Puzzling Etiology of Pulmonary Hypertension Resolved

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Section editor's note: Welcome to a new section in *Advances* titled "Pulmonary Hypertension Grand Rounds" (PHGR), which we are introducing in this issue. With this addition, *Advances* offers a unique opportunity for trainees and junior faculty interested in pulmonary hypertension (PH). This section will highlight cases with literature reviews written by young clinicians and researchers in PH. PHGR was created to use patient cases to integrate individual clinical expertise with the best available evidence from the literature to enable the best decisions for patients. As with the rest of the journal, our audience continues to be physicians, researchers, nurses, students, residents, and fellows interested in both the care of individual patients and the advances in our field. We welcome comments about the section and inquiries regarding submitting a case for publication. Please direct inquiries to advancesgrandrounds@PHAssociation.org

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, bronchoalvealoar 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 10^9/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 (antinuclear antibody, anti-RNA, anti-Ro, anti-La, anti-RNP, anti-double-stranded DNA, 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.[1,2] 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

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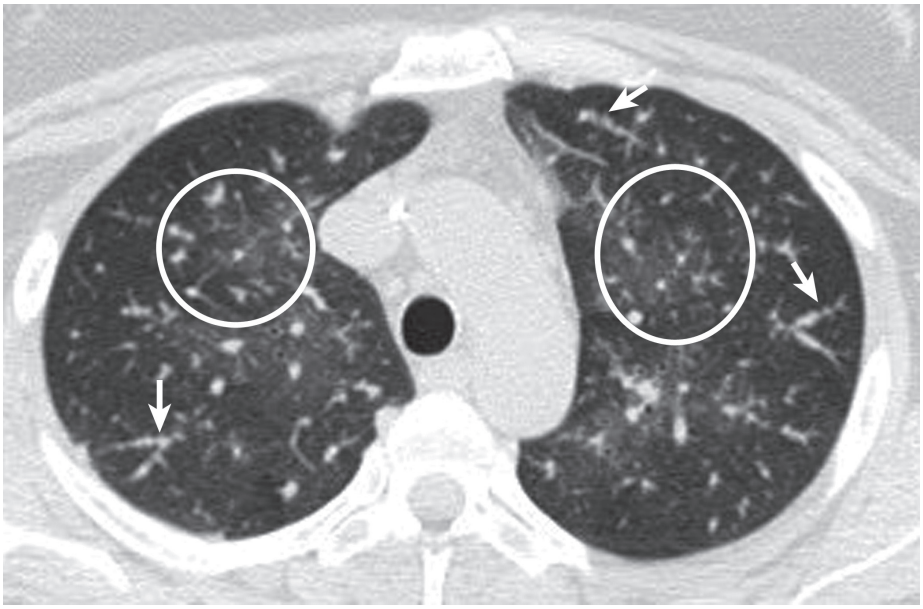

Figure 1. Noncontrast chest computed tomography demonstrating diffuse tree-in-bud micronodular opacities (circles) throughout both lungs and serrated-appearing pulmonary arteries (arrows).

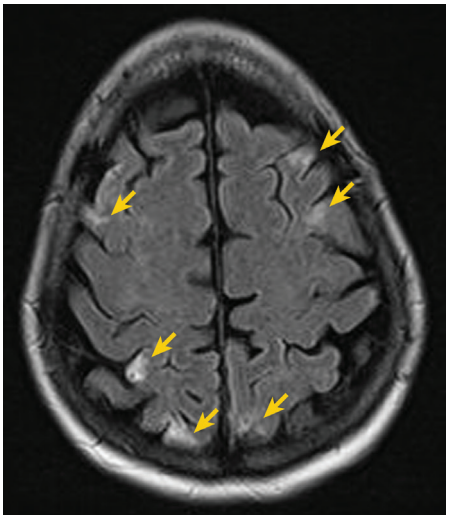

Figure 2. Brain MRI T2 FLAIR demonstrating multiple cerebral cortex infarcts in multiple vascular distributions (arrows).

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.

Diagnosis:
She was diagnosed with talc-induced PAH. She was treated with inhaled treprostinil, tadalafil, warfarin, and short-term amoxicillin (for the skin abscesses). After discharge, 6-minute walk distance was 395 meters, which at 1 year follow-up improved to 482 meters. At 1 year follow-up, she remained narcotic-free and had functional class I symptoms. Repeat right heart catheterization at that time demonstrated significant improvement in right-sided hemodynamics (Table 2) on PAH-directed therapies. Neurologic deficits fully resolved. At 3 years' follow-up, she remained functional class I and her right ventricular echo parameters normalized with TAPSE 20 mm, RV strain -27%, RVSP 41 mmHg, and RAP 5 mmHg (Table 1). Because of long-term anticoagulation concerns and her history of embolic stroke, the patient underwent percutaneous closure of her patent foramen ovale.

