CLINICAL VIGNETTE

Difficulty in Diagnosing and Treating Group 5 Pulmonary Hypertension:

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Introduction

Pulmonary hypertension (PH) affects 1% of the global population,[1] but there is wide variability in prevalence amongst certain patient groups depending on the specific etiology of PH. PH is characterized by an elevation in pulmonary arterial pressure, defined by a mean pulmonary arterial pressure (mPAP) of $\geq$ 25 mmHg at rest.[2] Normal mPAP is $\leq$ 20 mmHg at rest. PH can be due to primary elevation of pressure within the pulmonary arterial system or secondary to elevations of pressure within the pulmonary venous and/or pulmonary capillary systems. Although the rate of progression is highly variable, if left untreated, PH can be a fatal disease.[3,4] We present a case of a previously healthy middle-aged woman presenting with rapidly progressive dyspnea at rest and exertion over weeks, and she was ultimately discovered to have Group 5 PH based on inpatient work-up and unfortunately succumbed to her illness in the hospital.

Case Report

A 56-year-old woman with no known significant past medical history presented to her primary caregiver complaining of three weeks of progressively worsening fatigue, shortness of breath at rest and with exertion, as well as severely reduced exercise tolerance from a normal baseline normal. At presentation, she was only able to ambulate 10-20 feet before experiencing significant dyspnea. She denied other systemic complaints of unintentional weight change, fevers/chills, dizziness, chest pain, palpitations, cough, wheezing, abdominal pain, nausea/vomiting/diarrhea, or focal loss of strength or sensation. Of note, the patient did experience mild shortness of breath in 2009; at that time, a transthoracic echocardiogram was normal, and her symptoms did not warrant any additional diagnostic work-up. She was not taking any medications chronically and had no known allergies. She had no smoking history. She was previously from El Salvador but had migrated to the United Stated > 25 years prior to presentation. She was married, worked as a housekeeper, and lived at home with her husband and two sons. She denied any recent travel or other unusual exposures within the past year prior to onset of symptoms. Family history was unremarkable for any cardiac or pulmonary disease. Physical examination revealed normal vital signs, normal oxygen saturation on ambient air at rest, and was otherwise grossly unremarkable with normal cardiopulmonary findings. Due to concern for an underlying, progressively worsening systemic disease, she was admitted to the general internal medicine service for further work-up of her worsening shortness of breath/reduced exercise tolerance.

On admission, the patient was noted to have an elevated serum creatinine (1.7 mg/dL) and serum BNP (1076 pg/mL). Her other routine serum chemistries/blood counts were normal, and her routine urinalysis was unremarkable. CXR showed no evidence of pulmonary vascular congestion or edema/effusions. Given the elevated serum BNP, a transthoracic echocardiogram raised concern for severe pulmonary arterial hypertension (estimated mPAP 101 mmHg) with a severely dilated right ventricle with reduced right ventricular systolic function, and a severely dilated right atrium. The left atrium and ventricle were normal in size and systolic function (LVEF 55-60%). Work-up for secondary causes of newly diagnosed pulmonary hypertension included high-resolution non-contrast CT chest, which revealed findings suggestive of alveolitis or early fibrosis; lower extremity duplex ultrasound, which was negative for deep venous thrombosis; and a V/Q scan with intermediate probability for pulmonary embolism. CT pulmonary angiography was initially deferred given the patient's finding of renal insufficiency on admission. Therapeutic anticoagulation with IV heparin was initiated. After gentle IV hydration, CT pulmonary angiogram was negative for pulmonary thromboembolism but did demonstrate findings concerning for alveolitis versus early fibrosis as previously seen. Anticoagulation was subsequently discontinued, and an extensive rheumatologic work-up only revealed a positive ANA (titer of 1:160) and positive dsDNA (but negative dsDNA IFA). To further confirm the diagnosis of pulmonary hypertension, a right heart catheterization revealed a pulmonary arterial pressure of 85/38 with mPAP of 56 mmHg. Due to the inconclusive work-up of the etiology of the patient's severe pulmonary hypertension to date, the working diagnosis was Group 5 PH. The patient continued to remain clinically and hemodynamically stable, and she was planned to discharge home with close outpatient follow-up.

