Puzzling Etiology of Pulmonary Hypertension Resolved

Section Editor:
Deborah J. Levine, MD

Eric R. Fenstad, MD, MSc
Cardiovascular Fellow in Training
Instructor of Medicine
Mayo Clinic Division of
Cardiovascular Diseases
Rochester, MN

Benjamin L. Bick, MD
Internal Medicine Resident in Training
Mayo Clinic Division of Internal Medicine
Rochester, MN

Robert P. Frantz, MD
Professor of Medicine
Mayo Clinic Division of Cardiovascular Diseases
Rochester, MN

Presentation:
A 36-year-old female was referred to a tertiary hospital after development of progressive hypoxemic respiratory failure and diffuse neurologic deficits.

Past medical history was significant for migraine headaches and prior narcotic addiction status post chemical dependency treatment with reported nonuse for 1.5 years.

Seven months prior to admission, she developed severe headaches, left arm weakness, diplopia, and a right visual field defect. She was treated with penicillin G 20 million units daily for a right lower leg abscess 2 weeks prior to admission. At an OSH, she had a PE-protocol chest CT, bronchoalveolar lavage, and was transferred emergently to our hospital because of progressive hypoxic respiratory failure and worsening neurologic deficits.

Assessment:
On physical examination, the significant findings were: tachypnea on noninvasive ventilation with clear lung fields, increased P2 component of the second heart sound, no murmurs, and multiple nontender subcutaneous nodules. Pertinent labs included: leukocytosis 17.5 x 10^3/L, erythrocyte sedimentation rate 39 mm/1h, NT-BNP 7772 pg/mL, negative HIV test, negative antinuclear antibody cascade, normal liver enzymes, normal connective tissue disease panel (anticardiolipin, anticardiolipin IgG, anti-smooth muscle, and anti-Smith), and no growth on blood cultures. Repeat chest CT demonstrated diffuse tree-in-bud micronodular pulmonary infiltrates without pulmonary embolism (Figure 1). Brain MRI demonstrated multiple diffuse bilateral infarcts in the cerebral cortex and cerebellum concerning for embolism rather than vasculitis (Figure 2). Because of multiple neurologic deficits and concern for embolism, transesophageal echocardiogram was performed and was negative for valvular vegetations and left atrial appendage thrombus, but a patent foramen ovale with bidirectional shunt was present. Transthoracic echocardiogram demonstrated severe right ventricular enlargement, abnormally low right ventricular strain -20%, and low tricuspid annular plane systolic excursion of 17 mm with severely elevated right-sided pressures suggesting pulmonary hypertension (Table 1 and Figure 3). Ventilation-perfusion imaging demonstrated severe perfusion abnormalities without associated ventilation defects. Therefore, a right heart catheterization was indicated to assess left and right heart pressures. Hemodynamics were consistent with pulmonary arterial hypertension (Table 2). Vasodilator testing with inhaled nitric oxide was negative (positive only if mean pulmonary artery pressure decreases by ≥10 mmHg, to a value <40 mmHg, without decrease in cardiac index).

Although the patient had a patent foramen ovale, it was small and not consistent with other shunts responsible for PH due to volume and pressure overload as sometimes seen in the setting.

Key Words–pulmonary arterial hypertension, tak granulomatosis, toxic pulmonary hypertension
Correspondence: Fenstad.eric@mayo.edu
of large atrial septal defects. The embolic pattern on brain MRI and extensive micronodular bilateral lung process associated with vascular structures on chest CT suggested an infectious or other inflammatory pulmonary vascular process as the main etiology for his syndrome. Because we lacked a uniform diagnosis and ongoing atypical features, transbronchial biopsy was re-read and demonstrated perivascular hyperpolarizable material with non-necrotizing microgranulomas consistent with crushed pill injection (Figure 4). The patient eventually admitted to ongoing narcotic use and several episodes of crushed oxymorphone pill injection.

