A case report of an extremely rare and aggressive tumor: primary malignant pericardial mesothelioma

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Abstract

Primary pericardial malignant mesothelioma (PMPM) is extremely rare with an incidence less than 0.0022%. It comprises 0.7% of all mesothelioma cases. To date, approximately 350 cases of pericardial mesothelioma have been reported in the literature. Its typical presentation is insidious, with nonspecific signs and symptoms, and usually results in constric-tive pericarditis, cardiac tamponade and congestive heart failure either by a serous effusion or by direct tumorous constriction of the heart. With the exception of several case reports, the outcome is uniformly fatal, and patients typically die within six months of diagnosis. Here we report a 72-year-old Caucasian male with persistent pericardial and pleural effusion. He was diagnosed with PMPM after pericardectomy. He had only one cycle of chemotherapy with cisplatin and pemetrexed. He developed acute kidney injury as result of chemotherapy. He died 1 month after diagnosis and 6 months after the first symptoms.

Case Report

A previously healthy 72-year-old Caucasian male was transferred to our hospital because of persistent pericardial and pleural effusion in December 2010. His past medical history included lactose intolerance and gastroesophageal reflux (GERD) for which he took omeprazole on a daily basis. His past surgical history included remote hernia repair and appendectomy. He did not take any other prescribed medications or any over-the-counter medications. He denied any use of herbal medication or recreational drugs. He denied any medication allergies. He was a life-long non-smoker and occasional alcohol drinker. He was married and lived with his wife. He had 3 children who were all healthy. He worked as an electronic repairman for most of his life. He had no apparent history of occupational or incidental exposure to asbestos. He had a family history for pancreatic and liver cancer.

He presented to a local hospital with a 3-week history of intermittent chest pain and a 3 months history of a progressively worsening subjective feeling of head fullness when lying flat. He was initially treated for pneumonia with antibiotics. Soon after that he developed symptoms of congestive heart failure and was treated with standard cardiac medications. He was transferred to our hospital in December 2010 because of his persistent pericardial effusion and bilateral pleural effusions.

On presentation to our hospital, his vitals were stable. He was afebrile, heart rate was 70 beats per minute, respiratory rate was 16 per minute, his blood pressure was stable at 120/80 mmHg with a pulsus paradoxus of 12 mmHg, and his oxygen saturation was 94% on room air. He appeared in no respiratory distress. No lymphadenopathy or skin rash was appreciated. His cardiac exam revealed an elevated JVP and a positive Kussmaul’s sign. A distant S1 and S2 were heard with no murmur. A pericardial rub was intermittently heard along his left sternal border. His respiratory exam was consistent with bilateral pleural effusions. His abdomen exam did not reveal hepatosplenomegaly, mass or ascites. He had significant symmetrical pitting edema in his lower extremities bilaterally.

His blood work revealed a normocytic anemia with a hemoglobin (Hb) 114 g/dL and a white cell count (WBC) and platelet count. Both C-reactive protein (CRP) and erythrocyte sedimental rate (ESR) were elevated at 37 mg/L (0.0-8.0 mg/L) and 58 mm/hr (10-10 mm/hr) respectively. The rest of blood work was unremarkable. His lactate dehydrogenase (LDH) was 207 IU/L (100-235 IU/L).

An extensive work-up looking for infectious...
etiology such as TB and connective tissue disorders including antinuclear antibodies (ANA), extractable nuclear antigen (ENA), rheumatoid factor (RF) and complement 3/4 level were all negative. A thorough malignancy work-up was done including a computed tomography (CT) of head, neck, chest, abdomen and pelvis, a bone scan, a colonoscopy and serum biomarkers. CT chest revealed a heterogeneous, vague soft tissue-mass-like area with rim enhancement in the pre-carinal region, irregular thickening with diffuse enhancement of the parietal pericardium and complex, loculated bilateral pleural effusions without lung parenchymal mass lesions or pleural nodules (Figure 1). The rest of the studies did not reveal any malignancy or metastasis.

