78-Year-Old Man With Metastatic Squamous Cell Carcinoma, Dyspnea, and Hypotension

John P. Bois, MD*; Alfred G. Valles, MD†; and Lawrence J. Sinak, MD‡

A 78-year-old man with a 30 pack-year smoking history, hypertension, hyperlipidemia, and paroxysmal atrial fibrillation presented with several months of fatigue, nausea, vomiting, cough, and shortness of breath. Chest radiography suggested a right pulmonary mass and cardiomegaly. Subsequent computed tomography of the chest and abdomen revealed the following: a mass measuring 4.8 × 4.0 cm in the right middle lobe of the lung, right and left lower lobe nodules, abnormal perihilar lymph nodes, possible left adrenal metastasis, and a small pericardial effusion. Follow-up bronchoscopy with biopsy confirmed grade II squamous cell carcinoma. The patient was referred to Mayo Clinic for further work-up.

Outpatient evaluation revealed an anxious and dyspneic man. Findings were as follows: respiratory rate, 25 breaths/min; oxygen saturation, 97% while breathing room air; heart rate, to 102 beats/min (tachycardia), blood pressure, 85/45 mm Hg (hypotension), and no fever (temperature, 36.7°C).

The patient was admitted to the cardiology service for evaluation and management of dyspnea and hypotension. Cardiac examination with the head elevated to 45° revealed jugular venous distention at 10 cm that was increased by inspiration. Heart tones were distant with no murmurs, rubs, or gallops. Inspiratory crackles could be heard in the lower lung fields bilaterally, and the trachea was midline. Electrocardiography (ECG) demonstrated an irregularly irregular tachycardia with low voltages.

1. On the basis of this patient's initial presentation, which one of the following is the most likely diagnosis?

a. *Acute coronary syndrome (ACS)*
b. *Cardiac tamponade*
c. *Pneumothorax*
d. *Symptomatic atrial fibrillation*
e. *Pulmonary embolus*

All of these possibilities must be considered as part of the initial differential diagnosis.

The patient has 3 known Framingham risk factors for coronary events (smoking, hypertension, age). Even with appropriate lipid control, his 10-year risk of an ACS is estimated to be 21%.

Although the patient's risk for ACS is high and he has hypotension and dyspnea, which are common findings in ACS, we must remember the clinical context and that 2 of the following 3 criteria must be met for a diagnosis of ACS: chest pain, ECG changes, and abnormal cardiac biomarkers. He is not reporting the typical crushing chest pain seen in ACS, he has no ischemic ECG changes, and his cardiac biomarkers do not reveal a demonstrable change. He has recently been diagnosed as having metastatic pulmonary neoplasm, a known cause of nearly 34% of malignant pericardial effusions.[1] His jugular venous pressure is increased with inspiration, his heart tones are distant, and a pericardial effusion had been revealed on previously performed computed tomography, making cardiac tamponade the most likely diagnosis.

Normal inspiration is associated with an increased venous return that is easily accommodated by right ventricular expansion that allows for a decrease in jugular venous pressure. In tamponade, the pericardium and fluid within the pericardial space do not allow the right ventricle to expand and accept the increased venous return encountered with inspiration. Consequently, right atrial filling is impaired, and the jugular vein either does not collapse or is distended with inspiration. This abnormal jugular sign is known as the Kussmaul sign.

Pneumothorax is a rare manifestation of pulmonary malignancy, with 1 study quoting a less than 5% occurrence.[2] Biopsy-induced pneumothorax is also an uncommon occurrence, particularly in this case given that the biopsy was performed several months before the current presentation. The presentation of pneumothorax typically includes acute dyspnea, decreased breath sounds, and often deviation of the trachea away from the midline. The patient in the current clinical scenario did not have apparent tracheal deviation or decreased lung sounds.

The patient has known atrial fibrillation and has developed a "rapid ventricular response." This often causes a sense of dyspnea but rarely leads to hypotension when rates

*Resident in Internal Medicine, Mayo School of Graduate Medical Education, Mayo Clinic, Rochester, MN.
†Resident in Cardiovascular Diseases, Mayo School of Graduate Medical Education, Mayo Clinic, Rochester, MN.
‡Adviser to residents and Consultant in Internal Medicine, Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN.

See end of article for correct answers to questions.

Individual reprints of this article are not available. Address correspondence to Lawrence J. Sinak, MD, Division of Cardiovascular Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (sinak.lawrence@mayo.edu).

are less than 150 beats/min. In this clinical scenario, his tachycardia and hypotension are more likely a consequence of another acute illness rather than a primary cause of his decline.

