CASE REPORT

A rare cause of heart failure with preserved ejection fraction: primary pericardial mesothelioma masquerading as pericardial constriction

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SUMMARY

We present a case of a 30-year-old woman with a history of HIV and hepatitis C who sought medical attention because of severe oedema of the lower limbs and abdomen. CT of the chest showed a thickened pericardium, and cardiac catheterisation demonstrated constrictive physiology. She underwent pericardiectomy, but the procedure was unsuccessful because the pericardium was densely adherent to the myocardium. After consultation with several pathologists, she was diagnosed with primary pericardial mesothelioma (PPM), an exceedingly rare cardiac tumour with a fatal prognosis. She died within 3 months of presentation. The details of the case as well as pertinent literature are reviewed.

BACKGROUND

Primary pericardial mesothelioma (PPM) is a rare malignancy. Clinically, we initially suspected decompensated heart failure secondary to either HIV, hepatitis C (HCV) or tuberculous (TB) pericarditis. As we note, the pathologists initially suspected benign atypical mesothelial hyperplasia and then metastatic lobular carcinoma of the breast. Pathologists from multiple sites were consulted before reaching a definitive diagnosis of PPM. This case encouraged us to be aware of red herrings in the diagnostic process, such as HIV and HCV pericarditis. Furthermore, it emphasises that very rare pathologies may don the clinical garb of very common presentations and that a broad differential should be borne in mind when initial diagnoses do not satisfy a clinician's curiosity.

CASE PRESENTATION

PPM has an incidence of less than 0.002% and represents less than 5% of all mesotheliomas.[1 2] This ominous malignancy can present with heart failure, pericarditis, pericardial effusion and tamponade. It carries a uniformly poor prognosis and treatment options are very limited.[3] Pericardiectomy is most often performed for symptom relief and diagnosis. Patients only survive on average 6–10 months from diagnosis.[4 5]

A 30-year-old woman with a history of HIV and HCV presented to the emergency department with a 4-month history of gradual but progressive swelling of her lower limbs and abdomen. She denied any chest pain, dyspnoea, paroxysmal nocturnal dyspnoea or orthopnoea. Vitals were stable. Cardiovascular examination was remarkable for an elevated jugular venous pressure (JVP) of about 12 cm with a pronounced 'y' descent. There was a prominent pericardial knock sound heard over the praecordium. There was no pericardial rub or murmur. The lungs were clear to auscultation. The patient was markedly oedematous from the abdomen to the lower limbs. She was admitted for further diagnostic work-up and management. She was diagnosed with HIV around May 2010 and had been on antiretroviral therapy. She had not used illicit drugs for approximately 5–6 years.

Renal and hepatic diseases were ruled out through blood tests and imaging. Peritoneal fluid was negative for malignancy. Echocardiogram showed a thickened bright pericardium adjacent to the right heart border (figure 1) with parallel separation between epicardial and pericardial echoes (railroad track sign), septal bounce and lack of pericardial slide. Annulus paradoxus was demonstrated on tissue Doppler (figure 2). Left ventricular ejection fraction was 64%. The right ventricle was normal in size and function. There was moderate tricuspid regurgitation. There was no pericardial effusion, but the pericardial space was remarkable for debris. Constrictive physiology was demonstrated by Doppler study of tricuspid and mitral inflows (figure 3) during inspiration and expiration; diastolic flow reversal was also demonstrated in the hepatic veins during expiration. There was marked dilatation of the inferior vena cava with no change during inspiration or expiration.

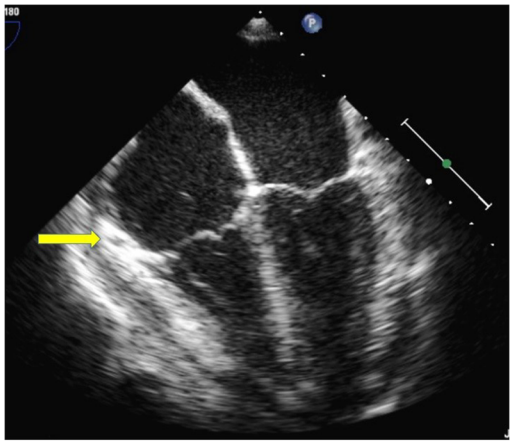

Figure 1 Transoesophageal echo. Hyperechoic and thickened pericardium around the ventricles (see arrow). No pericardial effusion is seen.

