

CLINICAL PROBLEM-SOLVING

Undercover and Overlooked

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In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.

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A 67-year-old overweight man was seen by his physician because of a two-month history of shortness of breath, a nonproductive cough, and bilateral swelling of the lower extremities. He also reported a tight sensation in the neck, occasional wheezing, and an increase in dyspnea after meals. The patient noted the onset of symptoms soon after a hunting trip in November. He had no other constitutional symptoms and had not ingested or had contact with anything unusual during his trip. His history was notable for gastroesophageal reflux and a remote pneumonia. He had no history of lung or heart disease, occupational exposure, allergies, or tobacco use.

The onset of symptoms after the patient's hunting trip raises the possibility of a relationship between this event and the illness. However, he reports no unusual exposures. Given his history of gastroesophageal reflux and increased dyspnea after meals, bronchospasm due to reflux may be a contributing factor. However, bilateral edema of the lower extremities is suggestive of a cardiac cause of his dyspnea. The patient's history suggests broadly either a pulmonary or cardiac disorder, so the differential diagnosis at this point is extensive, including pulmonary infection, pulmonary emboli, obstructive airway disease, hypersensitivity pneumonitis, pulmonary hypertension, and heart failure.

Because of worsening respiratory symptoms, the patient was admitted to a local medical center. At the time of his admission, he had a nonproductive cough and was able to walk only a short distance without stopping, because of dyspnea. He reported orthopnea but not paroxysmal nocturnal dyspnea. On examination, he was afebrile, his blood pressure was 150/86 mm Hg, his heart rate was 110 beats per minute, and his respiratory rate was 28 breaths per minute. His weight was 109 kg, with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 34.4 kg. The lung examination demonstrated scattered, brief expiratory wheezes in both lungs. The jugular venous pressure could not be visualized. The heart sounds were distant, with no audible murmur, rub, or gallop. The lower extremities had symmetric, pitting edema (2+).

The results of blood tests were as follows: hemoglobin, 13.1 g per deciliter; hematocrit, 40 percent; platelet count, 182,000 per cubic millimeter; white-cell count, 6000 per cubic millimeter, with a normal differential count; sodium, 136 mmol per liter; potassium, 5.0 mmol per liter; chloride, 105 mmol per liter; bicarbonate, 24 mmol per liter; blood urea nitrogen, 13 mg per deciliter (4.6 mmol per liter); serum creatinine, 1.1 mg per deciliter (97.2 μ mol per liter); blood glucose, 128 mg per deciliter (7.1 mmol per liter); total protein, 6.9 g per deciliter; albumin, 3.5 g per deciliter; total bilirubin, 1.0 mg per deciliter (17.1 μ mol per liter); aspartate aminotransferase, 33 U per liter; alanine aminotransferase, 33 U per liter; and alkaline phosphatase, 160 U per liter. Urinalysis and liver-function tests showed no abnormalities. Initial arterial-

blood gas analysis (with the patient breathing room air) revealed the following values: pH 7.47; partial pressure of carbon dioxide, 34 mm Hg; partial pressure of oxygen, 62 mm Hg; and bicarbonate concentration, 25 mmol per liter. A chest radiograph showed cardiomegaly and mildly increased pulmonary vasculature. An electrocardiogram showed sinus tachycardia at a rate of 110 beats per minute with diffuse T-wave inversions and low voltage. The values for creatine kinase and the MB fractions, measured serially, were normal.

Although cough and dyspnea may reflect either cardiac or pulmonary disease, the presence of orthopnea suggests elevated left ventricular filling pressure in the setting of increased venous return and points to a cardiac cause. Physical examination is often helpful in distinguishing the cause of these symptoms but provides little guidance in the present case. It is unfortunate that the jugular venous pressure could not be adequately evaluated, since an elevated pressure would point to possible heart failure. The findings on the chest radiograph are consistent with a cardiac condition. I would also want to know the level of B-type natriuretic peptide, since an elevated level would also support heart failure as the cause of dyspnea, particularly in the setting of left ventricular systolic dysfunction.

