Effusive-Constrictive Pericarditis due to Poorly Differentiated Carcinoma of the Mediastinum

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ABSTRACT

A 33-year-old male developed subacute effusive-constrictive pericarditis with recurrent pleural effusions and mediastinal lymphadenopathy. He was found to have poorly differentiated carcinoma of the mediastinum that led to constrictive physiology not amenable to medical or surgical management, ultimately requiring hospice. This case was remarkable for its rare etiology and presentation.

LEARNING OBJECTIVES

1. Describe the novel presentation of poorly differentiated carcinoma causing effusive-constrictive pericarditis
2. Explain physiology, diagnostic findings, and management of constrictive pericarditis
3. Compare outcomes of partial vs complete pericardiectomy
4. Describe management of poorly differentiated carcinoma of the mediastinum

HISTORY OF PRESENTATION

A 33-year-old man was transferred to an academic medical center for evaluation of recurrent pleural effusions and symptoms of dyspnea and lower extremity swelling refractory to medical management and thoracentesis.

The patient initially developed idiopathic pericardial effusion with tamponade two years prior, which was refractory to anti-inflammatory medications, and was ultimately treated with a pericardial window. Pericardial biopsy at the time demonstrated chronic fibrinous pericarditis. The procedure was complicated by vocal cord paralysis requiring tracheostomy. He underwent an autoimmune work up which was unremarkable, and no underlying etiology was identified.

After the pericardial window, the patient was asymptomatic and able to return to employment at a supermarket. After two years, the patient developed recurrent volume overload. Over the subsequent 9 months, he required frequent hospitalizations for intravenous diuresis. Transthoracic echocardiogram at the outside facility reportedly showed a complex circumferential pericardial effusion. He was transferred to our facility when his symptoms did not improve despite diuresis and thoracentesis.

On admission he was tachycardic to 108 beats/min with blood pressure 106/86 mm Hg. Heart auscultation revealed distant heart sounds with no murmur or pericardial friction rub. Jugular venous pressure was difficult to assess due to obesity. Skin was warm. His abdomen was distended, and his legs were markedly swollen. Laboratory results were as follows: electrolytes were remarkable for sodium of 122 mmol/l and bicarbonate concentration of 37 mmol/l, liver enzymes were remarkable for total bilirubin of 2.2 mg/dL and alkaline phosphatase of 261 IU/L. Whole blood lactate was 2.4 mmol/L.

An electrocardiogram revealed sinus tachycardia with premature ventricular contractions, bialtrial enlargement, and non-specific repolarization changes. A chest radiograph showed enlargement of the cardiac silhouette, mild pulmonary edema and a layering right pleural effusion. Echocardiography revealed calcified thickened echogenic material in the pericardial space and showed annulus reversus with early diastolic septal bounce and small LV cavity size - concerning for constrictive pericarditis (Figure 1).
PAST MEDICAL HISTORY

The patient had a history of effusive constrictive pericarditis status-post pericardial window with recurrent bilateral pleural effusions and ascites with unclear etiology.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included constrictive pericarditis (CP) related to malignancy, rheumatologic causes (scleroderma), or alternative causes (viral, idiopathic), chronic diastolic heart failure, or cardiac tamponade.

INVESTIGATIONS AND MANAGEMENT

Cardiac MRI showed a complex circumferential pericardial effusion in which the parietal and visceral layers of the pericardium were not distinctly identified from the complex fibrinous pericardial process. There was significant enhancement of the pericardial fluid on late gadolinium enhanced images, with small focal areas of calcifications in the pericardial space.

Due to concern for malignancy, the patient underwent a CT scan of his chest which demonstrated extensive mediastinal adenopathy with lymphangitic spread into the right lung, suggestive of lymphoma. The CT noted high density material within the expected pericardial space with irregularity of the epicardial fat, suggestive of soft tissue involvement. PET-CT showed intense activity corresponding to the complex pericardial fluid, mildly avid diffuse mediastinal lymph nodes, and heterogeneous increased background level activity throughout. His pleural fluid was exudative, culture-negative, lymphocytic-predominant, with negative cytology on multiple samples. Repeat autoimmune workup for serositis was negative.