Echocardiography (ECHO) revealed a thickened pericardium attached to the left ventricle and the presence of moderate pericardial effusion with constrictive features and bilateral pleural effusions. Both left and right ventricle function were normal on initial ECHO. A subsequent cardiac magnetic resonance imaging (MRI) confirmed ECHO findings, but revealed a hemodynamically relevant constrictive pericarditis (Figure 2). Pericardiocentesis and pleurocentesis were carried out. Both fluids were negative for infection, tuberculosis (TB) and malignancy.

A pericardiectomy was performed for both diagnostic and therapeutic purposes. The inspection of the epicardium by the surgeon showed a chronically thickened pericardium and 4 walnut-size, firm nodules located around his heart. A partial resection of pericardium and nodules was performed.

Microscopic examination from resected pericardial tissues and nodules revealed an infiltrating poorly differentiated malignant neoplasm. In some areas tumor cells demonstrated pleomorphic spindle cells with prominent nuclei, while in other areas the cells had an epithelioid appearance with high grade nuclear atypia (Figure 3). Tumor necrosis and frequent mitotic figures were noted. The tumor cells demonstrated diffuse positivity for pan-cytokeratin, cytokeratin 7, weak positivity for cytokeratin 20, and patchy positivity for calretinin. Immunostaining with cytokeratin 5/6 and EMA showed only focal weak reactivity. The tumors cells were negative for TTF-1, MOC-31, BER-EP4, S100, PSA, P63 and desmin. Given the morphology and the immunohistochemistry profile, the diagnosis of a biphasic primary malignant pericardial mesothelioma was favored.

Postoperatively, his symptoms were ameliorated. He was transferred to the medical oncology service after the diagnosis of PMPM was made. A repeat cardiac MRI was performed to serve as a baseline prior to chemotherapy. It showed recurrent thickening of the pericardium with recurrent constrictive features.

Figure 2. A) At initial presentation on 2010-12-06, computed magnetic resonance (CMR) revealed that the pericardium is thickened along the lateral wall of the left ventricle (LV) with septation noted along the right ventricle (RV) wall where most of the pericardial fluid collected. Abnormal septal motion with early inspiratory shift indicating constrictive pericarditis; B) One month post pericardectomy on 2011-01-26, CMR revealed that recurrent circumferentially thickening around the visceral pericardium with recurrent constrictive physiology.

Figure 3. A) Post-pericardiectomy specimen reveals hypercellular atypical cells with hyperchromatic nuclei and prominent nucleoli. These poorly differentiated malignant cells shows both spindled (shown here) and epithelioid morphology, characteristic for biphasic type of mesothelioma (Hematoxylin-eosin stain); B) the proliferation of atypical spindle cells infiltrates and invades fat tissue, which is regarded as typical feature of this type of malignancy. Immunohistochemically, the malignant cells are positive for calretinin (patchy); C) pancytokeratin (diffuse); D) and WT-1 (focal); E) the immunohistochemical profile is consistent with mesothelioma; F) Immunostaining with SV40, which has been suggested to be associated with mesothelioma, is negative in this case. As well, PCR with SV40 gene amplification is negative (not shown).
Primary malignant pericardial mesothelioma (PMPM) is extremely rare, although it is the third most common primary malignant pericardial tumor after angiosarcoma and rhabdomyosarcoma.1,4 It represents 0.7% of all mesothelioma cases, which occurs most common in pleural (60-70%) and peritoneum (30-35%).2,3 Interestingly, in the present case, the pericardium and pleura both appeared to be involved by mesothelioma. Autopsy strongly favored the pericardium as the origin of the tumor with extension into the pleura because of the prominent tumor volume and marked desmoplastic reaction in the pericardium compared with the pleura. His PMPM also metastasized to the liver at time of autopsy, which was not evident on CT image 1 month before his death. To our knowledge, liver metastasis from PMPM has never been reported in literature previously.

