69-Year-Old Woman With Ascites, Hypoxia, and Weight Loss

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A 69-year-old woman presented to her primary care physician with increasing abdominal distention and a 13-kg unintentional weight loss over 1 year. She also reported new lower extremity edema, mild dyspnea on exertion, and orthopnea. Her medical history was remarkable for type 2 diabetes mellitus, asymptomatic coronary artery disease, and peripheral vascular disease treated by remote aortoiliac repair. Vital signs were normal except for an arterial oxygen saturation of 87% measured by finger oximetry while the patient breathed room air. Pertinent examination findings included a 3/6 holosystolic murmur, heard best at the base of the heart, that increased in intensity with inspiration, loud pulmonic component of the second heart sound, jugular venous pressure of 13 cm H_2O, clear lung sounds on auscultation, marked abdominal distention with shifting dullness, palpable hepatosplenomegaly, and bilateral pitting pretibial edema.

Laboratory studies revealed the following (reference ranges shown parenthetically): alkaline phosphatase, 340 U/L (55-142 U/L); aspartate aminotransferase, 65 U/L (8-43 U/L); alanine aminotransferase, 32 U/L (7-45 U/L); and total bilirubin, 0.8 mg/dL (0.1-1.0 mg/dL). Her hemoglobin level was 9.4 g/dL (12.0-15.5 g/dL), and the serum albumin concentration was 3.5 g/dL (3.5-5.0 g/dL). The patient underwent paracentesis, which removed 4 L of serous fluid. Ascitic fluid levels of total protein and albumin were 3.60 g/dL and 1.76 g/dL, respectively.

1. **Which *one* of the following is the *most likely* etiology of the patient's ascites?**
   a. Cardiac disorder
   b. Cirrhosis
   c. Acute hepatic venous thrombosis (Budd-Chiari syndrome)
   d. Peritoneal carcinomatosis
   e. Nephrotic syndrome

The serum ascites albumin gradient (SAAG) is helpful in determining the etiology of a patient's ascites. The SAAG can be calculated by subtracting the ascitic fluid albumin concentration from the serum albumin concentration (in our patient, 3.5 g/dL − 1.76 g/dL = 1.7 g/dL). An SAAG of 1.1 g/dL or more is suggestive of portal hypertension. An ascitic fluid total protein level greater than 2.5 g/dL indicates a cardiac etiology. Our patient's elevated jugular venous pressure and heart murmur suggestive of tricuspid regurgitation, as well as an SAAG greater than 1.1 and a total protein level higher than 2.5 g/dL, are consistent with a cardiac source for the patient's portal hypertension–related ascites. Cirrhosis typically presents with a high SAAG and low ascitic protein level. Acute Budd-Chiari syndrome (hepatic venous thrombosis) classically presents with the triad of new ascites, right upper quadrant pain, and jaundice. Both peritoneal carcinomatosis and nephrotic syndrome would present with an SAAG lower than 1.1 g/dL.

Transthoracic echocardiography revealed an estimated right ventricular systolic pressure (RVSP) of 101 mm Hg, severe tricuspid valve regurgitation, decreased right ventricular systolic function, and normal left ventricular size and systolic function with an ejection fraction of 73%.

2. **To confirm the patient's suspected diagnosis, which *one* of the following is the *best* next step?**
   a. Six-minute walk test
   b. Polysomnography
   c. Right-sided heart catheterization
   d. Right- and left-sided heart catheterization
   e. Transesophageal echocardiography

Although a 6-minute walk test cannot confirm the diagnosis of pulmonary hypertension (PH), it is useful for monitoring functional capacity and providing prognostic information.[1-3] Obstructive sleep apnea should be considered as an aggravating stimulus in all

See end of article for correct answers to questions.

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patients with suspected PH. Polysomnography would confirm the diagnosis of obstructive sleep apnea but not PH. Right-sided heart catheterization is the criterion standard for diagnosis of PH and is indicated even when echocardiography strongly suggests PH.[4] Pulmonary hypertension is defined as a mean pulmonary artery pressure of 25 mm Hg or higher at rest. Right-sided heart catheterization is required to confirm the diagnosis of PH, quantify disease severity, and determine response to possible treatment.[4,5] Left-sided heart catheterization would not be indicated because the patient has no evidence of left-sided heart failure. In evaluating PH, transesophageal echocardiography does not routinely offer additional diagnostic information beyond that obtained by transthoracic echocardiography and cannot confirm the diagnosis.

