An Interesting Case of Sarcoidosis-Associated Pulmonary Hypertension

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BACKGROUND

Sarcoidosis-associated pulmonary hypertension (SAPH) is classified in World Health Organization group 5 pulmonary hypertension (PH) due to the various potential mechanisms of disease pathogenesis including pulmonary arterial hypertension (PAH), left heart disease, fibrotic lung disease, pulmonary vascular stenosis, compressive adenopathy, and fibrosing mediastinitis.[1,2] Although patients with sarcoidosis-associated advanced fibrotic lung disease are at the highest risk and comprise a majority of SAPH patients,[3,4] pulmonary sarcoidosis involving the pulmonary veins presents a unique management challenge and mortality risk. We present a patient with SAPH due to pulmonary vein compression from adenopathy who required multiple pulmonary vein balloon dilations and stents in the setting of large-volume hemoptysis and right heart failure.

PRESENTATION

A 40-year-old female with a history of cutaneous and pulmonary sarcoidosis presented to the emergency department (ED) with large volume hemoptysis. Symptoms began approximately 3 days prior with cough productive of light green sputum accompanied by increasing dyspnea, posttussive emesis, and chills. She estimated having 2 L of hemoptysis over the course of the day with active hemoptysis (650 mL) in the ED.

Before this presentation, she had been on chronic steroids for sarcoidosis, although she was noted to be a poor steroid responder. She had additionally been on methotrexate but notably had been out of her medications including prednisone, losartan, nicardipine, and Symbicort, for 3 weeks before her ED presentation.

On physical examination, she was hypotensive and tachycardic. Jugular venous distention was present, but no murmurs or gallops on auscultation. Pulmonary exam revealed inspiratory and expiratory wheezes and bibasilar crackles.

WORKUP AND THERAPEUTIC INTERVENTIONS

She was admitted to the Intensive Care Unit, and an emergent bronchoscopy was performed which demonstrated bleeding localized to the lingula in addition to hyperemia of the mucosa with bright red streaking capillaries. Due to persistent bleeding, the patient underwent an attempt at embolization with interventional radiology. However, no site of bleeding was identified by arteriogram. The patient was in shock on admission, requiring norepinephrine and dobutamine, presumed from severe right heart failure and PH.

Computed tomography chest revealed interlobular septal thickening and edema pattern predominantly in the upper lobes with significant mediastinal and hilar lymphadenopathy in addition to pulmonary vein stenoses (Figures 1 and 2). Transthoracic echo was performed and demonstrated severe right ventricular dysfunction in addition to severe PH and can be seen in Table 1. Ultimately, pulmonary venous hypertension second-

Key Words—sarcoidosis-associated pulmonary hypertension, pulmonary veno-occlusive disease, pulmonary venous hypertension, echocardiogram
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ary to pulmonary vein obstruction was presumed to be the underlying etiology. As such, she went for heart catheterization for further evaluation.

Right and left heart catheterization was performed which showed almost systemic pulmonary artery pressures with pulmonary capillary wedge pressure of around 30 but with left ventricular end diastolic pressure of only 11, consistent with pulmonary vein stenosis. Attempted decompression of the left lower and lingular pulmonary veins with balloon dilation was performed. Heart catheterization data both preballoon and postballoon dilation are presented in Table 2. Cardiac catheterization demonstrated a significant reduction in stenosis with less than 20% residual stenosis postdilation in the left lingular pulmonary vein and left lower pulmonary vein.

After pulmonary vein dilation, a cardiac magnetic resonance venous scan was completed, which demonstrated moderate stenosis of the right upper and right middle lobe pulmonary veins, no stenosis involving the left upper or left lower veins, and delayed myocardial enhancement at the inferior basilar wall, suggestive of myocardial sarcoidosis. Cardiac positron emission tomography was not pursued during or after her hospitalization, and her prior immunosuppressive regimen was continued. Vasopressors were weaned during admission, and she was successfully extubated. Lung transplantation was considered, but she was deemed not to be a candidate due to persistent tobacco use.

