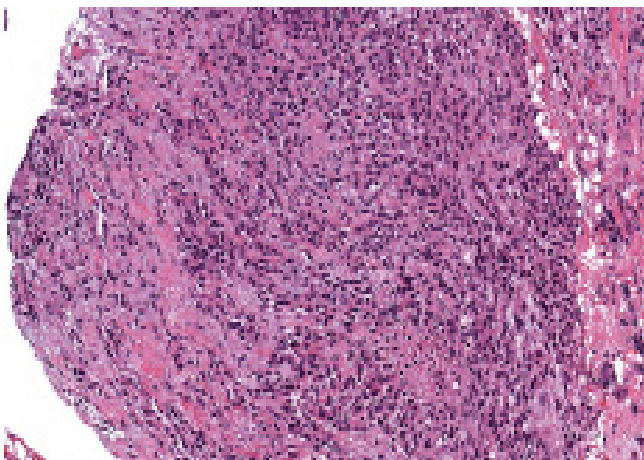


Figure 5: Microscopic examination of pericardial biopsy samples showing abundant pleomorphic malignant cells with epithelial appearance (hematoxylin and eosin stain).

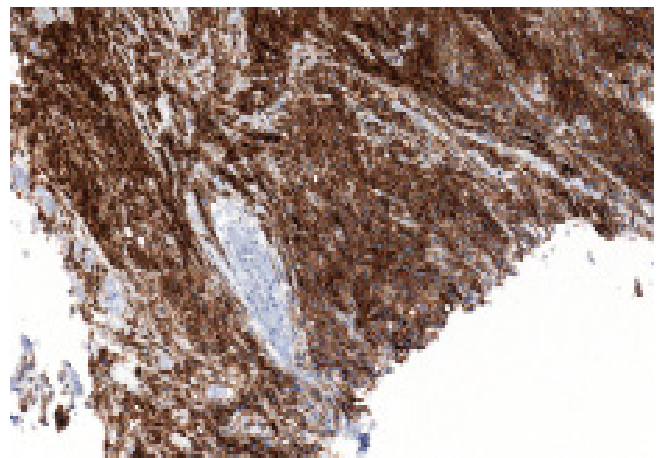


Figure 6: Immunochemical stain with calretinin, a highly sensitive and specific marker for malignant mesothelioma, showing extensive staining of tumor cells (brown).

enlarged cardiac silhouette. A computed tomography (CT) angiogram of the chest demonstrated a large pericardial effusion with significant pericardial thickening (Figure 1A). A nodular conglomerate with soft tissue attenuation was noted within the effusion and encasing the atria and great vessels (Figure 1B). No evidence of metastatic disease was found elsewhere in the chest. An echocardiogram confirmed a large circumferential pericardial effusion (Figure 2A) with fibrinous strands and septal bounce suggestive of constrictive pericarditis (Figure 2B). The patient underwent a pericardial window to relieve his symptoms. Pericardial fluid analysis showed a hemorrhagic exudate, however no bacterial growth or malignant cells were identified. The pericardial biopsy specimens showed nodular masses and infiltrative nests of tumor cells with a morphology highly suggestive of malignant mesothelioma (Figure 3A). Immunohistochemistry revealed that malignant cells stained positive for cytokeratin (CK)-5/6, calretinin (Figure 3B), Wilms Tumor 1 (WT1) and negative for Ber-EP4 and thyroid transcription factor-1 (TTF-1), which was consistent with malignant mesothelioma, epithelioid subtype. Cardiothoracic surgery was consulted for possible resection but given the advanced nature of the neoplasm and its proximity to the vasculature, cancer was deemed inoperable. Patient was subsequently started on palliative chemotherapy with pemetrexed and carboplatin. He completed 3 cycles of chemotherapy but repeat imaging showed progression of disease. He was readmitted with volume overload, respiratory and renal failure and died in the hospital. Post mortem analysis confirmed advanced pericardial malignant mesothelioma and constrictive pericarditis.

