68-Year-Old Woman With Chronic Cough and Recurrent Pleural Effusions

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A 68-year-old woman with a history of hypertension, paroxysmal atrial fibrillation, and liver transplant for primary sclerosing cholangitis (PSC) presented with a 2-month history of cough and shortness of breath. Her cough, which had gradually worsened, progressed to dyspnea after several feet of walking. She denied fever, chills, sick contacts, chest pain, palpitations, orthopnea, and paroxysmal nocturnal dyspnea. She had taken levofloxacin for a presumed upper respiratory tract infection with no relief and was receiving oral immunosuppressive therapy with 1 mg/d of prednisone and 25 mg of cyclosporine twice daily. Her other medications included losartan, metoprolol, mesalamine, and alendronate. Although she had no history of cardiac problems, examination revealed a mildly elevated jugular venous pressure (JVP) and trace peripheral edema.

1. Which one of the following is the most likely etiology for the patient’s symptoms of cough and dyspnea?
   a. Asthma
   b. Gastroesophageal reflux disease (GERD)
   c. Chronic bronchitis
   d. Heart failure
   e. Fungal pulmonary infection

Asthma can present in a 68-year-old patient with cough; however, it is uncommon and would not be associated with an elevated JVP. This patient also had no wheezing, which is the hallmark finding of asthma. GERD, a common cause of cough, is due to chemical irritation of the airways, is usually associated with symptoms of reflux, and does not cause dyspnea. It is unlikely in this patient who had no reflux and progressive dyspnea. Chronic bronchitis would typically be associated with a cough productive of colored sputum and would usually respond to antibiotics. This patient’s increased JVP, progressive dyspnea, and failure to respond to antibiotics is most consistent with heart failure. Fungal infection can occur in immunocompromised patients, but our patient had no fever, and this diagnosis would not explain the elevated JVP.

The patient’s dyspnea worsened, and she presented to the emergency department, where she was found to have decreased breath sounds over the right base. Laboratory testing revealed a hemoglobin of 12.7 g/dL, a leukocyte count of 6.5 × 10⁹/L, and a creatinine level of 2.8 mg/dL. Her liver function was stable, and she had no ascites on examination.

2. On the basis of the pleural fluid analysis, which one of the following is the most likely etiology for the patient’s bilateral pleural effusions?
   a. Uncomplicated parapneumonic effusion
   b. Complicated parapneumonic effusion
   c. Malignancy
   d. Hepatohydrothorax
   e. Heart failure

It is diagnostically helpful to classify pleural effusions as either transudates or exudates on the basis of Light criteria. An exudate is defined by Light criteria as a pleural total protein/serum total protein ratio greater than 0.5 or a pleural LDH/serum LDH ratio greater than 0.6. The patient’s pleural effusion is a transudate because the protein and LDH concentrations in the pleural fluid are very low compared with the serum values. Her pleural protein/serum protein ratio was 0.4, and her pleural LDH/serum LDH ratio was 0.37.

Both uncomplicated and complicated parapneumonic effusions occur in the setting of lower lung infection and present as exudates. The effusion is “complicated” if the pH is less than 7.2 or if the Gram stain is positive. Because this patient’s pleural fluid was transudative, parapneumonic effusions are unlikely to be responsible for her effusions.
Our patient had no infiltrates, fever, leukocytosis, or other findings of infection. Pleural effusions associated with malignancy are usually exudates as well. Our patient had no weight loss or other constitutional symptoms that would suggest malignancy. Hepatohydrothorax is a right-sided transudative pleural effusion caused by refractory ascites. It is due to increased intraperitoneal pressure from massive ascites and is difficult to treat. This patient has a history of liver transplant due to PSC, but she had no ascites on examination and had normal hepatic synthetic function. Heart failure is most often transudative and is the most likely explanation for this effusion.

Additional laboratory testing revealed a brain-type natriuretic peptide (BNP) level of 1067 pg/mL (reference range, <114 pg/mL), which further supports heart failure as a cause of her chronic cough and recurrent pleural effusions. Laboratory testing, chest radiography, and pleural fluid analysis are helpful in establishing a diagnosis of heart failure, but it is ultimately a clinical diagnosis. Our patient had trace peripheral edema but denied orthopnea or paroxysmal nocturnal dyspnea, which made heart failure probable but not certain at this point.