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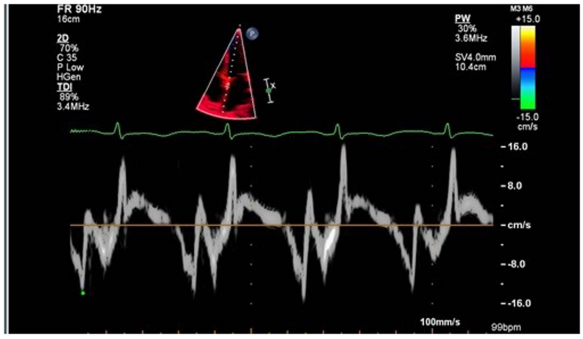

Figure 2 Annulus paradoxus. Tissue Doppler showing increased septal 'e' velocity of 13.7 cm/s.

CT of the chest revealed thickening of the pericardium with no evidence of calcification. There were no lung nodules. Bilateral pleural effusions and interstitial thickening were present in the lung bases. Cardiac MRI confirmed the presence of a diffusely thickened pericardium at 5 mm. The inferior vena cava and hepatic veins appeared plethoric. There was a rapid early diastolic filling and associated diastolic septal bounce secondary to hindered late diastolic filling (figure 4).

The patient showed a good response to diuresis. She underwent right and left heart catheterisation to confirm constrictive physiology.

INVESTIGATIONS

Haemodynamics

Mean right atrial pressure was markedly elevated at 28 mm Hg. Right ventricular pressure was 43/19 mm Hg with a mean of 28. Pulmonary artery pressure was 38/25 mm Hg with a mean of 32 mm Hg. Mean pulmonary capillary wedge pressure was markedly elevated at 29 mm Hg (figure 5). Diastolic equalisation of pressures, the haemodynamic hallmark of constrictive physiology, was demonstrated.

There was prominent 'y' descent noted in the arterial wave form. Discordance between right ventricular and left ventricular pressures during inspiration and expiration was noted. Interventricular dependence was demonstrated after 500 mL of saline challenge (figure 6).

The diagnosis of severe constrictive pericarditis causing decompensated heart failure was considered, and the patient was referred for pericardiectomy.

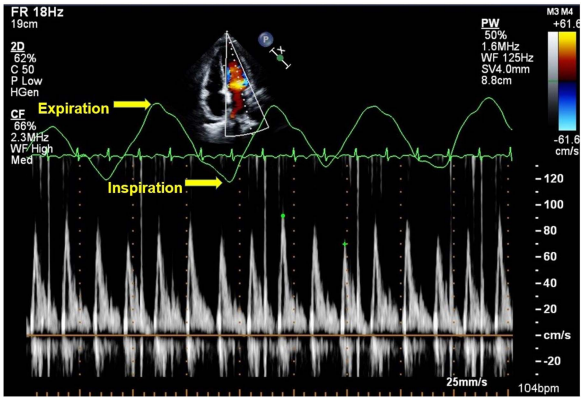

Figure 3 Transthoracic echo Doppler study across the mitral valve. Constrictive physiology demonstrated by Doppler study of mitral inflow. Difference in flow between inspiration and expiration is 24%, which is significant for constriction.

DIFFERENTIAL DIAGNOSIS

At this stage, we considered the following differential diagnoses given the patient's medical history and clinical presentation: (1) HIV pericarditis, (2) HCV pericarditis, (3) TB pericarditis, (4) autoimmune pericarditis and (5) idiopathic pericarditis.

TREATMENT

Operative details

The pericardium was very firm, taut and appeared to be calcified. The visceral and parietal surfaces were heavily involved and only a limited pericardiectomy was achieved as the visceral layer could not be completely released. Fibrocartilaginous changes were found to involve the visceral and parietal pericardial layers as well as parts of the myocardium. There was a marked venous bleeding secondary to elevated venous pressure, but estimated blood loss was minimal. Postoperatively, she was transferred to the coronary care unit because of hypotension and oliguria requiring pressor support and haemodynamic monitoring.