A transthoracic echocardiogram showed normal left ventricular size and function. The right ventricle was mildly thickened but not enlarged or hypcontractile. The aortic valve was thickened, with no stenosis or regurgitation. There was no other valvular abnormality. A perfusion imaging study was performed with the use of dobutamine and single-photon-emission computed tomography (CT). During infusion of dobutamine (30 μ g per kilogram per minute intravenously), the patient's heart rate increased to 132 beats per minute (85 percent of the predicted heart rate, 130 beats per minute). Perfusion imaging of the left ventricle was normal at the peak heart rate and at rest.

The echocardiographic finding of right ventricular thickening without evidence of dilation suggests that the pulmonary-artery pressure is elevated, but the absence of tricuspid regurgitation precludes estimation of the right ventricular (and thus, pulmonary-artery) systolic pressure. There was no apparent left ventricular systolic dysfunction or valvular abnormality. It would be useful to know

whether there was echocardiographic evidence of diastolic dysfunction. The results of myocardial perfusion imaging suggest that myocardial ischemia is not the cause of the patient's dyspnea.

Spiral CT scanning of the chest, which was performed with the intravenous administration of contrast material, showed no evidence of pulmonary embolus or infiltrate. Hilar, subcarinal, and pretracheal lymph nodes that were small and calcified and a small right-sided pleural effusion were noted. An ultrasound study of the bilateral lower extremities showed no evidence of deep venous thrombosis.

The patient sought a second opinion at another regional medical center. Pulmonary-function testing there showed a forced vital capacity (FVC) of 2.5 liters (59 percent of the predicted value), a forced expiratory volume in one second (FEV_1) of 1.9 liters (65 percent of the predicted value), a ratio of FEV_1 to FVC of 76 percent, a forced expiratory flow (between 25 percent and 75 percent of FVC) of 1.5 liters per second (54 percent of the predicted value), a total lung capacity of 5.4 liters (85 percent of the predicted value), and a residual volume of 1.9 liters (77 percent of the predicted value). There was no response to bronchodilator testing. A sleep study showed 21 apneic and 12 hypopneic epi-



Figure 1. Radiograph of the Chest Showing Cardiomegaly and Increased Interstitial Markings.

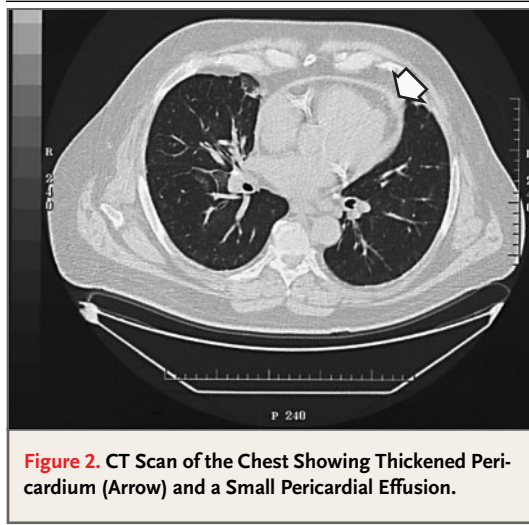


Figure 2. CT Scan of the Chest Showing Thickened Pericardium (Arrow) and a Small Pericardial Effusion.

isodes per hour of sleep, with a minimal oxygen saturation of 83 percent. Treatment with nasal continuous positive airway pressure (CPAP) of 17 cm of water resulted in a reduction in apneic and hypopneic episodes to 20 per hour and a minimal oxygen saturation of 90 percent. Nocturnal CPAP and empirical therapy with oral diuretics were started.