FOLLOW UP

Recurrent hemoptysis in the months after her initial admission raised concern for recurrent pulmonary vein obstruction. Radiographic workup showed continued mediastinal lymphadenopathy and improved interstitial edema from prior study. Transthoracic echocardiogram was obtained 4 months after initial presentation and showed mild increase in pulmonary artery pressure, right ventricular dysfunction, and reduction in right ventricular size. Echocardiogram data are shown in Table 1. Magnetic resonance imaging and magnetic resonance angiography showed severe stenosis of the left upper pulmonary vein which was unchanged from prior, stable left upper lobe hypoperfusion with slight decrease in the left inferior pulmonary vein narrowing, minimal decrease in stenosis at the confluence of the right upper and middle pulmonary veins, as well as normal left and right ventricular systolic function.

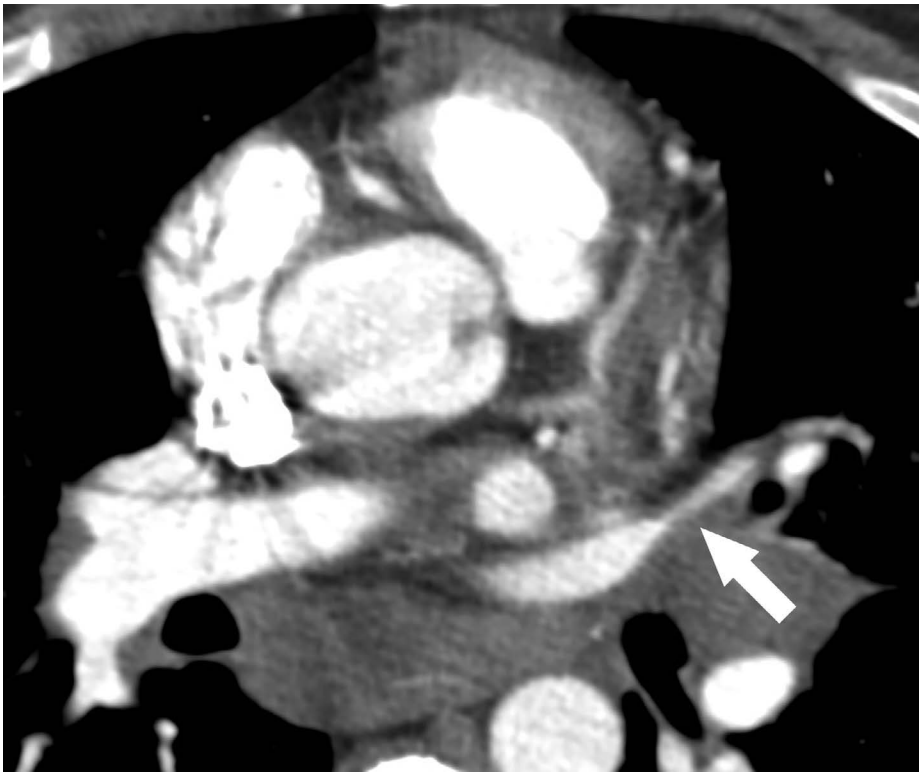

Figure 1: Contrast-enhanced chest computed tomography image shows stenosis of the left superior pulmonary vein (arrow) and left hilar and subcarinal lymphadenopathy.

