The Role of Estrogen in Pulmonary Hypertension

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Case Overview

Pulmonary hypertension is an indolent disease that without proper management can lead to irreversible and potentially deadly consequences. This disease disproportionately affects women when compared to men and is hypothesized to be due to differences in lifetime estrogen exposure.

History of Present Illness

EP is a 66-year-old female patient with past medical history of hypertension, COPD, pulmonary hypertension and diffuse small B-cell lymphoma who initially presents to the emergency department with dyspnea, lower extremity edema, and abdominal swelling. Beyond her usual symptoms of breathlessness with activity for the past several years, her symptoms have worsened over the past week. She had not seen a pulmonologist for 5 years. She is now experiencing dyspnea at rest. She denies fever, nausea/vomiting, headache or cough. Her supplemental oxygen needs increase in the ED. She requires multiple breathing treatments and heated high flow nasal cannula at 20L. She has hypotension requiring pressor support with norepinephrine and she is subsequently admitted to the ICU.

Pertinent History

- Medical: COPD typically on 2L O2 Nasal cannula, hypertension, pulmonary hypertension, diffuse small B-cell lymphoma s/p chemotherapy in 2015
- Surgical: None
- Medications: Lisinopril and home oxygen. Of note, patient has discontinued both medications due to a combination of social and personal barriers.
- Social History: 45 year 1.5 ppd smoking history, quit in 2013. No alcohol or other substance use.
- She has been a caregiver for her elderly husband for several years so has neglected her recommended therapy for some time.

Pertinent Laboratory Evaluation

- Arterial Blood Gas on admission to ICU: pH 7.23, pCO2 59, pO2 55

Physical Exam

- General Appearance: Pt in respiratory distress with cyanosis of lips
- Vitals Signs: HR: 110 (tachycardic), RR: 25, labored, SpO2 91% on 20L HHFNC, BP: 110/72 on 8mg IV norepinephrine, BMI: 26.3
- Head: Normocephalic, atraumatic. Dry mucous membranes with some evidence of cyanosis

- Eyes: No conjunctival injection or pallor, PERRLA
- Heart: Tachycardic, without murmur or gallop
- Abdomen: Distended, bowel sounds present. Spleen and liver non-palpable.
- Pulmonary: Increased respiratory effort and mild respiratory distress. Diffuse expiratory wheezing and rales bilaterally.

Assessment

EP is a 66-year-old female in acute respiratory failure secondary to untreated pulmonary hypertension. Abdominal distention and bilateral lower extremity edema suggest there is a cardiac dysfunction leading to IVC and portal vein dilation. Echocardiogram demonstrates extensive right ventricular dilation with severe tricuspid valve regurgitation, suggesting a clinical picture of Cor Pulmonale secondary to pulmonary hypertension. Cor Pulmonale is caused by enlargement of the right ventricle leading to RV heart failure and as the RV dilates, the heart loses the ability to contract leading to increased pressures in the liver and abdomen. Diuresis is recommended to reduce these pressures, reduce stress on the RV, and allow better contractility. She was treated in the ICU with escalated oxygen therapy, diuretics, and a prostacyclin vasodilator (other PH treatments considered but not used include endothelin receptor antagonists or phosphodiesterase-5 inhibitors) targeted for the lungs. Despite this, she was volume overloaded and developed acute renal failure, no longer responding to the diuretics and requiring continuous renal replacement therapy. Her oxygen demand continued to climb and after extensive discussion with both the patient and her family the decision was ultimately made to shift toward hospice/comfort care.

Discussion

Pulmonary hypertension (PH) is defined as elevated pulmonary arterial pressure and classified into 5 separate groups: (I) Pulmonary arterial hypertension (PAH), (II) PH secondary to Left Ventricular disease, (III) PH secondary to pulmonary disease, (IV) PH secondary to thromboembolism, and (V) PH secondary to unclear, multifactorial disease mechanisms [1]. Its prevalence is estimated to be 1% of the world's population and is more common in patients >65 years old and is often due to the cumulative deleterious effect of years of cardiac or pulmonary diseases such as COPD, heart failure, and chronic lung disease [1]. It is a slowly developing disease that if left untreated can lead to complications such as Cor Pulmonale, portal vein hypertension, or hepatorenal syndrome [2,3].

In general, women are at a greater risk for developing pulmonary hypertension, and more often fall into the group I (PAH) yet most of the general population has Group II PH from Left Ventricular disease [4,5]. PAH often progresses to cause further damage to pulmonary vasculature and has a <60% 3 year survival rate [3]. The increased incidence in PAH in women compared to men is observed in Caucasians (3.2:1), Hispanics (4.7:1) and African Americans (5.5:1) [6]. Interestingly, while women are more likely to be diagnosed with pulmonary hypertension, men have greater mortality rates, but when treated, women tend to have better outcomes [7]. One hypothesis for this is the "estrogen paradox" due to the role that estrogen plays in lung vasculature and cardiac remodeling. In animal models, estrogen has been shown to be either protective or deleterious to lung vasculature depending on the animal model.

Estrogen has been shown to play an important role in the risk of developing PAH but acts as a cardioprotective agent for right ventricular heart failure because of its protective qualities in RV remodeling [8].

While estrogen may be cardioprotective, it does not completely protect against the downstream effects of untreated PAH. It is important to highlight the increased risk that women have of developing PAH when compared with men, likely due to higher levels of lifetime estrogen exposure. It is also important to note the role that estrogen plays in this disease process when considering female patients using contraceptives that contain estrogen or patients on hormone replacement therapy. Due to the indolent and non-specific early symptoms associated with PAH, diagnosis is often made at late stages of the disease. Despite an increase in disease awareness amongst physicians and patients, patients continue to experience a delay in diagnosis [9]. This case is an example of the deleterious nature of untreated PAH and a reminder of the importance of early diagnosis and treatment.

Reducing the time to diagnosis is a key aspect of early intervention and improved survivability. This requires more proactive screening for PAH in populations that present with symptoms of dyspnea, exertional shortness of breath, chronic fatigue or breathlessness. Groups to consider include individuals with connective tissue diseases, COPD, congestive heart failure, or portal hypertension. Individuals who are biologically female with these comorbidities should be considered at higher risk given what we know about the role of estrogen in the pathophysiology. If PAH is suspected, current guidelines recommend echocardiograms as the gold standard for evaluating pulmonary artery pressure [10]. Additional tests such as pulmonary function tests and B-type natriuretic peptide level can be used to investigate further if the diagnosis is unclear.

While our ability to diagnose and treat pulmonary hypertension has improved, the morbidity and mortality of the disease has not. This is most likely due to its indolent course and non-specific presentation which leads to delays in diagnosis and overall worse outcomes. Increasing awareness and development of screening algorithms are key steps in helping physicians identify patients early. In doing so, we can diagnose patients and start treatments earlier leading to reduced morbidity and mortality of the disease. This patient may not have understood the ramifications of delayed treatment for her PH, as indolent as it may present and progress. Her gender role as a caregiver and prioritization of someone else's debility may have influenced her years of interrupted care and delay of presentation.

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