Pulmonary thromboembolism, a possible cause of dyspnea and hypoxemia, is probably not the cause of the patient's symptoms on the basis of the chest CT scan. The results of pulmonary-function testing indicate a mixed restrictive and obstructive process. The patient's obesity may contribute to restrictive lung disease. Presumably, sleep apnea was suspected on the basis of the patient's obesity, hypertension, and significant edema. However, dyspnea is not a common symptom of sleep apnea. A minority of patients with obstructive sleep apnea have pulmonary hypertension, a condition that has been associated with an elevation of left ventricular filling pressure and the duration of oxygen desaturation. Sleep apnea is associated with left ventricular systolic and diastolic dysfunction, which may improve with CPAP therapy.

Despite these interventions, the patient had worsening dyspnea and edema. His weight increased to 130 kg. He presented to our institution for evaluation nine months after his initial symptoms developed. A chest radiograph showed mild cardiomegaly and increased interstitial markings with possible septal lines (Fig. 1). To evaluate for possi-

ble interstitial lung disease, a high-resolution CT scan of the chest was ordered; it showed no evidence of pulmonary disease but did show a thickened pericardium (Fig. 2).

The focus of attention has shifted from the pulmonary system to the cardiovascular system. A repeated CT scan of the chest showed a thickened pericardium, which raises the possibility of constrictive pericarditis. Although radiographic evidence of pericardial thickening is the anatomical hallmark of constrictive pericarditis, this finding is not specific for constrictive pericarditis and may occur in patients without physiological constriction. Conversely, patients with constrictive pericarditis may not have pericardial thickening on imaging studies. Hemodynamic measurements during cardiac catheterization may be necessary to diagnose constrictive pericarditis if noninvasive methods, such as echocardiography or pericardial imaging, are not conclusive.

The patient underwent right- and left-heart catheterization, which showed the following hemodynamic values: mean right atrial pressure, 20 mm Hg; right ventricular pressure, 48/20 mm Hg; pulmonary-artery pressure, 48/22 mm Hg (mean pressure, 30 mm Hg); mean pulmonary-capillary wedge pressure, 20 mm Hg; left ventricular pressure, 130/20 mm Hg; and aortic pressure, 130/80 mm Hg. Simultaneous right and left ventricular diastolic pressures showed equalization and a dip-and-plateau waveform pattern; simultaneous measurements of ventricular systolic pressure showed discordance, a finding that is consistent with increased ventricular interaction (Fig. 3). Cardiac output, as measured by the Fick method, was 5.3 liters per minute, and the cardiac index was 2.2 liters per minute per square meter of body-surface area. The left ventricular ejection fraction was normal. There were no clinically significant coronary-artery stenoses present.

The hemodynamic findings of equalized diastolic pressures and rapid early filling of the ventricles (a dip-and-plateau waveform pattern) is suggestive of constrictive pericarditis. However, these findings are not specific for constrictive pericarditis and may be present in other causes of heart failure, particularly restrictive cardiomyopathy. A number of hemodynamic criteria have been used to differentiate constrictive pericarditis from restrictive cardiomy-

COMMENTARY

opathy, since the two conditions are similar with respect to the clinical presentation, findings on physical examination, and catheterization results. However, the diagnosis of constrictive pericarditis should be based on two physiological findings: a dissociation of intrathoracic and intracardiac pressures and an increased ventricular interaction.

In normal persons, changes in intrathoracic pressure during respiration are transmitted to the heart through the pericardium, resulting in decreased intracardiac pressure during inspiration and increased intracardiac pressure during expiration. In patients with constrictive pericarditis, the heart is “shielded” from these changes in intrathoracic pressure. Increased interaction between the left and right ventricles occurs because of the decreased distensibility of the pericardium. Since ventricular filling is limited by a relatively fixed cardiac volume, increased venous return and filling of the right ventricle during inspiration impair left ventricular filling. This interdependence, evident as respiratory discordance of left and right ventricular systolic pressures, is a highly reliable hemodynamic factor for distinguishing constrictive pericarditis from other causes of heart failure.