Right-sided heart catheterization confirmed severe PH (mean pulmonary artery pressure, 67 mm Hg) with mildly elevated pulmonary arterial wedge pressure (14 mm Hg). Vasoreactivity testing yielded negative results.

3. Which *one* of the following tests is indicated to determine the etiology of the patient's new diagnosis?

a. Empiric trial of oral calcium channel blockers
b. Genetic testing
c. Ventilation-perfusion ($\dot{V}/\dot{Q}$) scan
d. Pulmonary angiography
e. Lung biopsy

Although calcium channel blockers may benefit patients with PH who have vasoreactivity, they are associated with several adverse effects and should not be used empirically. They do not aid in diagnosis. Although some patients with PH may have an associated germline mutation, genetic counseling and possible testing should be considered after ruling out more common etiologies. Chronic thromboembolic PH (CTEPH) is a potential complication of acute pulmonary embolism and may manifest as chronic PH. Because CTEPH is potentially curable with surgical pulmonary thromboendarterectomy, it should be ruled out in patients with newly diagnosed PH. A $\dot{V}/\dot{Q}$ scan is the best screening test to rule out CTEPH.[6] If CTEPH is suspected on $\dot{V}/\dot{Q}$ scan, invasive or computed tomographic pulmonary angiography is indicated to confirm the diagnosis.[1,6] Lung biopsy is an extremely high-risk procedure in patients with PH and should only be considered if it would confirm or exclude a diagnosis for which an established therapy would be likely to substantially affect outcome, so that the potential benefits outweigh the risk.

A $\dot{V}/\dot{Q}$ scan revealed no perfusion defects in our patient, making CTEPH unlikely. With a new diagnosis of severe PH and no identified etiology, the patient was referred to a subspecialty cardiology clinic for additional history and physical examination. She reported a history of Raynaud phenomenon for the previous 5 years. Additional physical examination revealed skin tightening over the proximal interphalangeal joints, capillary dilatation in her fingernail beds, and multiple telangiectasias on her lips, face, and upper portion of the back. Chest radiography revealed enlarged pulmonary veins. Pulmonary function testing documented a mild restrictive pattern with decreased diffusing capacity at 32% of predicted. She had normal findings on overnight oximetry and a negative human immunodeficiency virus test result. The antinuclear antibody titer was 8.3 U (<1.0 U), anticentromere antibody titer was more than 8.0 U (<1.40 U), and SS-A result was 1.5 U (<1.0 U). Test results for ribonucleoprotein antibody, SS-B, anti-Scl-70 antibody, and anti-Jo-1 antibodies were negative.

4. In view of the patient's clinical condition and findings thus far, which *one* of the following is the *most likely* diagnosis?

a. Schistosomiasis
b. Idiopathic PH
c. Diffuse cutaneous systemic sclerosis
d. Limited cutaneous systemic sclerosis
e. Dermatomyositis

Although schistosomiasis is one of the most frequent causes of PH worldwide, it is an unlikely cause in the United States.[7] The patient's clinical picture suggests an underlying rheumatologic condition, and thus the patient likely does not have idiopathic PH. Diffuse and limited cutaneous systemic sclerosis can be differentiated by the degree of cutaneous involvement. Diffuse cutaneous systemic sclerosis is characterized by truncal and proximal extremity skin involvement, as well as a positive anti-Scl-70 antibody test result.[7] Limited cutaneous systemic sclerosis

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is characterized by more limited skin involvement, typically just affecting the hands and face. It is also characterized by sclerodactyly, Raynaud phenomenon, telangiectasias, and an elevated anticentromere antibody titer. Our patient has these classic findings of limited cutaneous systemic sclerosis. Dermatomyositis classically presents with proximal muscle weakness and skin rash and is not typically associated with PH.

Limited cutaneous systemic sclerosis was diagnosed. and the patient was evaluated for further treatment options.