DISCUSSION

Histopathology

Four pieces of rubbery, tan pericardial tissue, the largest of which was 10.2×5.2×0.6 cm, were sent for histopathological studies. On cut section, the centre of the tissues was white and firm with an irregular border expanding centrifugally (figures 7 and 8). Low-power microscopy of H&E staining showed a proliferation of epithelioid-like cells with ample cytoplasm and pleomorphic nuclei very deep within the pericardial tissue, suggesting a mesothelial origin (figure 9). In few sections, there was evidence that the cells lined up in a single file, suggesting a possible metastatic lobular carcinoma of the breast (figure 10). They did appear to be lining an anatomical structure, but it was not discernable whether this was a vessel or some other structures. No significant inflammatory cells were noted in the tissue background (figure 11).

Histopathological differential diagnosis at this stage was atypical mesothelial hyperplasia, malignant mesothelioma, angiosarcoma and metastatic lobular carcinoma of the breast. An immunohistochemistry panel was suggested to define the epithelioid cell type precisely.

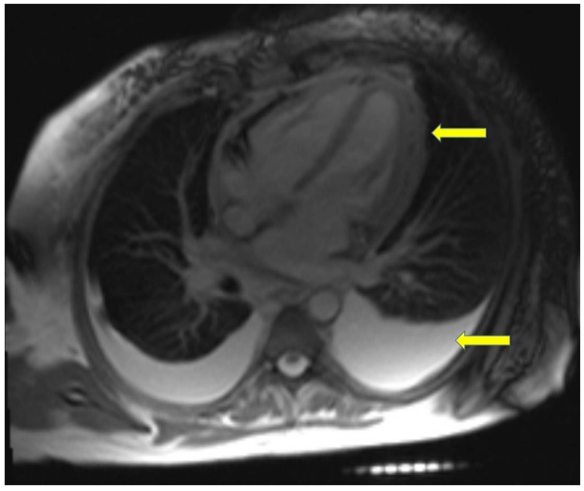

Figure 4 Cardiac MRI. Diffusely thickened pericardium 5 mm and pleural effusions demonstrated on cardiac MRI (see arrows).

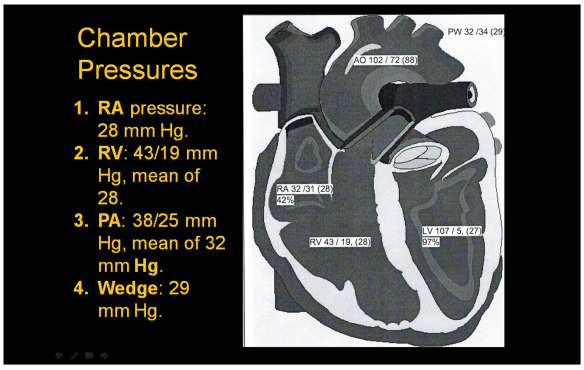

Figure 5 Cardiac catheterisation: chamber pressures. Markedly elevated RA pressure. Diastolic elevation and equalisation of pressures in all chambers—classic for constrictive physiology. AO, aortic; LV, left ventricular; PA, pulmonary artery; RA, right atrial; RV, right ventricular.

The epithelioid-like cells in question stained positively for vimentin, D240 and calretinin, highlighting them as mesothelial cells. However, immunohistochemistry on its own does not differentiate benign, atypical or malignant mesothelial cells and, clearly, the distinction between benign and malignant mesotheliomas is a crucial decision. This distinction is often very difficult for pathologists.[6] Owing to inconsistent results with immunohistochemical markers,[7–9] the diagnosis of benign versus malignant mesothelioma is largely based on morphology.[8 10] There are a number of features found in benign proliferations that can mimic malignancy, including cytological atypia, mitotic activity, architectural complexity, high cellularity, necrosis, the formation of papillary groups and the entrapment