The patient was referred to a cardiothoracic surgeon for pericardiectomy. Inspection of the pericardium revealed dense thickening of nearly 10 mm in regions. Pericardiectomy without cardiopulmonary bypass was performed with resection of the anterior pericardium between the right and left phrenic nerves and from the great arteries superiorly to the diaphragm inferiorly. During the procedure, central venous pressure decreased from 24 mm Hg after induction to 12 mm Hg at the conclusion of the procedure. Histologic examination of the pericardium revealed fibrosis with granulomatous inflammation (Fig. 4). Stains and cultures for bacteria, fungi, viruses, and acid-fast bacilli were negative. The patient was discharged home five days after surgery. He has returned to a normal level of activity, with no dyspnea on exertion, and has required only low-dose oral diuretic therapy for mild edema of the bilateral lower extremities.

Although granulomatous inflammation was present in the resected pericardium, this finding is observed in several conditions, including infectious, metabolic, and rheumatologic diseases.

This case demonstrates the challenges in recognizing a slowly progressive and uncommon cause (constrictive pericarditis) of a very common clinical syndrome (heart failure). Constrictive pericarditis is defined as chronic fibrous thickening of the wall of the pericardial sac that results in abnormal diastolic filling.¹ In patients who have symptoms and signs of heart failure with preserved ventricular systolic function, the diagnosis of constrictive pericarditis as well as causes of abnormal myocardial relaxation or compliance (including myocardial hypertrophy, ischemia, restrictive cardiomyopathy, and infiltrative diseases) should be considered. Determination of the cause of left ventricular systolic dysfunction has been found to have prognostic implications for long-term survival.² This case illustrates that identification of the cause of diastolic heart failure, which is often overlooked, may lead to definitive therapy for the condition.

Why was there such a delay between the onset of the patient’s symptoms and the diagnosis of constrictive pericarditis? The course of the disease is typically quite slow, and its symptoms and signs are not specific. As a result, in many cases symp-

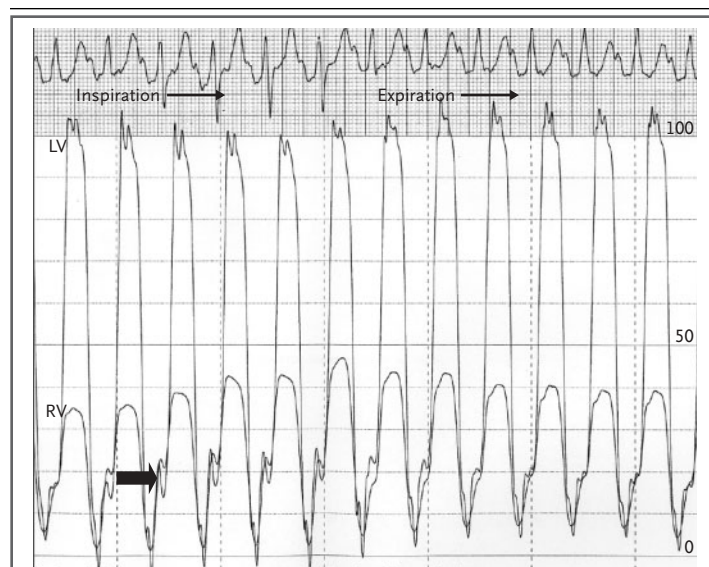


Figure 3. A Hemodynamic Tracing of Simultaneous Right Ventricular (RV) and Left Ventricular (LV) Pressures, Showing Discordant Systolic Pressures during Respiration (Thin Arrows) and Equalization of Diastolic Pressures (Thick Arrow).

toms are present for 12 months or longer before a diagnosis is established.³ Prior pericarditis, cardiac surgery, and radiation therapy are the most commonly identified causes of constrictive pericarditis, accounting for approximately 50 percent of cases, but one third of cases remain idiopathic in origin.³ This patient's medical history did not suggest a cause of constrictive pericarditis. Furthermore, the findings on physical examination may be difficult to appreciate. The jugular venous pressure and waveforms, which can offer important clues to the diagnosis, may not have been appreciated because of the patient's body habitus and the marked elevation of the venous pressure. An audible pericardial "knock," caused by the cessation of early diastolic ventricular filling (which, in turn, was caused by the constrictive pericardium),⁴ is not a sensitive sign of constrictive pericarditis, particularly in the absence of pericardial calcification.⁵