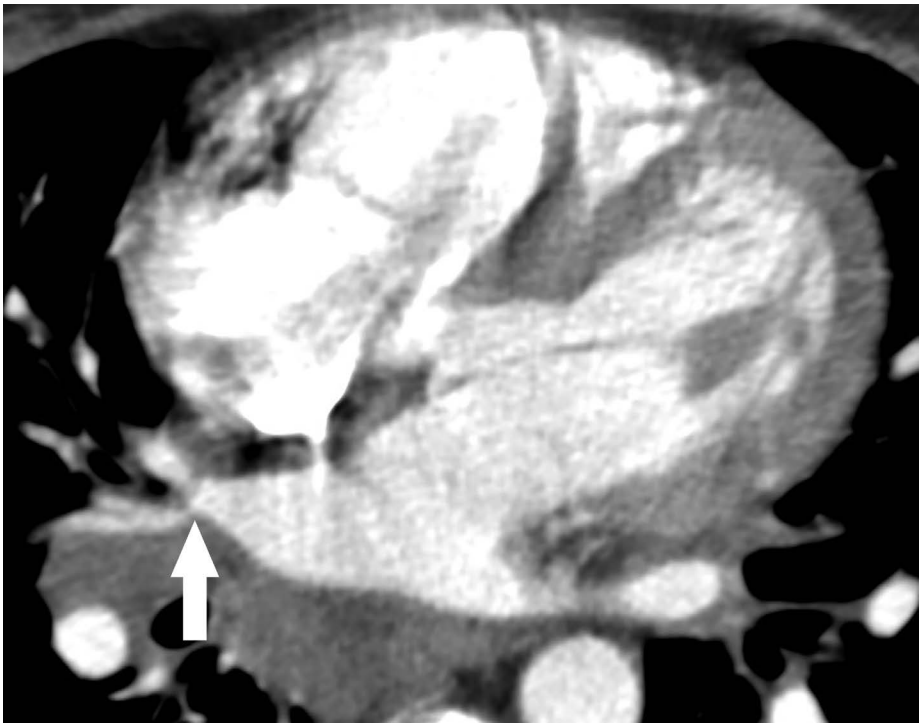

Figure 2: Contrast-enhanced chest computed tomography image shows stenosis at the confluence of the middle lobe pulmonary veins (arrow) and right hilar and subcarinal lymphadenopathy.

Table 1. Echocardiographic data from initial presentation, both preballon and postballoon angioplasty of left lingular and left lower pulmonary veins; 4-month follow up; 12-month urgent evaluation of right heart function before stenting; 21 months later, both preballoon and postballoon angioplasty; and admission for severely progressive pulmonary hypertension requiring veno-arterial extracorporeal membrane oxygenation

	Initial presentation		Time from initial presentation (mo)				
			4	12	21		29
Echocardiogram	Baseline	Postballoon	Baseline	(Limited exam)	Baseline	Postballoon	Baseline
LVEF (%)	85	70	65	70	70	65	70
LV size (mm)	28.5	37.4	24.3	NA	36.8	45.9	33.5
LVOT peak velocity (cm/s)	196	115.9	127	NA	124.1	125.8	129
PA peak pressure (mmHg)	106	50	62	91	70	77	109
RV size (mm)	43.7	NA	39	NA	36.1	41.3	42.7
TAPSE (cm)	1.3	1.8	2.4	NA	2.3	2	1.7
Estimated CVP (mmHg)	25	NA	8	15	5	5	15
RV function	Severely reduced	Normal	Mildly reduced	Moderately reduced	Moderately reduced	Mildly reduced	Moderately reduced
RA size	43.7	NA	39	NA	36.1	41.3	42.7
PV regurgitation	Moderate	Mild	None	Mild	Mild	Mild	Mild
TV regurgitation	Moderate	Mild	Mild	NA	Moderate	Mild	Moderate
AV regurgitation	Mild	Moderate	None	NA	Mild	Mild	Mild
MV regurgitation	Mild	Trivial	None	NA	None	None	None

Abbreviations: AV, aortic valve; CVP, central venous pressure; LV, left ventricle; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MV, mitral valve; NA, not applicable; PA, pulmonary artery; PV, pulmonic valve; RA, right atrium; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TV, tricuspid valve.

Due to persistent significant thoracic adenopathy despite compliance with prednisone and methotrexate, she was initiated on infliximab, which unfortunately did not result in any shrinkage of her hilar and mediastinal lymphadenopathy and was ultimately discontinued.

She subsequently underwent multiple pulmonary vein stents and balloon dilations performed at 12, 21, and 29 months after her initial presentation, and catheterization data are presented in Table 2. Left lower pulmonary vein, left upper pulmonary vein, and right lower pulmonary vein stents were placed 1 year after her initial hospitalization for hemoptysis. Nifedipine was initiated for possible pulmonary venodilation effect but was ineffective.