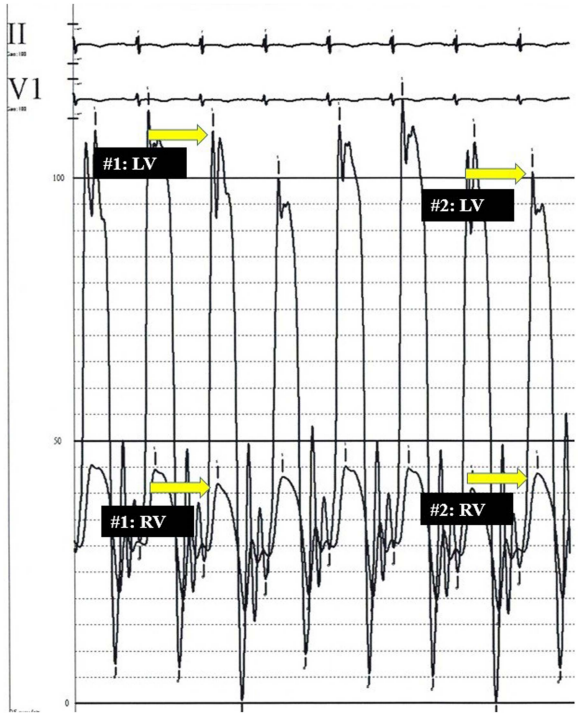

Figure 6 Ventricular discordance. Simultaneous recording of left (LV) and right ventricular (RV) pressure curves illustrating ventricular interdependence. Arrow set 1: maximum LV systolic pressure coincides with minimum RV systolic pressure. Arrow set 2: minimum LV systolic pressure coincides with maximum RV systolic pressure.

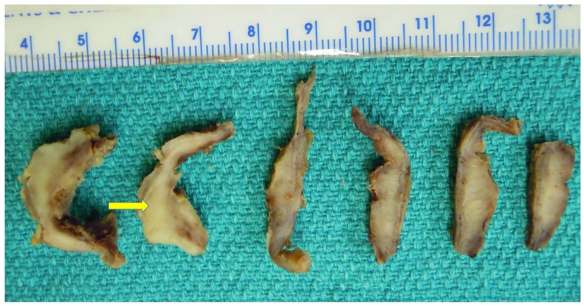

Figure 7 Cross-sections of pericardium. Expansile, firm, white mass expanding centrifugally.

of mesothelial cells within fibrosis that mimics invasion.[10 11] Cellular architecture and inflammation can help to differentiate benign from malignant proliferation. Reactive samples tend to have uniform growth with regular sheets and sweeping fascicles of bland spindle cells that respect mesothelial boundaries. Conversely, mesotheliomas tend to have disorganised growth and intersecting proliferations. Inflammation is also common in reactive tissue, whereas there is minimal inflammation in malignancy.[10] The invasion of stroma (muscle or fat) is the most reliable indicator of malignancy.[6 8 10–13]

Given the depth of infiltration of the mesothelial cells into the pericardium, some irregular cytological features, and no obvious background inflammatory reaction to account for this change, a tentative diagnosis of atypical mesothelial proliferation was considered. Cross verification was sought, and histology slides were sent to an expert in mesothelioma, whereby the mesothelial origin of the cells was confirmed. The fact that these cells were also producing their own mucoid stroma confirmed their malignant potential. This ominous histological feature, combined with the depth of the mesothelial aggregates into the pericardium, favoured a diagnosis of malignant pericardial mesothelioma.

