PH GRAND ROUNDS

When a Clot Is Not a Clot: An Unusual Cause of Progressively Worsening Dyspnea in a Previously Healthy Woman

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PRESENTATION

A 61-year-old Caucasian female presented with a 4-month history of dyspnea on exertion. She was previously healthy, worked out regularly, and had no prior tobacco exposure. Her symptoms were preceded by a sharp, inspiratory chest pain (left sided), which was initially intermittent and later became persistent. A few days into her symptom course, she developed exertional dyspnea. A contrasted high-resolution computed tomography (HRCT) scan of the chest ordered by her primary care provider showed minimal, peripheral-appearing upper lobe and right middle lobe ground-glass opacities without any evidence of pulmonary emboli (PE) (Figure 1). She was given a course of antibiotics, 20 mg of prednisone for 5 days, and referred to a pulmonologist. With this, her chest pain improved but her dyspnea persisted. At the pulmonary evaluation a few weeks later, she was noted to be significantly hypoxemic. She was started on supplemental oxygen therapy. Given her persistent symptoms, she received 3 different additional courses of oral antibiotic therapy for a possible "resistant" pneumonia to no avail. Given the lack of improvement in her symptoms, her prednisone dose was increased, and she was subsequently referred to our institution.

ASSESSMENT

On physical examination at the time of initial evaluation at our institution, the patient was afebrile with pulse oximetry revealing an oxygen saturation of 100% on 5 L/min of supplemental oxygen. Oral exam was notable for several telangiectasias on her hard palate. Cardiac and pulmonary exams were unremarkable with a normal sounding P2 and no murmurs. Jugular venous pulse was not elevated. Musculoskeletal exam was negative for muscle or joint tenderness. On skin exam, several telangiectasias were noted across her anterior chest wall. There was no evidence of sclerodactyly or digital ulceration. There was neither

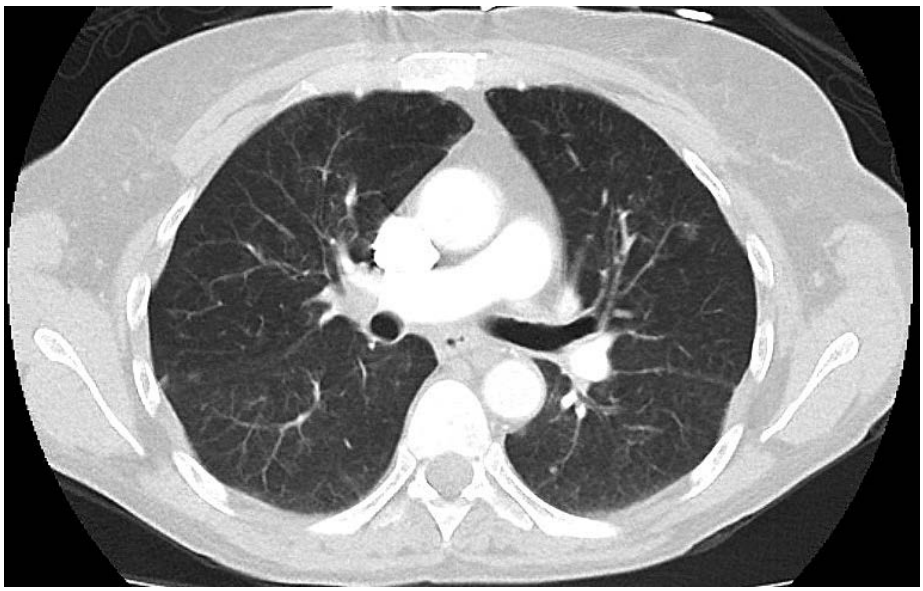

Figure 1: Initial contrasted chest computed tomography with minimal, peripheral, ground-glass opacities. No evidence of acute pulmonary emboli.

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Table 1. Pertinent PFT Values (PFTs Notable for Reduction in D_LCO)

PFT parameters	Predicted	Measured	% Predicted
FVC, L	2.88	3.23	112%
FEV1	2.22	2.50	113%
FEV/FVC, %		77	
TLC, L	4.20	4.89	116%
RV, L	1.58	1.66	105%
D_LCO, mL/mm Hg per minute	16.6	9.3	56%

Abbreviations: PFT indicates pulmonary function test; DLCO, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; TLC, total lung capacity measured using plethysmography; RV, residual volume.

cyanosis nor edema at the peripheries of her extremities. Her neurologic exam was also unremarkable.