Although right and left ventricular diastolic pressures are equalized in constrictive pericarditis because of limitation of diastolic filling by the pericardium, symptoms and signs of right-sided heart failure (including edema in the lower extremities and ascites) predominate. That is especially true early in the course of the disease, since the filling pressures are normally lower in the right ventricle

than in the left ventricle. Consequently, the diagnosis of constrictive pericarditis should be considered in patients with evidence of right-sided heart failure that is out of proportion to the severity of pulmonary or left-sided heart disease. With progression of the disease and the associated increase in diastolic filling pressures (to levels above 15 mm Hg), symptoms and signs of left heart failure may develop.

Echocardiography is very useful for evaluating hemodynamic changes in constrictive pericarditis.^{6,7} A dissociation between intrathoracic and intracardiac pressures can be detected as reciprocal changes in diastolic flow velocities across the tricuspid and mitral valves during respiration.^{6,7} However, such measurements may not be routinely performed unless the diagnosis of constrictive pericarditis is suspected. As in the present case, echocardiography may be ordered to rule out common causes of heart failure, such as left ventricular systolic dysfunction or valvular disease, and signs of constrictive pericarditis are not assessed. Not infrequently, the broad, descriptive term of diastolic dysfunction is applied in the setting of symptoms or signs of heart failure with normal left ventricular systolic function.⁸ Instead, a detailed examination of the diastolic filling pattern should be performed to confirm and characterize abnormal diastolic function and, potentially, to determine its specific cause.

Visualization of a thickened pericardium (3 mm or greater) by CT or magnetic resonance imaging may suggest the diagnosis of constrictive pericarditis, as it did in this patient. This finding, although a hallmark in the traditional definition of this disease,¹ has limited sensitivity,⁹ and pericardial thickness may not be abnormal early in the disease process. Because of the limited sensitivity of this finding, multiple diagnostic approaches are often necessary to confirm the diagnosis of constrictive pericarditis before therapeutic intervention is undertaken.

Surgical pericardiectomy is a highly effective and potentially curative treatment for heart failure due to constrictive pericarditis. However, long-term survival is worse for patients with severe symptoms of heart failure than it is for those with milder symptoms,³ a factor that underscores the need for early diagnosis and treatment of this frequently overlooked condition.

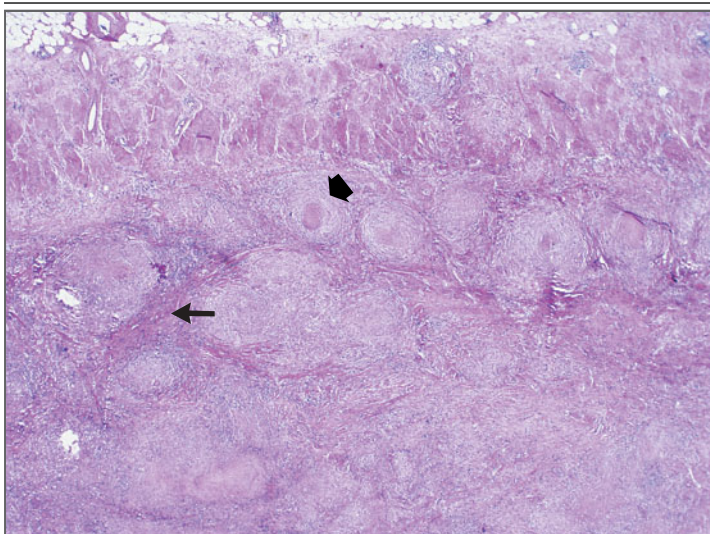


Figure 4. A Histologic Specimen of the Pericardium, Showing Fibrosis (Long Arrow) and Granulomatous Inflammation (Short Arrow) (Hematoxylin and Eosin).

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