This diagnosis was confirmed by molecular fluorescence in situ hybridisation (FISH), which showed that 38% of the proliferating mesothelial cells had a homozygous deletion for p16, putting them in the malignant range. The homozygous loss of p16 gene, involved in cell cycle regulation and present in all normal cells, is evolving as a promising genetic target for malignant mesothelioma. In fact, 70% of malignant mesotheliomas have deletion of 9p21, the locus where p16 is located.[6 7 10 14 15]

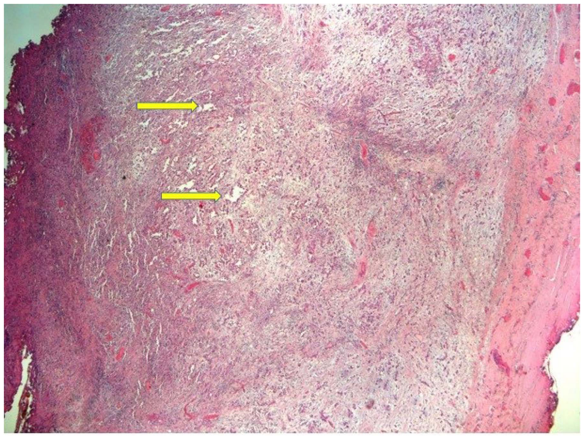

Figure 8 Photomicrograph H&E, ×2—poorly circumscribed expansile mass with tumour cells lining spaces (arrows).

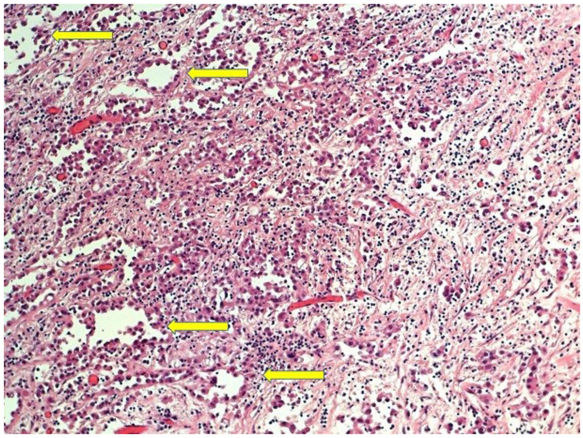

Figure 9 Photomicrograph H&E, ×4—proliferation of mesothelial cells that line spaces aggregate deep in the pericardium (see arrows).

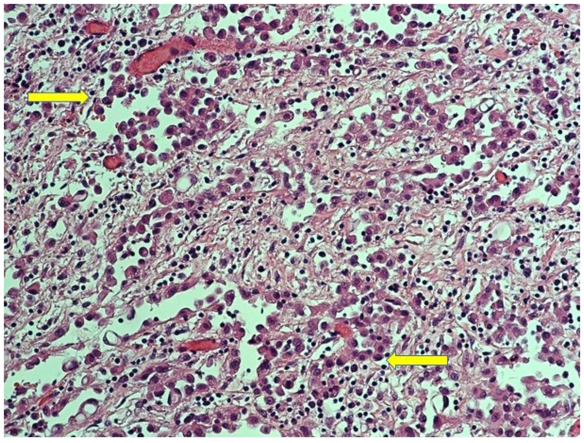

Figure 11 Photomicrograph H&E, ×10—plump, epithelioid cells (see arrows) with noticeable lack of inflammatory cells in the stroma.

Since only 70% of malignant mesotheliomas show a homozygous loss of p16, the presence of p16 does not exclude malignant mesothelioma as a diagnosis.[6] Conversely, if a homozygous deletion was present, it would confirm, or at least strongly suggest, the diagnosis. Homozygous deletions of p16 are not only diagnostic, but also prognostic.[10] It has been demonstrated that patients with malignant mesotheliomas and a homozygous p16 deletion have a decreased survival.[10 16–18]

On confirmation of this ominous diagnosis, medical oncology was consulted, and chemotherapy and radiotherapy for further management were not recommended by the oncologists. The patient's condition deteriorated in hospital. Eventually, she coded on pulseless electrical activity. She was successfully resuscitated and started on inotropes for haemodynamic support. However, her condition continued to deteriorate and after discussing with the family, compassionate terminal care was instituted. The patient was kept comfortable and died in the coronary care unit.

DISCUSSION

PPM is a rare malignancy with a uniformly fatal prognosis. According to autopsy studies, primary cardiac tumours have an incidence of 0.001–0.28%. Metastatic cardiac tumours are approximately 40 times more common than primary tumours.