5. **Which *one* of the following treatments is *most appropriate* for this patient?**
   a. Digoxin
   b. Pulmonary transplant
   c. Prednisone
   d. Diltiazem
   e. Oxygen supplementation

Digoxin may improve right ventricular ejection fraction in patients with biventricular failure and is also indicated in patients with PH and superimposed supraventricular tachycardias. Referral for pulmonary transplant should only be considered for patients in whom medical management has failed or who have rapidly progressive disease. Corticosteroids have no role in the treatment of PH and essentially no role in the treatment of CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia) syndrome except in specific instances such as the presence of myositis. Our patient did not respond to vasodilator therapy and thus would not be a candidate for therapy with diltiazem. Although no controlled trials exist to evaluate the efficacy of continuous oxygen therapy in patients with PH, supplemental oxygen therapy is recommended for all patients with PH and hypoxemia. Importantly, patients with Raynaud phenomenon may have inaccurate digital pulse oximetry readings. Accurate oximetry readings must be ensured before oxygen therapy is initiated.

Oxygen and sildenafil therapy were initiated in our patient, and her symptoms improved.

DISCUSSION

Pulmonary hypertension is a chronic progressive condition affecting up to 100 million people worldwide. It is defined as a mean pulmonary arterial pressure of 25 mm Hg or higher on right-sided heart catheterization.[8] The clinical classification of PH is based on the underlying pathophysiologic mechanisms, clinical presentation, and therapeutic approaches.[9,10] Group 1 pulmonary arterial hypertension (PAH) includes idiopathic PAH and associated PAH. The underlying pathology is related to intimal medial thickening due to cellular proliferation.[7] Group 2 PH is caused by left-sided heart disease and is the most common type. Group 3, caused by underlying pulmonary disease, is a result of hypoxia-induced vasoconstriction and parenchymal disease. Group 4 is defined as chronic thromboembolic PH. Group 5 is associated with to various mechanisms including myeloproliferative disorders, sarcoidosis, and glycogen storage disorders.[5]

Patients with PH can present with numerous symptoms including dyspnea, fatigue, chest pain, syncope, edema, or no symptoms at all. Findings on physical examination may include jugular venous distention, palpable right ventricle impulse, increased pulmonic component of the second heart sound, and a murmur of tricuspid regurgitation.[7,11]

In a patient with symptoms suggestive of PH, chest radiography and transthoracic echocardiography should be performed. Chest radiography documents abnormalities in 90% of patients with PH and may reveal right ventricular enlargement with marked prominence of the central pulmonary arteries.[5] Normal findings on chest radiography do not rule out PH, however. Echocardiography may yield a variety of findings, including elevated RVSP, right ventricular and atrial enlargement, and possible left ventricular or valvular dysfunction. Although RVSP is commonly used to estimate pulmonary artery pressures, the RVSP can overestimate or underestimate pulmonary pressure. A variety of factors such as tricuspid regurgitation and body habitus may influence the ability of RVSP to accurately estimate pulmonary artery pressures.[7] Thus, right-sided heart catheterization is the criterion standard for diagnosis and should be performed in any patient with an unexplained diagnosis of PAH.[1] Right-sided heart catheterization also measures pulmonary arterial wedge pressure, a surrogate marker for underlying left ventricular dysfunction. If results of right-sided heart catheterization are consistent with PAH, the

patient should also undergo vasoreactivity testing to determine whether calcium channel blockers would be safe and beneficial.

Patients with newly diagnosed PAH should undergo a complete evaluation to determine the etiology.[7] Pulmonary function testing and arterial blood gas measurement are important to evaluate for intrinsic pulmonary disease as well as to document baseline pulmonary function. A 6-minute walk test should be administered to determine the effect of PAH on functional capacity, to establish a baseline, and to provide prognostic information. Ventilation-perfusion scan should be ordered to rule out CTEPH, even in patients with no known history of pulmonary embolism or deep venous thrombosis.[12] Testing for human immunodeficiency virus, routine chemistry panels, complete blood cell count, and thyroid and liver function tests are also recommended in all patients.[7] An antinuclear antibody titer should be obtained to screen for autoimmune diseases, and further testing based on history and examination findings may include serologic evaluation for scleroderma.[5] Overnight oximetry should be performed to screen for obstructive sleep apnea.[7]

Management of a patient with PH involves treating the underlying etiology if possible, in addition to symptom control.[3] Oxygen supplementation is recommended to keep oxygen saturation greater than 90% at all times.[11] Although no randomized controlled trials studying diuretics have been performed in patients with PAH, these agents are beneficial in the management of symptoms. Digoxin and other inotropic agents are useful for symptom control, but there is no data suggesting long-term benefits. Anticoagulation is recommended in patients with idiopathic PAH, as well as those with CTEPH.[11] Those with advanced PAH of other types may be candidates for anticoagulation as well. Mortality benefit with warfarin, however, has been described only in patients with PAH.[11,12] Patients with underlying interstitial lung diseases should be treated with appropriate disease-specific therapy.