Two and a half years from initial presentation, she was again hospitalized for severe PH and right heart failure with hemoptysis and possible pneumonia. Mechanical ventilation, inotropic support, and veno-arterial extracorporeal membrane support was provided, but she unfortunately suffered a subarachnoid hemorrhage, and life-supporting measures were withdrawn.

DISCUSSION

In our patient, pulmonary venous hypertension due to pulmonary vein obstruction secondary to compressive adenopathy from underlying sarcoidosis was temporized with pulmonary vein dilation and stenting with subsequent improvement in pulmonary vascular pressures and functional status. Agents including prednisone, methotrexate, and infliximab were unfortunately unsuccessful in significantly improving her compressive adenopathy. Despite this, pulmonary vein balloon dilations and stenting were able to provide 2.5 additional years and allow her to return home.

Pulmonary sarcoidosis is not limited to the lung parenchyma and lymph nodes but can affect the pulmonary vasculature as well. This can be from compressive adenopathy or granuloma formation within the pulmonary arterial and venous systems. On autopsy, granulomas have been observed in multiple pulmonary venous vascular layers, causing vessel fibrosis and luminal narrowing.[5] Our patient was diagnosed with postcapillary PH secondary to pulmonary venous obstruction from compressive mediastinal and hilar adenopathy in the setting of underlying sarcoidosis. As in our patient, pulmonary venous stenosis can present with massive hemoptysis, which can be life threatening and difficult to diagnose on routine imaging.[6] Corticosteroids are the foundation of sarcoidosis management, but their efficacy for SAPH has been mixed.[7] If the pulmonary venous stenosis is secondary to extrinsic compression from bulky mediastinal and hilar adenopathy, then corticosteroids can lead to an improvement in pulmonary vascular pressures. In a study by Nunes et al,[8] treatment with corticosteroids led to a reduction in systolic pulmonary arterial pressures in patients with nonfibrotic SAPH, but there was no benefit in patients with fibrotic SAPH. In our patient, corticosteroids

Table 2. Left and right heart catheterizations from initial presentation, both preballoon and postballoon dilatation of left lingular and left lower pulmonary veins; 12 months later, both pre-intravascular and postintravascular stenting of left lingular, left lower, and right lower pulmonary veins; 21 months later, both preballon and postballoon dilatation of in-stent and native stenosis of the left lower, left upper, and right lower pulmonary veins; and 29 months later, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) insertion and attempt balloon angioplasty of pulmonary veins

Cardiac catheterizations, mean pressure (mmHg)	Initial presentation		Mo after initial presentation				
			12		21		29
	Preballoon	Postballoon	Prestent	Poststent	Preballoon	Postballoon	VA-ECMO, balloon dilatation
RA	15	17	12	NA	10	12	NA
RVEDP	27	25	10	NA	15	NA	108
PA	NA	NA	NA	49	51	NA	66
LPA	66	66	51	NA	49	NA	NA
RPA	66	NA	48	NA	50	NA	42
LPCWP	30	23	NA	NA	NA	NA	NA
RPCWP	26	NA	18	14	15	NA	29
Ao	79	88	NA	NA	75	NA	80
LVEDP	11	NA	NA	14	10	NA	NA
LA	11	12	10	14	10	NA	11
LLPV	16	26	28	14	14	12	12
LLiPV	68	25	NA	NA	NA	NA	NA
LUPV	25	NA	38	14	35	12	NA
RUPV	NA	NA	14	14	11	11	NA
RLPV	NA	NA	35	14	22	12	NA
% Stenosis							
RLPV	60–70	NA	NA	NA	NA	NA	50
LLiPV	70–80	<20	NA	NA	NA	NA	NA
LLPV	70	<20	NA	NA	NA	NA	50–75
LUPV	NA	NA	NA	NA	NA	NA	100

Abbreviations: Ao, aorta; LA, left atrium; LLiPV, left lingular pulmonary vein; LLPV, left lower pulmonary vein; LPA, left pulmonary artery; LPCWP, left pulmonary capillary wedge pressure; LVEDP, left ventricular end diastolic pressure; LUPV, left upper pulmonary vein; NA, not applicable; PA, main pulmonary artery; RA, right atrium; RLPV, right lower pulmonary vein; RPA, right pulmonary artery; RPCWP, right pulmonary capillary wedge pressure; RUPV, right upper pulmonary vein; RVEDP, right ventricular end diastolic pressure.

were not effective in improving pulmonary venous obstruction and PH.