3. Which one of the following is the most appropriate next test in the diagnostic evaluation of this patient?
   a. Transthoracic echocardiography (TTE)
   b. Transesophageal echocardiography
   c. Coronary artery catheterization
   d. Right heart catheterization
   e. Cardiac magnetic resonance imaging

Transthoracic echocardiography is the most appropriate next test in the evaluation of obvious or suspected heart failure. It assesses both systolic and diastolic function and allows a good evaluation of heart valves. Transesophageal echocardiography can also assess systolic function and has better resolution of the left atrium and mitral valve. However, it is invasive and requires sedation, making noninvasive TTE the best next test in this case. Transesophageal echocardiography would be preferred to TTE in certain clinical situations, such as evaluating vegetations in suspected infective endocarditis or ruling out left atrial thrombus before electrical cardioversion, but such scenarios are not relevant to the current case.

Ischemic cardiomyopathy is a common cause of heart failure, and coronary artery catheterization is the criterion standard for detection of coronary artery disease. Although coronary artery catheterization is often required in evaluating for heart failure, a noninvasive TTE should be performed first. If left ventricular systolic function is reduced (ie, decreased ejection fraction) and ischemic cardiomyopathy is suspected, then it would be reasonable to next conduct a functional cardiac study to detect hibernating myocardium and consider coronary angiography. To proceed directly to coronary artery catheterization at this point would be premature. Right heart catheterization is useful for exact measurement of pulmonary artery pressures. It would be used to confirm or quantify pulmonary hypertension or constrictive pericarditis but would never be done without first obtaining a noninvasive TTE. Cardiac magnetic resonance imaging is a new technology that provides excellent morphologic assessment of the myocardium and pericardium and, indeed, is considered to be the criterion standard for measurements of pericardial thickness. However, respiratory variations in cardiac hemodynamics, the hallmark finding of constrictive physiology, may not be as readily appreciated as on Doppler echocardiography.

The patient underwent TTE, which showed a left ventricular ejection fraction of 62%, with normal left and right ventricular size and function. Because echocardiography revealed normal left ventricular systolic and diastolic function, it was not certain that heart failure was the cause of her symptoms despite her pleural effusions and elevated BNP level. She was treated symptomatically with a plan for a follow-up TTE in 3 months if her symptoms persisted.

With the aid of a respirometer, echocardiography revealed reciprocal respiratory ventricular interdependence. Specifically, blood flow velocity varied during mitral inflow with respiration, and blood flow in the hepatic veins reversed during diastole. The cardiology service was consulted and interpreted these new findings of altered mitral and tricuspid inflow velocities with respiration as classic findings for constrictive pericarditis.

4. Which one of the following most likely led to the pericardial calcification that resulted in this patient’s condition?
   a. Prior radiation therapy
   b. Autoimmunity
   c. Idiopathic or viral etiology
   d. Tuberculosis
   e. Medications

Prior radiation therapy is a known cause of constrictive pericarditis, but our patient had no such history. Connective tissue diseases, such as rheumatoid arthritis and systemic lupus erythematosus, have been reported to cause 3% to 7% of constrictive pericarditis, but our patient had no history of...
such disease. A Her history of PSC may have played a role, but no formal reports of this specific association have been made. The most common cause of constrictive pericarditis is idiopathic or viral, and that was the presumed etiology in this case. Although common in developing countries, tuberculosis pericarditis is rare in the United States. It is frequently associated with pericardial calcification and is a consideration in this patient, especially given her immunosuppression. Findings on a serum mycobacterium Quantiferon test for tuberculosis were negative. Medication-induced constrictive pericarditis is uncommon but has been reported with procainamide and hydralazine.

Once a diagnosis of constrictive pericarditis was confirmed for our patient, we formulated a treatment plan.