**Discussion:**

Foreign body granulomatosis from injection of crushed pills is a rare but potentially lethal cause of PAH. Despite the rare cause of PAH, the initial workup followed the updated diagnostic approach to rule out potential etiologies of PH such as connective tissue disease, liver disease, HIV, congenital heart disease, pulmonary disease, chronic thromboembolic disease, and left-sided heart disease. Retrospective autopsy observation reported PAH findings in 13 of 21 patients with pulmonary talc granulomas secondary to intravenous drug injection, while review of a single-center experience documented PAH in 5 of 9 patients with talc pulmonary granulomatosis. Deposition of insoluble excipients (eg, talc, methylcellulose, crospovidone) used as binders and fillers results in acute embolization within the small pulmonary arteries and arterioles. Foreign material initially causes arteritis with neutrophil infiltration and cytokine production and on occasion thrombosis. As talc crystals migrate through the arterial wall, they are engulfed by giant cells and macrophages resulting in granulomatous inflammation, coalescence of the giant cells and mononuclear cells into nodules, and varying degrees of perivascular and interstitial fibrosis. Repetitive exposures may lead to

Table 1. Echocardiographic variables at baseline and at 3-year follow-up.

<table>
<thead>
<tr>
<th></th>
<th>RVSP (mmHg)</th>
<th>RAP (mmHg)</th>
<th>TR velocity (m/sec)</th>
<th>TAPSE (mm)</th>
<th>RIMP</th>
<th>TVLASV (m/sec)</th>
<th>EF (%)</th>
<th>RV Strain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>88</td>
<td>14</td>
<td>4.3</td>
<td>17</td>
<td>0.69</td>
<td>0.09</td>
<td>54</td>
<td>-20</td>
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<tr>
<td>3-year follow-up</td>
<td>41</td>
<td>5</td>
<td>3.00</td>
<td>20</td>
<td>0.56</td>
<td>0.10</td>
<td>66</td>
<td>-27</td>
</tr>
</tbody>
</table>

RVSP, right ventricular systolic pressure; RAP, right atrial pressure; TR, tricuspid regurgitant; TAPSE, tricuspid annular plane systolic excursion; RIMP, right ventricular index of myocardial performance; TVLASV, tricuspid valve lateral annulus systolic velocity; EF, ejection fraction; PA, pulmonary artery.
emphysema, interstitial lung disease, and/or pulmonary hypertension. Talc-induced PAH can be challenging to diagnose as the patient history may not be volunteered freely and the definitive diagnosis requires a tissue biopsy with demonstrated perivascular fibrosis, giant cells, and talc crystals which are birefringent under polarized light. Optimal pulmonary hypertension treatment remains unknown, however Farber et al noted oral hydralazine in 6 patients with foreign body granulomatosis attenuated exercise-induced increases in PVR and mean pulmonary artery pressure.5 Echocardiography can be an effective imaging tool to follow patients as RV strain and TAPSE are predictive of RV function and outcome in PAH.6,7 Although the current case is unusual, we highlight the thought process and workup of all patients with signs or symptoms of elevated right-sided pressures and treat the underlying process similarly to other causes of PAH.

Table 2. Right heart catheterization hemodynamics.

<table>
<thead>
<tr>
<th>Phase</th>
<th>RAP (mmHg)</th>
<th>RVSP (mmHg)</th>
<th>mPAP (mmHg)</th>
<th>PAWP (mmHg)</th>
<th>CI (L/min/m²)</th>
<th>PVR (Wood Units)</th>
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</thead>
<tbody>
<tr>
<td>Baseline Rest</td>
<td>13</td>
<td>100</td>
<td>62</td>
<td>9</td>
<td>1.45</td>
<td>20.0</td>
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<tr>
<td>Vasodilator</td>
<td>ND</td>
<td>ND</td>
<td>61</td>
<td>26</td>
<td>1.83</td>
<td>10.45</td>
</tr>
<tr>
<td>1 Year F/U</td>
<td>11</td>
<td>49</td>
<td>29</td>
<td>14</td>
<td>2.26</td>
<td>3.79</td>
</tr>
</tbody>
</table>

RAP, right atrial pressure; RVSP, right ventricular systolic pressure; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; ND, not done; F/U, follow-up.