Patients with pulmonary venous obstruction due to external vascular compression can undergo pulmonary vein angioplasty and stenting to relieve the obstruction in an effort to improve pulmonary vascular pressures and right heart failure.[9,10] In a small case series, pulmonary vein angioplasty and stenting in the setting of pulmonary vascular compression from bulky lymphadenopathy led to clinical and hemodynamic improvement.[9] Pulmonary vein angioplasty and stenting is a viable option for patients interested in prolonging life or as a bridge to lung transplantation.

Based on small series and nonrandomized trials, pulmonary vasodilator therapy may have a role in treatment of patients with precapillary SAPH but carries an increased risk of developing pulmonary edema and respiratory failure in patients with postcapillary component. Despite the increased risk, there have been case reports and small case series of pulmonary veno-occlusive disease (PVOD) patients improving with pulmonary vasodilator therapy.[11,12] For example, a small case series demonstrated hemodynamic improvement with cautious epoprostenol therapy as a bridge to lung transplant in 12 patients with PVOD.[13] In SAPH patients, granuloma formation may not be limited to the pulmonary venous system but can involve the pulmonary arterial system, a scenario in which PH vasodilatory therapy could be beneficial.

Patients with SAPH have poor long-term prognosis, with a 5-year survival ranging from 40%–55%.[10] The multifactorial nature of these patients' PH can create diagnostic dilemmas when trying to elucidate the primary driver of right ventricular failure, which in turn leads to difficulty while choosing the most appropriate treatment options. Ultimately, lung transplantation is the curative treatment option but carries its own risks and benefits. These patients