Patients with pulmonary malignancy have an increased risk of deep venous thrombosis and pulmonary embolism, with an estimated incidence between 1.8% and 13.6%.[3] The pathophysiology is thought to be related to a hypercoagulable state in the setting of increased coagulation factors and tissue necrosis with associated acute phase reactants. Although pulmonary embolism is possible in this patient, he has no difficulties with oxygenation, and a pulmonary embolism would not account for his findings on cardiac examination.

Initial laboratory results were unremarkable except for the following: an elevated creatinine level suggestive of decreased renal perfusion, slight hypokalemia (potassium, 3.5 mEq/L), a normal thyroid-stimulating hormone level, and slightly elevated levels of serial troponins without a demonstrable change (0.02 ng/mL, 0.01 ng/mL, 0.02 ng/mL).

Chest radiography demonstrated small bibasilar effusions greater on the right side than the left, with prominent pulmonary vascularity and an enlarged cardiac silhouette. Subsequent ECG revealed ST-segment elevation in the inferior leads, which raises concern for acute ischemia.

Emergent echocardiography demonstrated a large pericardial effusion.

2. Which <u>one</u> of the following characteristics of this patient's presentation does <u>not</u> indicate tamponade and the need for emergent pericardiocentesis?

a. *Large pericardial effusion*
b. *Rapid accumulation of pericardial effusion*
c. *Hypotension*
d. *Elevated creatinine level*
e. *Dyspnea*

The timing of tamponade development depends more on the rate of pericardial fluid accumulation than on the amount of fluid present. When fluid accumulates slowly, the pericardium has time to stretch and therefore can accommodate up to 2 liters before hemodynamic compromise occurs.[4] Therefore, emergent pericardiocentesis would not be indicated in patients with large pericardial effusions, provided that they are hemodynamically stable. Conversely, rapid accumulation of even a small amount of pericardial fluid can trigger tamponade. Recent computed tomography of the chest showed that our patient had a small pericardial effusion. Transthoracic echocardiography revealed a large pericardial effusion suggestive of rapid accumulation of pericardial fluid and the need for pericardiocentesis.

With tamponade patients develop hypotension, 1 of the key components of the Beck triad[5] (hypotension, distant heart sounds, and elevated jugular venous pressure) and a low cardiac output state. This contributes to end organ hypoperfusion and, as in this patient, often results in acute renal failure.[6] Therefore, any acute end organ hypoperfusion that is attributed to cardiac tamponade is an indication for pericardiocentesis.

Dyspnea despite appropriate oxygen saturation is one of the most common presenting symptoms in patients with cardiac tamponade and is an indication for pericardiocentesis.[6] Emergent pericardiocentesis was performed. The patient was administered 50 µg of fentanyl and 3 mg of midazolam. With echocardiographic guidance, a 16-gauge angiocatheter was introduced via the periapical approach along the 4th left intercostal space in the midclavicular line, and 450 mL of sanguineous fluid was retrieved.

Analysis of this fluid yielded the following results: glucose effusion, 208 mg/dL; serum glucose level, 204 mg/dL; protein effusion, 5.1 g/dL, serum protein level, 6.3 g/dL, and hemolyzed lactate dehydrogenase (LDH). Cytology was negative for malignancy.

3. Given the results of the pericardial fluid analysis, which <u>one</u> of the following is the <u>most likely</u> diagnosis?

a. *Chronic heart failure*
b. *Uremic effusion*
c. *Nephrotic syndrome*
d. *Malignant effusion*
e. *Myxedema*

Despite some controversy, the same Light criteria used to analyze pleural effusion can be effectively used to examine pericardial effusions. An exudate is defined as a ratio of total protein effusion to total serum protein of greater than 0.5 or a ratio of LDH effusion to serum LDH greater than 0.6. This test is highly sensitive (98%) but less specific (72%).[7] Unfortunately, in this case the LDH sample hemolyzed. Nonetheless, the total protein effusion to serum ratio was 5.1 divided by 6.3 or 0.81, thus indicating an exudate. Chronic heart failure, uremia, and nephrotic syndrome usually present with transudative effusions.

Malignancies cause an exudative process and, despite the negative findings on cytology, remain the most likely diagnosis. Studies have demonstrated that pericardial effusions in patients with non–small cell lung cancer are most likely a result of their underlying malignancy regardless of cytology.[8] Indeed, the sensitivity of cytology for identifying malignancy within effusions is often low and increases with repeated testing.[9] In this case, the hemorrhagic nature of the effusion was thought to be the major reason for the negative cytology results.