Right heart catheterization showed elevated and equilibrated right and left ventricular end-diastolic pressure (24 to 28 mm Hg). At the time of catheterization, the mean pulmonary artery pressure was 35 mm Hg, with pulmonary vascular resistance of 3.14 WU. A dip-and-plateau pattern was noted, with rapid x and y descents on right atrial pressure with ventricular interdependence. Fick cardiac index was noted to be 1.36 L/min/m2.

The patient was started on high dose diuretics. A trial of low dose dobutamine did not provide clinical benefit. He had already failed to benefit from anti-inflammatory medications previously. There was no free fluid to remove by pericardiocentesis. As he was not responding to medical management, the patient was taken by cardiothoracic surgery for mediastinal exploration with a plan for pericardiectomy. Upon access to the mediastinal space, diffuse lymphadenopathy with necrotic lymph nodes were noted. The pericardium was diffusely thickened and densely adherent to the epicardium, which prohibited pericardiectomy. Biopsies of the pericardium and surrounding lymph nodes were taken along with sampling of the pericardial fluid.

The patient was briefly initiated on steroids for possible lymphoma per oncology, which were discontinued when his pericardial fluid flow cytometry was negative. The final pathology report of his pericardium and surrounding lymph nodes was significant for high grade poorly differentiated carcinoma of the mediastinum (figures 2 and 3).

Figure 2: Hematoxylin and eosin stain of pericardial biopsy showing poorly differentiated carcinoma (10x magnification).

Figure 3: Hematoxylin and eosin stain of mediastinal lymph node showing poorly differentiated carcinoma (5x magnification).
OUTCOMES & FOLLOW-UP

The patient continued to deteriorate from cardiogenic shock. He required mechanical ventilation via his tracheostomy, but his respiratory status continued to worsen. He developed sepsis due to ventilator-associated pneumonia. Given his rapid deterioration in the setting of an aggressive malignancy with limited treatment options, oncology determined he would be unlikely to benefit from anti-cancer directed therapy. Ultimately, the patient and family decided to transition to comfort-based care at an inpatient hospice facility.

DISCUSSION

This report highlights a case of poorly-differentiated carcinoma of the mediastinum causing constrictive pericarditis, a pathophysiologic entity that has not been previously described based on our literature review. We will discuss the background and management of effusive-constrictive pericarditis, the association with malignancy, and the management of poorly differentiated carcinoma of the mediastinum.

Effusive-Constrictive Pericarditis

Chronic inflammation of the pericardium can lead to thickening, fibrosis, and calcification of the pericardium. This leads to inelasticity, which prevents diastolic filling of the ventricles. Patients develop low stroke volume, which decreases their cardiac output. Patients typically present with signs of right-sided heart failure, such as jugular venous distension, edema/anaasarca, ascites, and pleural effusions. Idiopathic, viral, and post-procedural (cardiac surgery, radiation therapy) are the most common causes in the developed world, while infectious (tuberculosis) etiologies are the most common in developing countries. Patients with more severe cases of pericarditis (fever, large effusion, tamponade, failure to respond to NSAIDs) are more likely to develop constrictive pericarditis.

Management of Constrictive Pericarditis

Constrictive pericarditis is often initially treated with anti-inflammatory medications such as colchicine and NSAIDs. Cardiac MRI can be used to assess for active inflammation to guide treatment. Some patients will have improved pericardial compliance with resolution of inflammation. Specific therapies can be tailored to the underlying etiology - e.g., tuberculous pericarditis should be treated with anti-tuberculous therapy. Diuretics can be used for symptom relief. However, patients will often have elevated filling pressures even if euvolemic. Percardiocentesis can be performed if pericardial effusion or tamponade are present.