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

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

RVSP, right ventricular systolic pressure; RAP, right atrial pressure; TR, tricuspid regurgitant; TAPSE, tricuspid annular plane systolic excurstion; RIMP, right ventricular index of myocardial performance; TVLASV, tricuspid valve lateral annulus systolic velocity; EF, ejection fraction; PA, pulmonary artery.

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[1] 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,[3] while review of a single-center experience documented PAH in 5 of 9 patients with talc pulmonary granulomatosis.[4] 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 neutrophilic 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

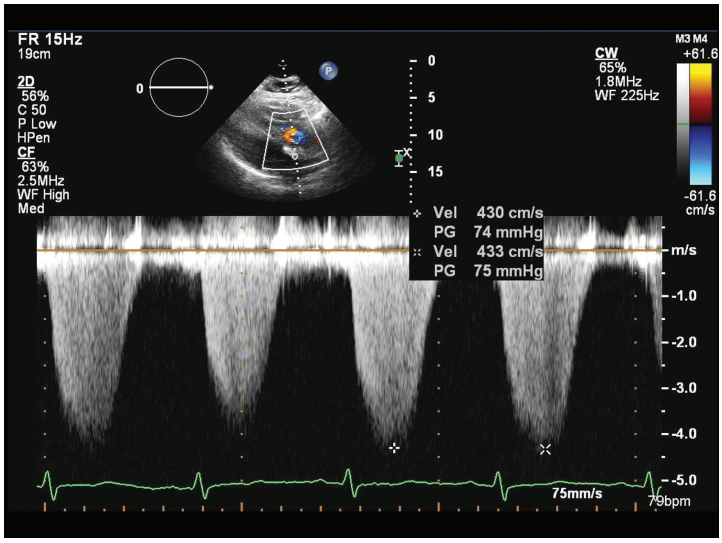

Figure 3. Transthoracic echocardiography continuous wave Doppler of the tricuspid regurgitant velocity consistent with elevated right ventricular systolic pressure.

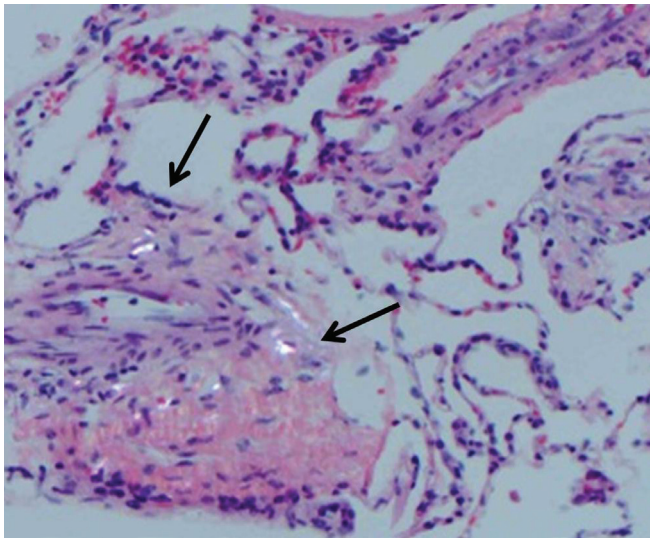

Figure 4. Birefringent material with polarized light (black arrows) with granulomatous perivascular inflammation consistent with foreign body (talc) granulomatosis from crushed pill injection.

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.

Phase	RAP (mmHg)	RVSP (mmHg)	mPAP (mmHg)	PAWP (mmHg)	CI (L/min/m^2)	PVR (Wood Units)
Baseline Rest	13	100	62	9	1.45	20.0
Vasodilator	ND	ND	61	26	1.83	10.45
1 Year F/U	11	49	29	14	2.26	3.79

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.

References

1. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D42-50.
2. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D34-41.
3. Arnett EN, Battle WE, Russo JV, Roberts WC. Intravenous injection of talc-containing drugs intended for oral use. A cause of pulmonary granulomatosis and pulmonary hypertension. *Am J Med*. 1976;60(5):711-8.
4. Griffith CC, Raval JS, Nichols L. Intravascular Talcosis due to Intravenous Drug Use Is an Underrecognized Cause of Pulmonary Hypertension. *Pulm Med*. 2012;2012:617531.
5. Farber H, Glauser FL. The effect of oral hydralazine on the pulmonary hemodynamics of patients with pulmonary foreign body granulomatosis. *Chest*. 1982;82(6):708-12.
6. Fine NM, Chen L, Bastiansen PM, et al. Outcome prediction by quantitative right ventricular function assessment in 575 subjects evaluated for pulmonary hypertension. *Circ Cardiovasc Imaging*. 2013;6(5):711-21.
7. Forfia PR, Fisher MR, Mathai SC, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. *Am J Respir Crit Care Med*. 2006;174(9):1034-41.