Myxedema is a known cause of pericardial effusion.[10] However, it often induces a transudative process rather than an exudative one. Moreover, this patient's thyroid studies revealed a normal thyroid-stimulating hormone level with low T_3 and T_4 levels indicative of sick euthyroid syndrome rather than myxedema.

A pericardial catheter was left in place for intermittent aspiration. For pericardial pain the catheter was used to intermittently administer 10 mL of 1% xylocaine. In addition, oral naproxen in combination with omeprazole was given for 14 days.

4. Which <u>one</u> of the following is the <u>most likely</u> complication in this patient after pericardiocentesis?

a. *Pleuropericardial fistula*
b. *Pneumothorax*
c. *Recurrent effusion*
d. *Bacteremia*
e. *Cardiac perforation*

A 2002 Mayo Clinic study examined complication rates of pericardiocentesis in 1127 patients.[11]

Pleuropericardial fistula occurred 0.8% of the time and was the third most common complication.

Pneumothorax was the second most common complication with a 1.1% incidence (8 patients had a small pneumothorax evident on radiography and 5 had pneumothoraces that required a chest tube).

Recurrent effusion was by far the most common complication. In this study, pericardial effusion recurred more frequently in patients who did not have extended pericardial drainage via a pigtail catheter than in those who did (27% vs 14%). In a subset study of patients with malignant pericardial effusion, the rate of recurrent effusion was 36% without and 12% with extended catheter drainage.[12] Postprocedural bacteremia likely associated with catheter placement during pericardiocentesis was documented in 0.1% of patients. This was the rarest of the adverse effects. Cardiac perforation was also exceedingly rare, with 0.4% of patients experiencing this complication.

After pericardiocentesis, the patient's clinical status and symptoms initially improved. However, approximately 1 hour later his dyspnea recurred. Telemetry showed an irregularly irregular rhythm without discernible P waves.

On physical examination, the patient's vital signs were as follows: heart rate, 150 beats/min; blood pressure, 80/40 mm Hg; respiratory rate, 24 breaths/min with an oxygen saturation of 93%. Heart sounds were easily auscultated. Suction was applied to the pigtail catheter without return. Emergent radiography with a portable X-ray unit revealed stable small bilateral pleural effusions and a normal-sized cardiac silhouette; findings were otherwise unremarkable.

5. Which <u>one</u> of the following would be the <u>next best</u> step in the treatment of this patient?

a. *Follow-up echocardiography*
b. *A second emergent pericardiocentesis*
c. *Pleurocentesis*
d. *Administration of broad-spectrum antibiotics*
e. *Electric cardioversion*

Follow-up echocardiography would be useful if recurrent pericardial effusion, free wall rupture, or stunned myocardium were of concern. Cardiac perforation is a remote possibility given the recent procedure. However, the likelihood of recurrent pericardial effusion in this case is small. As mentioned, the incidence of cardiac perforation with echocardiography-guided pericardiocentesis is exceedingly low (0.4% incidence). In addition, cardiac heart tones were not muffled, and no drainage was obtainable via the pigtail catheter, making a second pericardiocentesis unnecessary.

Given the stability of chest radiographic findings, a cardiac rather than pulmonary etiology is the favored diagnosis. Therefore, pleurocentesis is not indicated.

Broad-spectrum antibiotics are indicated for suspected sepsis. A diagnosis of sepsis can be established when 2 of the following 4 criteria for systemic inflammatory response syndrome are met: temperature higher than 38.5°C or lower than 35.0°C; heart rate greater than 90 beats/min; respiratory rate greater than 20 breaths/min or $Paco_2$ less than 32 mm Hg; and white blood cell count greater than 12.0×10^9/L, less than 4.0×10^9/L, or greater than 10% immature (band) forms in the context of known or suspected infection. This patient meets 2 of these 4 criteria, but there is no clinical concern for or obvious nidus of infection.

Atrial fibrillation often causes hypotension and can cause pulmonary edema when the ventricular response rate is greater than 150 beats/min. With an increased heart rate, there is decreased diastolic filling time, resulting in decreased stroke volume and higher wedge pressures. As a result, blood pressure decreases and pulmonary edema ensues.

The patient underwent direct current cardioversion with a biphasic defibrillator at 80 J, resulting in conversion to sinus rhythm, normalization of blood pressure (110/70 mm Hg), and resolution of symptoms.

The patient's pigtail catheter had minimal drainage and was removed the following day. He maintained sinus rhythm and was discharged with orders to continue flecainide at his home dosage.