5. Which one of the following is the best management plan for this patient’s condition?
   a. Medical management with outpatient diuresis: 40 mg/d of furosemide orally
   b. Medical management with inpatient diuresis: furosemide drip at 10 mg/h titrated for a goal diuresis of 1.5 L/d
   c. Surgical management: proceed directly to median sternotomy and complete pericardiectomy
   d. Surgical management: coronary angiography followed by median sternotomy and complete pericardiectomy
   e. Referral to a hospice

No good medical treatment exists for constrictive pericarditis. Whether the patient’s heart failure is managed on an inpatient or outpatient basis, diuresis alone will not improve her symptoms and is not adequate therapy. Surgical pericardiectomy is curative in constrictive pericarditis and is the appropriate management in this case. However, surgery should not be performed without coronary angiography for several reasons. First, angiography can determine whether coronary artery atherosclerosis is present. If high-risk lesions (eg, left main disease or multivessel disease) are detected, coronary artery bypass grafting can be done at the same time as pericardiectomy with little added morbidity. The detection of coronary artery disease would also help assess whether coronary ischemia was contributing to the patient’s heart failure. Pericardiectomy is the definitive treatment for constrictive pericarditis and should be performed promptly, but not until coronary angiography has been completed. Hospice referral would not be indicated in this case because the patient’s heart failure is likely reversible with pericardiectomy.

Coronary angiography was performed, revealing minimal coronary artery disease, with 20% to 40% stenosis of the major vessels. No interventions were made. On the basis of these findings, we consulted the cardiothoracic surgery service, which recommended proceeding to pericardiectomy. During the operation, extensive plate-like calcification of the pericardium, between 0.4 and 1 cm thick, was observed. The pericardium was successfully removed, and the patient’s postoperative course was uneventful. At her 6-month cardiology follow-up visit, her cough and pleural effusions had completely resolved, and she had normal exercise tolerance. Follow-up echocardiography showed normal cardiac function without constrictive physiology.

DISCUSSION

This case is a good illustration of how challenging the diagnosis of constrictive pericarditis can be. Diagnosis is often delayed, as it was in our patient. Key factors in the delay of her diagnosis were the long-time presence of pericardial calcification and the initial lack of peripheral edema. Findings on TTE can appear normal in patients with constrictive pericarditis, especially early on in its course, as occurred in this case. The etiology of constrictive pericarditis was studied in a series of 163 patients. The most common cause was idiopathic (46%), followed by prior cardiac surgery (37%), radiation treatment (9%), and miscellaneous (8%). Patients present with signs of fluid overload, such as peripheral edema or ascites, or with diminished cardiac output, such as dyspnea on exertion. In one series, 67% of patients presented with heart failure symptoms. Our patient’s presentation was unusual because she had pleural effusions without substantial peripheral edema. The Kussmaul sign (lack of inspiratory decline and/or inspiratory rise in jugular pressure) may be present in patients with constrictive pericarditis but may also be confused with large “V” waves, as seen in patients with severe tricuspid valvular disease or right-sided heart failure. In a recent series of 135 patients with constrictive pericarditis, only 21% of patients had the Kussmaul sign. Our patient did not have the Kussmaul sign.

The distinction between constrictive pericarditis and restrictive cardiomyopathy is critical because the treatment approaches and associated outcomes are highly disparate. Surgical pericardiectomy for constrictive pericarditis is curative, whereas patients with restrictive cardiomyopathy are managed medically and have a relatively poor prognosis. No single test can completely distinguish constrictive pericarditis from restrictive cardiomyopathy, but echocardiography is the most informative. Respiratory variation in ventricular filling and central venous flow velocities is seen in constrictive pericarditis. Indeed, this patient’s constrictive pericarditis was not diagnosed until she underwent echocardiography with a respirometer that showed ventricular interdependence, reciprocal changes in the atrioventricular valve Doppler signals (early passive mitral inflow velocity: increased during expiration, decreased
during inspiration, and converse for tricuspid inflow), and end-diastolic hepatic vein flow reversal during expiration.8

Tissue Doppler echocardiography is also useful in making the diagnosis. In restrictive cardiomyopathy, the myocardial mitral annular velocity is diminutive, whereas in constrictive pericarditis it is high normal or increased. The ratio of early passive filling velocity to early diastolic mitral annular velocity is known as the E/e’ ratio, a measurement of left ventricular filling pressures. This ratio is increased significantly in restrictive cardiomyopathy but is normal in constriction.

Large series have demonstrated the efficacy of pericardiectomy for constrictive pericarditis,9 but early deaths occur from low-output syndrome regardless of surgical technique.4 One recent study showed that patients with abnormal left ventricular contractility and relaxation properties assessed by preoperative cardiac catheterization had a higher mortality rate.10 Patients who have constrictive pericarditis due to radiation therapy also have poorer long-term outcomes.

REFERENCES

Correct answers: 1. d, 2. e, 3. a, 4. e, 5. d