DISCUSSION

Primary cardiac neoplasms are uncommon, with a prevalence of approximately 0.02%–0.056%.³ Secondary involvement of the heart by direct invasion or metastatic disease is 100 to 1000 times more prevalent, and most commonly results from neoplasm of the lungs, breast, melanoma and lymphoma. Primary neoplasms from the pericardium are exceedingly rare, with an estimated prevalence of 0.001 to 0.007% and include malignant mesotheliomas and teratomas.^{4,5} Malignant mesothelioma arises from the serous epithelial cells of the mesothelium. The most common locations are the pleura (60-70%) and peritoneum (30-35%), while primary pericardial mesothelioma accounts for only 1% of all mesotheliomas but is the most common primary malignancy of the pericardium and third most common neoplasm of the heart after angiosarcoma and rhabdomyosarcoma, with slightly more than 300 cases published in the literature

so far. Pericardial mesothelioma occurs with a 2:1 male predominance and a median age of 46 years, with a range between 19 to 76 years.⁶ The etiology remains unclear. Although there is a strong association between asbestos exposure and pleural mesothelioma, this association has not been observed in pericardial mesothelioma. There are no identifiable risk factors responsible for the development of PMPM or for its prevention.

Primary pericardial mesothelioma exists in three variants: epithelial, biphasic (mixed), and fibrous (spindle cell)—with epithelial cell being the most common.⁷ The tumor is usually confined to the pericardium and the surrounding lymph nodes.⁸ However, metastatic disease is found in approximately 50% of the cases, most commonly to the lungs.⁹

Patients with pericardial mesothelioma initially present with vague symptoms such as weight loss or dyspnea. Chest pain, cough and palpitations may also occur. A picture of constrictive pericarditis, pericardial tamponade or heart failure invariably arises as invasion and compression of the heart and surrounding structures develops from effusion or direct tumoral invasion.¹⁰ Arrhythmias may also occur.^{9,10}

Although the diagnostic approach usually begins with plain radiography of the chest or transthoracic echocardiography, the value of these imaging modalities is limited.¹¹ Chest radiographs may show an enlarged cardiac silhouette. While echocardiography is very useful to evaluate tamponade or constrictive physiology, its sensitivity for detection of pericardial thickening and masses is low.^{10,11} Cross-sectional imaging, on the other hand, plays a key role in the evaluation of these lesions. CT and magnetic resonance imaging (MRI) have a superior yield in identification of pericardial masses and associated mediastinal findings.¹² CT scan findings of enhanced soft tissue nodules infiltrating the pericardium may be a clue for diagnosis. These modalities allow further tissue characterization and provide findings that can guide further diagnostic and therapeutic interventions.^{5,12}

Given the predominance of secondary lesions involving the heart and pericardium, histopathology is mandatory for the diagnosis of primary pericardial mesothelioma. Pericardiocentesis and cytology examination of pericardial fluid is frequently nondiagnostic¹³ because of the difficulties in differentiating malignant mesothelioma cells from reactive cells. Biopsy typically reveals tumor composed of epithelial areas, which may form tubulopapillary structures resembling a carcinoma. Spindled areas similar to a sarcoma or a biphasic/mixed pattern may also be noted. The spindled areas usually demonstrate some evidence

of mesotheliomatous differentiation when examined with ultrastructural or immunohistochemical techniques. Other microscopic features include necrosis and extensive cellular pleomorphism.^{10,12} Given the ultrastructural similarities with the more common metastatic pericardial malignancies, a panel of antibodies should be used for the diagnosis of pericardial mesothelioma.¹⁰ Mesothelioma cells show high frequency of reactivity for markers such CK-5/6, WT-1 in addition to calretinin and negative for nonserous adenocarcinoma markers such as B72.3, MOC-31, BG8, and Ber-EP4.¹⁴

No standard treatment guideline for pericardial mesothelioma has been established yet. Surgical resection is the treatment of choice in localized disease. However, excision is not possible for most patients who present with locally advanced disease. Radiation has little effect on this tumor. Chemotherapy also has a limited role in treatment but unresectable cases are usually treated with combination of pemetrexed and cisplatin or carboplatin in hope of disease regression or to prolong survival.¹⁵ However, despite the best efforts, no significant difference has been achieved in regards to prognosis, and the median survival time is approximately six months from diagnosis in most of the cases.

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