The oncology service was consulted to continue its work-up while the patient was hospitalized, ultimately deciding that he should initiate systemic chemotherapy

at an institution nearer to his home. He was subsequently discharged in stable condition.

DISCUSSION

Patients with non–small cell lung cancer have cardiac involvement 15% to 35% of the time.[8] The pathophysiologic mechanism responsible for the development of pericardial effusion varies from hematogenous spread to direct extension. However, retrograde lymphatic migration is considered the most common etiology.[13]

Pericardial effusion in patients with non–small cell lung cancer could result from malignancy, myxedema, radiation, medications, infection, or uremia or be autoimmune or idiopathic in nature. As discussed in the current case, pericardial fluid analysis with cytology has variable sensitivity, but specificity approaches 100% when positive.[7] Other more sensitive options, such as pericardial biopsy, have limited applicability given the morbidity associated with the procedure.

Systemic chemotherapy has been the mainstay of treatment for malignant pericardial effusion. However, studies have questioned the applicability of systemic therapy, noting both low (20%-50%) and brief response rates. Experts have more recently favored regional application of chemotherapy via intrapericardial access using agents such as cisplatin.[12] With this approach, one trial demonstrated an 80% response rate, but the study was limited by its small size and lack of comparison to systemic chemotherapeutic treatment.[12]

Prognosis is poor in patients with non–small cell lung cancer and concomitant pericardial pathology. When present, pericardial involvement is directly responsible for the cause of death in up to 85% of patients.[13] Median overall survival for this patient population is estimated at approximately 75 days, with less than 8% of patients surviving at 1 year.[7]

REFERENCES

1. Gornik HL, Gerhard-Herman M, Beckman JA. Abnormal cytology predicts poor prognosis in cancer patients with pericardial effusion. *J Clin Oncol*. 2005;23:5211-5216.

2. Chan SN, Okuno SH, Jatoi A. Causes and outcomes of spontaneous pneumothoraces in solid tumor cancer patients: an update for the medical oncologist. *J Thorac Oncol*. 2006;1:335-338.

3. Khorana AA, Connoly GC. Accessing risk of venous thromboembolism in the cancer patient. *J Clin Oncol*. 2009;27(29):4839-4847.

4. Shabetai R. Diseases of the pericardium In: Schalant RC. Alexander RW, eds. *Hurst's the Heart: Arteries and Veins*. 6th ed Vol.1. New York, NY: McGraw-Hill; 1994:1647-1674.

5. Sternbach G. Claude Beck: cardiac compression triads. *J Emerg Med*. 1988;6:417-419.

6. Spodick DH. Acute cardiac tamponade. *N Engl J Med*. 2003;349(7):684-690.

7. Burgess LJ, Reuter H, Talijaard JJ, Doubell AF. Role of biochemical tests in the diagnosis of large pericardial effusions. *Chest*. 2002;121(2):495-499.

8. Wang PC, Yang KY, Chao JY, Liu JM, Perng RP, Yen SH. Prognostic role of pericardial fluid cytology in cardiac tamponade associated with non-small cell lung cancer. *Chest*. 2000;118(3):744-749.

9. Garcia LW, Decatman BS, Wang HH. The value of multiple fluid specimens in the cytological diagnosis of malignancy. *Mod Pathol*. 1996;7(6):665-668.

10. Alsever RN, Stjeernholm MR. Cardiac tamponade in myxedema. *Am J Med Sci*. 1975;269(1):117-121.

11. Tsang TSM, Enriquez-Sarno M, Freeman WK, et al. Consecutive 1127 therapeutic echocardiography guided pericardiocentesis: clinical profile, practice patterns, and outcomes spanning 21 years. *Mayo Clin Proc*. 2002;77(5):429-436.

12. Tsang TSM, Seward JB, Barnes ME, et al. Outcomes of primary and secondary treatment of pericardial effusion in patients with malignancy. *Mayo Clin Proc*. 2000;75(3):248-253.

13. Tamura A, Matsubara O, Yoshimura N, et al. Cardiac metastasis of lung cancer: a study of metastatic pathways and clinical manifestations. *Cancer*. 1992;70:437-442.

12. Moriya T, Takiguchi Y, Tabeta H, et al. Controlling malignant pericardial effusion by intrapericardial carboplatin administration in patients with primary non-small cell lung cancer. *Br J Cancer*. 2000;83:858-862.

13. Thurber DL, Edwards JE, Achor RWP. Secondary malignant tumors of the pericardium. *Circulation*. 1962;26:228-241.

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