If anti-inflammatory treatments are not successful, the inelasticity of the pericardium is likely irreversible, and the next step would be to surgically strip the pericardium (pericardiectomy). Pericardiectomy historically carried high surgical risk, with a reported hospital mortality ranging from 4.9% to 12%. However, survival without surgery is poor, and surgery can improve symptoms and functional status in the majority of patients. Patients with low left ventricular ejection fraction, right ventricular dilatation, atrial fibrillation, poor functional class, hepatomegaly or hepatic dysfunction, diabetes, coronary artery disease, COPD, renal dysfunction, or effusive-constrictive pericarditis prior to surgery have poorer outcomes. Earlier surgery may improve outcomes, specifically if performed within 6 months of symptom onset. Among patients who survived to discharge, survival at five years after surgery ranges from 78-94.6%. One study of 97 patients undergoing surgery for constrictive pericarditis had a 30-day survival rate of 81.4%, 1-year survival of 66.5%, and 5-year survival of 51.6%, with no difference based on underlying etiology.

Surgical approach is still controversial. There are more conservative approaches, such as an anterior pericardiectomy that only removes the anterior pericardium between both phrenic nerves. A more aggressive complete pericardiectomy removes the anterior, inferior (diaphragmatic), and left lateral pericardium. Cardiopulmonary bypass may or may not be necessary. There are mixed results regarding risk and benefits of either approach. In one study of 130 anterior pericardiectomies, 91% initially had NYHA functional class III or IV, whereas at 1 year after surgery, 88% of patients were NYHA functional class I or II. This indicates that anterior pericardiectomy may be sufficient. However, another study of 37 anterior pericardiectomies and 53 complete pericardiectomies actually showed better survival rate, functional status, right ventricular systolic pressure, and less tricuspid regurgitation in patients with complete pericardiectomy. One study of 395 patients showed that patients undergoing partial pericardiectomy had worse outcomes including higher operative mortality, more post-operative low-output syndrome, longer hospitalization, worse long-term survival, slower functional recovery, and increase risk of recurrent symptoms compared to complete pericardiectomy.

Patients may have an outer rind that is easily removed, but a second epicardial covering causes continued constriction. If it is not possible to remove the pericardium completely, then the peel may be incised to create non-contiguous constriction.

Interestingly, tricuspid regurgitation (TR) often accompanies CP, and moderate to severe TR is associated with worse survival in patients with CP. While still controversial, some experts recommend concomitant tricuspid valve repair at the time of pericardiectomy to improve long-term survival.
Management of poorly differentiated carcinoma of the mediastinum

Poorly differentiated carcinoma of the mediastinum is a rare tumor in which the primary site of origin is unable to be identified based on histopathological features. This rare type of tumor has low survival. Further investigation can often identify the underlying diagnosis, which may have specific therapeutic options. If levels of α-fetoprotein or HCG are elevated, then patients should be treated for mediastinal nonseminomatous germ cell tumor. If bronchoscopy shows an endobronchial lesion, then the patient should be diagnosed with lung cancer. If there are neuroendocrine features, then the patient should be treated for small-cell lung cancer. Without any other clear evidence, the patient should be treated for non-small cell lung cancer. Poorly differentiated carcinoma with neuroendocrine features among patients without lung cancer risk factors should be treated with platinum/etoposide with or without paclitaxel. Surgical resection and local radiation can treat tumors confined to the mediastinum, usually along with chemotherapy. One study treated 43 patients with poorly differentiated carcinoma or adenocarcinoma with cisplatin-based chemotherapy. 13 patients (30%) had complete response, and 7 patients (16%) are long-term disease-free survivors. Therefore, patients should be treated based on the specific tumor type that is identified with further analysis, and platinum/etoposide-based chemotherapy should be used in patients whose specific tumor could not be identified2.

If constriction and malignancy were detected in our patient at an earlier stage in the disease process, he may have benefitted from early pericardial stripping. This may have provided more time with improved functional status, during which he may have been stable enough to receive treatment for the underlying malignancy with platinum/etoposide. Unfortunately, by the time he arrived at our institution, he could not undergo pericardial stripping because the tumor had invaded into the myocardium, and he was too unstable to undergo treatment for his malignancy.

REFERENCES