Introduction

Pulmonary veno-occlusive disease (PVOD) is a rare cause of pulmonary arterial hypertension (PAH).\(^1\,^2\) Despite being described over 70 years ago, PVOD is poorly understood and difficult to diagnose. PVOD is associated with connective tissue disorders, bone marrow transplantation, infection, sarcoidosis, and exposure to chemotherapeutic agents including mitomycin, bleomycin, and carmustine.\(^1\) It is characterized by intimal and medial fibrosis of the pulmonary venules and veins of the lobular septa. We present a case of a patient with PVOD receiving mitomycin C for the treatment of breast cancer.

Case Report

A 73-year-old female presented with progressive dyspnea over six weeks. She had a twelve-year history of breast cancer treated with mastectomy, radiation, and multiple chemotherapeutic regimens including mitomycin. She also had a history of chronic obstructive pulmonary disease, trastuzumab-induced cardiomyopathy, and arthritis.

She was admitted for congestive heart failure (CHF) with hypoxemia, diffuse pulmonary infiltrates, and bilateral pleural effusions. She was diuresed and symptomatically improved. She was discharged home on three liters oxygen. However, her symptoms worsened despite diuresis and she presented again with progressive hypoxemia on her discharge oxygen. Her chest x-ray revealed diffuse bilateral infiltrates similar to her prior presentation.

On examination, she was afebrile with tachycardia, tachypnea, and oxygen saturation of 88% on three liters. Auscultation of the chest revealed bibasilar rales, but no jugular venous distension or peripheral edema was noted. She had bilateral Bouchard and Heberden’s nodes with ulnar deviation of her hands. Her laboratory data did not reveal leukocytosis. A viral respiratory panel was negative and renal function was preserved.

On admission, a work-up of an alternative diagnosis to CHF ensued. A CT of the chest was performed (Figure 1). An echocardiogram confirmed normal chamber dimensions and systolic function with elevated pulmonary artery pressures. A right heart catheterization was performed (Table 1). The radiographic imaging combined with the pulmonary hypertension on right heart catheterization and exposure to mitomycin made the diagnosis of PVOD highly suspicious. Given her pulmonary hypertension and hypoxic respiratory failure, the risk of open lung biopsy outweighed potential benefits. She was treated with steroids and sildenafil, but eventually succumbed to her disease within three months of diagnosis.

A limited autopsy revealed intimal and medial fibrosis of septal veins consistent
with PVOD (Figure 2). There also was arteriolarization of pulmonary venules, some of which contained organized or recanalized thrombi. The adjacent lung parenchyma showed fibrosis with hemosiderosis with calcium encrustation. The pulmonary arteries and arterioles had thickened walls consistent with moderate pulmonary hypertension.

Table 1. Right-sided cardiac catheterization measurements.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Value</th>
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<tbody>
<tr>
<td>Systolic pulmonary artery pressure</td>
<td>56 mmHg</td>
</tr>
<tr>
<td>Diastolic pulmonary artery pressure</td>
<td>29 mmHg</td>
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<tr>
<td>Mean pulmonary artery pressure</td>
<td>38 mmHg</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure</td>
<td>11 mmHg</td>
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<tr>
<td>Transpulmonary pressure gradient</td>
<td>27 mmHg</td>
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<tr>
<td>Pulmonary vascular resistance</td>
<td>7.8 wood units</td>
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Figure 1. Small bilateral pleural effusions, right greater than left, was seen on CT of the chest with contrast. Patchy ground glass opacities were observed throughout the lungs bilaterally with upper lobe predominance. Interlobular septal prominence and mild dependent atelectasis also were noted.

Figure 2. Pulmonary changes seen at autopsy: (A) Intimal and medial fibrosis of a septal pulmonary vein was observed. Fibrosis with bluish calcium encrustation and hemosiderin laden macrophages in the alveoli are seen adjacent to the vein. (B) Arteriole (A) is observed with a thickened wall and a narrowed lumen. Venule (V) has a recanalized thrombus in the lumen and thickened wall consistent with arteriolarization seen in PVOD. (Hematoxylin and eosin, (A) x160; (B) x220).
Discussion

The patient described above was on multiple anti-neoplastic regimens over a decade, but her symptoms started after receiving the fifth cycle of mitomycin therapy. Okuno et al.\(^3\) described a range of 2 to 5 cycles of mitomycin therapy before development of PVOD. Definitive diagnosis of PVOD requires lung biopsy which can be risky in patients with severe pulmonary hypertension and hypoxemia.\(^4\) The majority of cases are diagnosed clinically based on radiographic features and excluding other causes of PAH. The presence of two or three radiological abnormalities including lymph node enlargement, thickened septal lines, and centrilobular ground-glass opacities had a sensitivity of 75% and a specificity of 84.6% for the detection of PVOD.\(^2\) The imaging in this case was classic for PVOD and autopsy confirmed the clinical diagnosis.\(^4\)

Our patient had a long history of arthritis, but no formal diagnosis of rheumatoid arthritis. Interestingly, her rheumatoid factor and anti-cyclic citrullinated peptide levels were elevated, and perhaps connective tissue disease could be another factor contributing to development of PVOD.\(^5\) This possibility could not be ruled out completely by autopsy as PVOD secondary to mitomycin and connective tissue disease have identical pathologic findings. Based on the temporal relationship in this case, mitomycin seems to be the likely etiology.

Treatment remains a challenge as exposure to pulmonary vasodilators used to treat PAH may precipitate acute pulmonary edema in patients with PVOD. However, phosphodiesterase-5 inhibitors have been used successfully to treat PVOD, but no prospective studies exist and they should be prescribed only by someone with expertise in pulmonary hypertension and PVOD management. The use of steroids in PVOD has mixed results and lung transplantation is the definitive treatment.\(^2\)

PVOD should be considered in cancer patients with hypoxia, diffuse infiltrates, pulmonary hypertension, and exposure to mitomycin. It is equally important to differentiate PVOD from other causes of PAH as standard therapy for PAH can be detrimental in PVOD. Although not an option for our patient, early diagnosis may allow for lung transplantation in a patient without contraindications to transplant.

References


Keywords: mitomycin, pulmonary veno-occlusive disease, breast cancer, pulmonary arterial hypertension