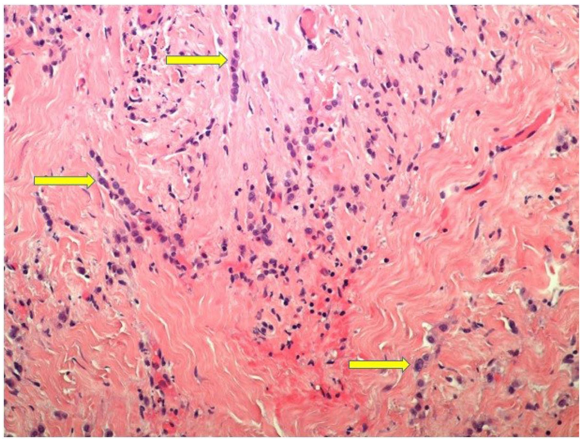

Figure 10 Photomicrograph H&E, ×10—misleading single file architecture requiring necessity to rule out metastatic lobular carcinoma of the breast (see arrows).

Fortunately, 75–80% of cardiac tumours are benign and are amenable to treatment. Benign cardiac tumours include myxomas, papillary fibroelastoma, lipoma, fibroma, rhabdomyoma, hamartoma and haemangiomas. Malignant cardiac neoplasms include sarcoma, lymphoma and malignant fibrous histiocytoma. Mesothelioma and paragangliomas can be either benign or malignant. Pericardial mesotheliomas can present with heart failure, pericarditis, tamponade, or as in this case, constriction.[3]

Malignant mesothelioma arises from the serous mesothelial cells lining bodily cavities such as the pleural cavity, peritoneum, pericardium and the tunica vaginalis of the testicles.[3 7 8 19 20] Although malignant mesothelioma of the pleural cavity is classically associated with asbestos exposure, no such link has been established between this exposure and PPM.[21] Risk factors for malignant mesothelioma include simian virus 40 infection (SV40: a DNA tumour virus), radiation exposure, thorotrast, tuberculosis and exposure to non-asbestos materials such as erionite.[22]

PPM has an incidence of less than 0.002% and represents less than 5% of all mesotheliomas.[1 2] It is the third most common primary malignant pericardial tumour after angiosarcoma and rhabdomyosarcoma.[23–26] The disease has a higher incidence in men and the median age is 46 years.[27] In total, 88.8% of malignant mesotheliomas originate from the pleura, 9.6% in the peritoneum, 0.6% involve the pleura and peritoneum, 0.7% involve the pericardium and 0.2% involve the tunica vaginalis of the testis.[28] The three subtypes of pericardial mesothelioma include epithelial, spindle cell and mixed types.[27 29]

PPM can be localised to the pericardium or it can infiltrate the myocardium, atria, coronary sinuses, coronary arteries and even the conduction system. It can also encase the heart completely depending on its malignant potential and intent. The insidious nature of this lethal malignancy makes it difficult to diagnose, and in one series of 120 patients, 75% of the diagnoses were made postmortem.[29] Our patient had presented with advanced heart failure symptoms and signs, although we believe that aetiological diagnosis was delayed because of low index of suspicion of malignant pericardial constriction. In fact, our initial investigations did not include a malignant workup as we favoured HIV, TB, HCV and idiopathic pericarditis in our scheme of investigations.

Clinical presentation of PPM encompasses a wide spectrum of symptomatology. Chest pain, new onset atrial fibrillation,

orthopnoea, cough, pedal oedema and ascites are non-specific and may mislead the unwary clinician. Right atrial and ventricular compression with intracardiac thrombus has been reported, and in one series, a 14% incidence of pulmonary embolism has been reported.[29] Tumour embolism may occur, although it is less common. Cardiac tamponade, a life-threatening haemodynamic emergency, is a feared but rare initial presentation of this malignancy.