Unfortunately, on the planned day of discharge (hospital day #10), the patient had a syncopal event and was found to be hypotensive with SBP 60 mmHg; she was transferred to the intensive care unit. There was initial concern for evolving right groin hematoma from site of recent right heart catheterization,

but this was ruled out with negative imaging. The patient had worsening signs and symptoms of acute right heart failure attributable to severe pulmonary hypertension. She was refractory to a trial of diuresis, given she had received IV fluid hydration prior to CT pulmonary angiography with negative evaluation for acute coronary syndrome, pneumonia/sepsis, worsening renal failure, and/or other obvious cardiopulmonary or systemic pathology. The patient continued to decompensate and ultimately required intubation for worsening hypoxemic respiratory failure. Due to her overall poor prognosis, the patient and family decided to withdraw treatment, and she expired after two weeks of hospitalization.

Discussion

The World Health Organization (WHO) classifies pulmonary hypertension into one of five groups based on etiology and pathophysiology: Group 1 (pulmonary arterial hypertension), Group 2 (pulmonary hypertension due to left heart disease), Group 3 (pulmonary hypertension due to chronic lung disease), Group 4 (chronic thromboembolic pulmonary hypertension, or CTEPH), and Group 5 (pulmonary hypertension due to unclear multifactorial mechanisms such as systemic or metabolic diseases).[5] The diagnostic work-up to evaluate the etiology of PH is strongly guided by the medical history of the patient. This can include extensive cardiac, pulmonary, hematologic, and/or rheumatologic laboratory/diagnostic studies. In addition, all patients ultimately require a right heart catheterization for definitive diagnosis of pulmonary hypertension, which is the gold standard for diagnosis of PH.[6]

Our patient had several potential culprits that may explain her diagnosis of pulmonary hypertension, thus leading her to be classified as having Group 5 PH. She had "renal insufficiency" at time of admission without clear etiology. Labs were remarkable for a positive ANA and positive dsDNA (though negative IFA), without other clinical findings to meet diagnostic criteria for systemic lupus erythematosus (SLE). Chest imaging revealed "alveolitis and/or early fibrosis," but additional evaluation was not pursued due to her rapid decline.

Prompt diagnostic evaluation and initiation of treatment for PH is crucial as the disease often progresses rapidly. In the REVEAL registry, 21% of patients with idiopathic (i.e., Group 5) PH had symptoms for more than two years before a diagnosis of PH was made.[7] In our patient case, she appears to have possibly had initial symptoms of shortness of breath seven years prior to her current admission at which time her disease acutely worsened. As the disease further progresses, patients may not be as responsive to advanced therapies such as prostacyclin pathway agonists and endothelin receptor antagonists.[5] This is particularly true in patients with Group 5 PH, given the multifactorial causes of the disease in these patients. In general, treatment of Group 5 PH is directed toward treating the underlying condition with consideration of PH-specific therapies based on clinical characteristics on a case-by-case basis.[8] Adding to the complexity of treating Group 5 PH is the fact that the underlying condition is often not obvious. Thus, having an early clinical suspicion for the disease is important in order to initiate prompt workup, confirm the diagnosis, and initiate appropriate treatment before the disease rapidly progresses.

Conclusion

Although there have been recent advances in the treatment of PH, Group 5 PH remains particularly difficult to treat. Delayed diagnosis may contribute to this difficulty. Given nonspecific presenting symptoms, additional work-up may not be warranted until the disease has progressed and patients are more symptomatic, at which time effective treatments - targeted toward an underlying condition or PH specifically - may be too late.

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