Calcium channel blockers may have a role for treatment of patients with PAH who exhibit vasoreactivity during cardiac catheterization.[1] Generally, long-acting nifedipine, diltiazem, or amlodipine are the agents of choice because of the negative inotropic effects of verapamil.[1] Those who receive calcium channel blockers should be monitored closely to assess clinical improvement.

Prostanoids are also useful agents that act via vasodilation and inhibition of platelet aggregation. Phosphodiesterase 5 inhibitors such as sildenafil and tadalafil have also been recognized as important agents in managing patients with PAH.[7] These agents act by augmenting the vasodilatory effects of endogenous nitric oxide, allowing for vasorelaxation. Patients with PAH derive symptomatic and hemodynamic benefit from epoprostenol and treprostinil. Endothelin receptor antagonists are also important agents to consider when treating PAH. Bosentan and ambrisentan, specifically, have been shown to improve 6-minute walk test performance and reduce the rate of clinical decline.[11]

Pulmonary thromboendarterectomy is the treatment of choice in patients with CTEPH. Invasive angiography is performed to determine the feasibility of pulmonary thromboendarterectomy, and once this is confirmed, surgery should be pursued if chronic thrombus is surgically accessible. Group 4 PH, associated with pulmonary embolism, is the only potentially curable form of PAH. Although lung transplant is an option for some patients with PAH, this procedure carries its own risk of morbidity and mortality and is generally considered a last resort.

Patients with PAH require close outpatient follow-up. Six-minute walk performance, oxygen saturation, and N-terminal pro-B-type natriuretic peptide levels should be monitored for decline, which may indicate the need to optimize medications. Cardiac catheterization generally does not need to be repeated unless there is a plan to change therapy or if echocardiography is thought to be unreliable.

Despite current treatment modalities, the prognosis of PH is poor.[8] The median survival in patients with idiopathic PAH and PAH has increased from about 2 to 3 years to about 7 years in the modern treatment era. Early diagnosis and initiation of appropriate treatment is key to optimizing patient outcomes. Because of the complexities of accurate diagnosis and establishing optimal treatment, generalists are encouraged to collaborate early with centers specializing in PH management when they believe their patient may have this disorder.

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REFERENCES

1. Badesch DB, Champion HC, Sanchez MA, et al. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009;54(1, suppl):S55-S66.
2. Grünig E, Lichtblau M, Ehlken N, et al. Safety and efficacy of exercise training in various forms of pulmonary hypertension. *Eur Respir J*. 2012;40(1):84-92.
3. McGoon MD, Kane GC. Pulmonary hypertension: diagnosis and management [published correction appears in *Mayo Clin Proc*. 2009;84(4):386]. *Mayo Clin Proc*. 2009;84(2):191-207.
4. Nishimura RA, Carabello BA. Hemodynamics in the cardiac catheterization laboratory of the 21st century. *Circulation*. 2012; 125(17):2138-2150.
5. Galiè N, Hoeper MM, Humbert M, et al; ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT) [published correction appears in *Eur Heart J*. 2011;32(8):926]. *Eur Heart J*. 2009;30(20):2493-2537.
6. Tunariu N, Gibbs SJ, Win Z, et al. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. *J Nucl Med*. 2007;48(5): 680-684.
7. McLaughlin VV, Davis M, Cornwell W. Pulmonary arterial hypertension. *Curr Probl Cardiol*. 2011;36(12):461-517.
8. Galiè N, Manes A, Negro L, Palazzini M, Bacchi-Reggiani ML, Branzi A. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. *Eur Heart J*. 2009;30(4): 394-403.
9. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2009; 54(1, suppl):S43-S54.
10. Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation*. 1984;70(4):580-587.
11. McLaughlin VV, Archer SL, Badesch DB, et al; American College of Cardiology Foundation Task Force on Expert Consensus Documents; American Heart Association; American College of Chest Physicians; American Thoracic Society, Inc; Pulmonary Hypertension Association. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol*. 2009;53(17):1573-1619.
12. Johnson SR, Granton JT, Mehta S. Thrombotic arteriopathy and anticoagulation in pulmonary hypertension. *Chest*. 2006;130(2): 545-552.

CORRECT ANSWERS: 1. a. 2. c. 3. c. 4. d. 5. e