Diagnosis of PPM is challenging primarily because of its rarity. Pericardial fluid cytology often yields negative results and diagnosis requires histopathological study after surgery or at autopsy.[29] The distinction between benign mesothelial hyperplasia and malignant mesothelioma remains one of the most challenging issues in histopathology. The patient was initially diagnosed as 'atypical mesothelial hyperplasia', an all-encompassing term for benign mesothelial hyperplasia, premalignant mesothelial proliferations and early well-differentiated malignant mesotheliomas. It does not suggest any specific diagnosis, and conventional wisdom recommends observation of these patients. However, this approach is flawed as there are cases reported in the literature where patients initially diagnosed with atypical mesothelial hyperplasia have uniformly developed malignant mesotheliomas.[30] Cardiac MRI may provide diagnostic clues and provide information about the location and extent of the tumour as well as help determine its resectability.

PPM does not respond well to radiotherapy. Chemotherapy with doxorubicin, vincristine and cyclophosphamide has been known to at least reduce tumour burden.[31] Given the insidious onset of the disease, rarity and diagnostic delays, patients may present very late at which point treatment is often palliative and may involve pericardiectomy to relieve constriction. A pericardial window to instil chemotherapy is also an option.[32] However, complete surgical resection is often impossible as in this case because the visceral pericardium was densely adherent to the myocardium. New chemotherapy regimens such as pemetrexed-based doublets or triplets after complete tumour removal can prolong survival.[33–35] Reardon *et al*[36] have documented that aggressive radiation therapy in a patient who failed chemotherapy may offer survival benefit. Maruyama *et al*[33] report one case in whom triple therapy with cisplatin, gemcitabine and vinorelbine enabled the patient to be disease free for 24 months without any evidence of disease progression. However, such therapeutic feats are anecdotal and only underline the highly aggressive and lethal nature of this tumour.

Recently, it has been observed that lovastatin, a cholesterol-reducing drug, primarily inhibits cell growth, induces apoptosis and reverses doxorubicin resistance in malignant mesothelioma.[29] Its potential as an adjunctive treatment in patients with mesothelioma needs further evaluation.

Newer therapeutic strategies hold promise and warrant further clinical evaluation. These include tumour-targeted therapy with antiangiogenesis drugs, biological response modifiers and photodynamic therapy. Gene therapy with vectorial delivery of lost or mutated genes into the host's genome may pave the way for a clinical revolution in the management of this unforgiving disease.[37]

PPM has a dire prognosis. Kaul *et al*[4] note that patients with the disease only survived, on average, for 10 months after the diagnosis is made.

At 30 years of age, the patient was below the median age of 48 years for PPM. Although she denied any symptoms of heart failure, she presented with decompensated heart failure. In a review of 28 cases of this disease by Thomoson *et al*, dyspnoea was the most common subjective symptom in 46% of patients. Furthermore, 67% of patients had an enlarged cardiac silhouette. An effusion was detected by echo in 88% of patients, whereas a thickened pericardium was present in only 19% of patients by echocardiography. In keeping with our pathological findings, a diffuse growth on histopathological study was present in 72% of patients.[21] The patient died within 3 months of presentation, which is consistent with other case reports given the vague symptoms, the extremely rare prevalence of this disease and the diagnostic challenge.

PPM is an enigma wrapped in a mystery. Unlike its pleural and peritoneal counterparts, its aetiology is largely unknown, and it is an extremely rare malignancy. However, it may masquerade as heart failure with preserved ejection fraction. Signs and symptoms are non-specific, and diagnosis is challenging. Management is frustrating, and the disease is uniformly fatal. Newer therapeutic strategies hold promise but must undergo further evaluation before entering the clinical arena.

Learning points

- Primary pericardial mesothelioma (PPM) is an extremely rare malignancy, unrelated to asbestos exposure, with a uniformly fatal prognosis.
- PPM may masquerade as heart failure with preserved ejection fraction.
- Benign atypical mesothelial hyperplasia is not a conclusive diagnosis and may be a harbinger of malignant mesothelioma. A definitive diagnosis should be pursued rigorously.
- Diagnostic workup of PPM is all the more challenging because of the low index of suspicion. Expert opinion should be sought whenever there is a marked discrepancy between clinical features and histological picture.
- Pericardiectomy for PPM is unsuccessful because of the highly aggressive nature of the tumour.

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Competing interests None.

Patient consent Obtained.

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