The incidence of PMPM is less than 0.0022% from a very large autopsy report.1 A Canadian epidemiology study reported its annual incidence as 1 in 40 million.4 A literature review revealed that a higher incidence is observed among men than women.4 Median age is 46 (range from 19 to 76), but occurring most often in the 5th to 7th decade.4

Although there is a strong association between asbestos exposure and pleural mesothelioma, this association is still controversial in pericardial mesothelioma.2 A recent report from a highly industrialized region of Northern Italy showed a convincing relationship between asbestos exposure and pericardial mesothelioma.4 In the present case, both the patient and his wife denied an apparent occupational or incidental exposure to asbestos. Nonetheless, he worked as an electrician and so he might have exposure to asbestos that he was not aware of. We have performed a lung asbestos body analysis using a bleach digestion method, which is regarded as a gold standard methodology to identify asbestos exposure. It showed a high normal amount of asbestos body in his dissected lung tissue. Other suspected risk factors are radiation exposure, SV40, TB and exposure to non-asbestos mineral fiber such as erionite.5 SV40 virus has also recently been linked to the pathogenesis of mesothelioma.3 The virus has been shown to cause mesothelial tumorigenesis in a number of animal models, and specific SV40 DNA sequences have been discovered in malignant pleural mesotheliomas.2 Carbone et al., report that at least 60% of mesotheliomas in the United States contain and express SV40, which results in suppression of tumor suppressors p53 and Rb, thereby leading to tumor development.2 We have performed both PCR and immunostaining with SV40 on his pericardial tissues which are both negative in our case. In addition, we have not identified any other risk factors described as above from history in our patient.

Symptoms arising from PMPM usually result from constriction of the heart or compression of surrounding structures either from serous or hemorrhagic effusion with fibrinous adhesions or direct tumorous infiltration, ranging from chest pain, dyspnea and cough.4 Clinical
manifestations of PMPM are pericardial effusion, constrictive pericarditis, cardiac tamponade and congestive heart failure. Unfortunately, a prompt clinical diagnosis is notoriously difficult because of the insidious and nonspecific initial clinical presentation. The radiological findings are sometimes noncontributory and cytological analysis from the pericardial fluid is often negative for malignant cells. Most cases of pericardial mesothelioma have been diagnosed by histology after surgery or autopsy, and as in most cases, a definitive diagnosis was made only after pericardectomy in our present case.

To date, there is no standard treatment for PMPM because of its rarity. Surgical resection remains the main treatment modality in PMPM. However, complete tumor eradication is often unachievable. Pericardectomy and resection of the tumor may result in temporary relief of symptoms in critical cases presenting with pericardial constriction. Notably, this type of surgery carries a high mortality rate. The role of chemotherapy and radiotherapy is limited in non-resectable cases. Thus, the prognosis of this disease remains extremely poor due to its late presentation, inability of complete tumor eradication by surgery and the poor response of PMPM to radiotherapy or chemotherapy. A median survival time from the onset of symptoms is six months. Recently, newer chemotherapeutic regimens such as pemetrexed based doublets or triplets after complete excision of the tumor have shown prolonged survival times. One case report showed that aggressive radiation therapy after failing of chemotherapy may significantly extended survival times. However, one may easily argue towards the potential toxicities of radiation therapy such as radiation-induced early and delayed onset of pericarditis that may complicate and worsen the patients' condition. In the present case, our patient had one cycle of standard dose of pemetrexed and cisplatin. At autopsy, tumor necrosis was observed in both the pericardium as well as the pleura. It may suggest a microscopic response to chemotherapy. However, it may also be simply related to rapid tumor growth. In addition, the tumor was likely too advanced to treat. It involved the pericardium, pleura and liver. While the mechanism of his death is unclear, we suspect that it may relate to sudden decreased cardiac output from impeded ventricular filling imposed by a rigid and thickened pericardium.

References