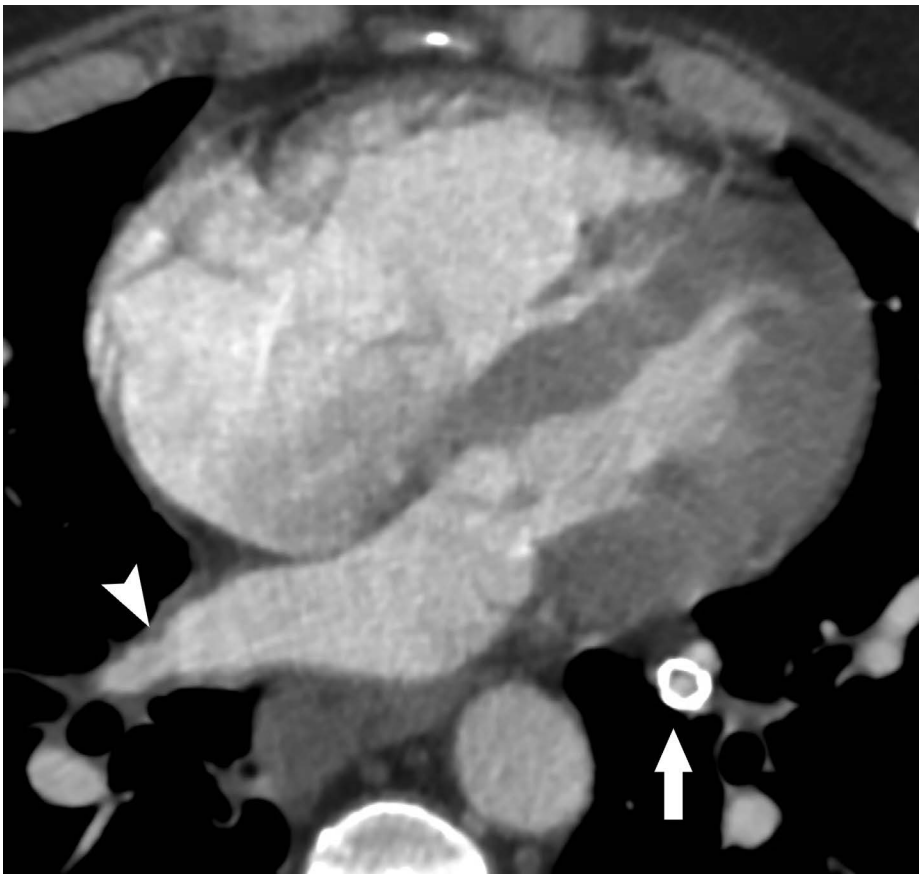

Figure 3: Contrast-enhanced chest computed tomography image shows mild stenosis of the right inferior pulmonary vein (arrowhead) and stent in a left inferior pulmonary vein branch (arrow).

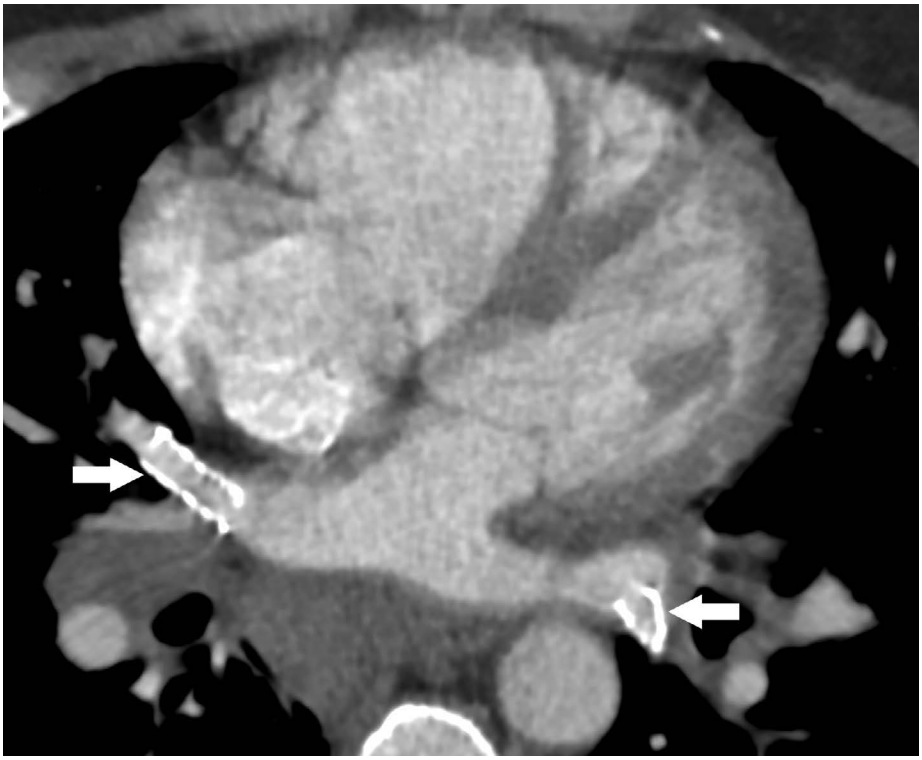

Figure 4: Contrast-enhanced chest computed tomography image shows patent pulmonary venous stents (arrows) in a middle lobe vein branch and in the left inferior pulmonary vein. Lymphadenopathy persists.

should be managed in an experienced PH center given the complex nature of their PH.

TEACHING POINTS

1. SAPH has several mechanisms of pathogenesis including PAH, left heart disease, fibrotic lung disease, pulmonary vascular stenosis, compressive adenopathy, and fibrosing mediastinitis.
2. Hemoptysis is a rare presentation of SAPH from pulmonary venous obstructive disease.
3. The multifactorial pathogenesis of SAPH portends high mortality and diagnostic challenges, with 5-year survival estimated at 40%–55%.
4. There is insufficient data with corticosteroids improving SAPH from all mechanisms.
5. Pulmonary venous stenosis from compressive adenopathy may initially be treated with corticosteroids, with consideration for balloon angioplasty if there is no improvement.
6. Vasodilator therapy can be cautiously considered in patients with SAPH if granulomatous involvement of the pulmonary arterial system is a suspected mechanism.

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