Her pulmonary function tests were normal except for an isolated reduction in the diffusing capacity of the lungs for carbon monoxide (D_LCO) (Table 1). Her 6-minute walk distance was reduced at 290 m with a significant oxygen desaturation to 92% on 4 L/min. Her initial laboratory workup demonstrated a normal complete blood cell count panel as well as normal renal and liver function panels, and her serum levels of cardiac biomarkers were within normal limits. Her electrocardiogram was unremarkable as was her chest x-ray. We then ordered a repeat contrasted HRCT scan of her chest which demonstrated a worsening of the previously described airspace opacities. Her imaging now showed increased prominence of the upper lobe ground-glass opacities, again without any evidence of acute PE. The airspace opacities were peripheral in position and appeared to have a vascular predilection, and some of the opacities had a nodular appearance to them (Figure 2). An echocardiogram demonstrated a preserved ejection fraction with normal left and right ventricular size and function. There were no signs of valvulopathy or pulmonary hypertension (PH).

MANAGEMENT AND MONITORING

Further workup was pursued with an extensive autoimmune panel, including a myositis antibody panel and a hypersensitivity antibody panel, all of which were negative. Her creatine kinase level was within normal limits. Eventually, she underwent a bronchoscopy with transbronchial biopsies, which were unrevealing. Broncho-alveolar lavage was noted to be lymphocyte predominant. Cytology was unremarkable and negative for fungal organisms and malignant cells. Cryptogenic organizing pneumonia was the initial diagnosis of exclusion and so she was started on therapy with high-dose prednisone (1 mg/kg) and concomitant pneumocystis prophylaxis with trimethoprim-sulfamethoxazole. With steroid therapy, her symptoms improved initially, and her oxygen requirement decreased to 3 L/min during rest. However, after 8 weeks on high-dose prednisone, she returned to the clinic with worsening dyspnea and hypoxemia.

Given her persistent symptoms, low D_LCO, a vascular distribution of her airspace opacities, and severe hypoxemia, pulmonary vascular disease continued to remain a possibility. She then underwent a ventilation/perfusion (V/Q) scan that returned positive for bilateral unmatched wedge-shaped perfusion defects, suggestive of pulmonary thromboembolic disease (Figure 3). Pulmonary veno-occlusive disease (PVOD) was also entertained as a possibility given her profound hypoxemia. She was started on systemic anticoagulation with rivaroxaban. A subsequent evaluation with a hypercoagulable panel did not reveal any underlying thrombophilia. A right heart catheterization (RHC) was consistent with mild PH and an elevated pulmonary vascular resistance (Table 2). She was then referred to the nearest pulmonary thrombo-endarterectomy center where a fluoroscopic pulmonary angiogram was completed. Interestingly, her pulmonary angiogram did not show any filling defects in the pulmonary vascular tree. The venous phase of the angiogram also showed normal emptying, making this unlikely to be pulmonary thromboembolic disease or PVOD. Ultimately, without a clear diagnosis, we pursued an urgent video-assisted

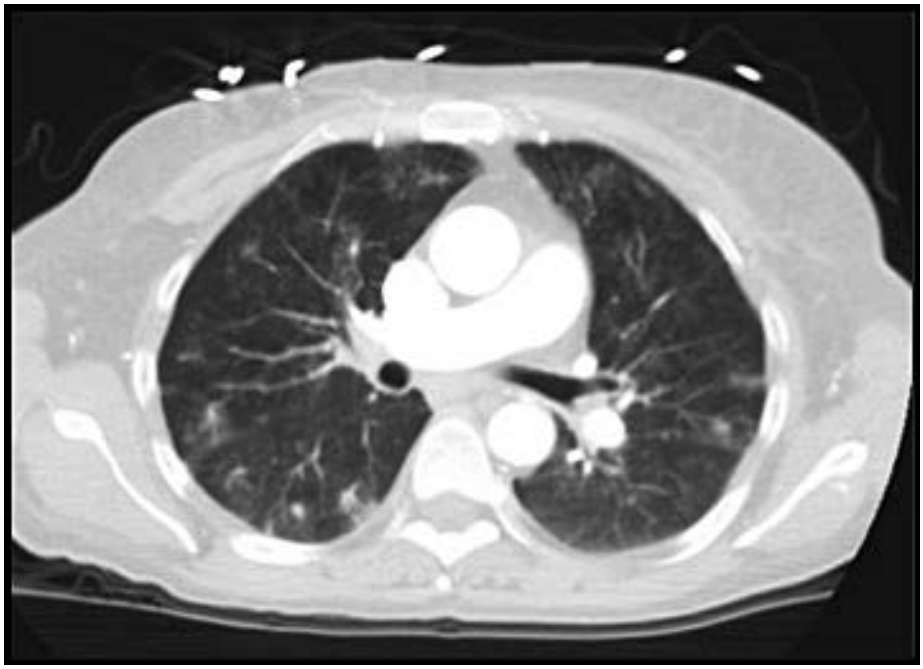

Figure 2: Repeat contrasted chest computed tomography with increased number and prominence of the peripheral, ground-glass opacities. No evidence of acute pulmonary emboli.

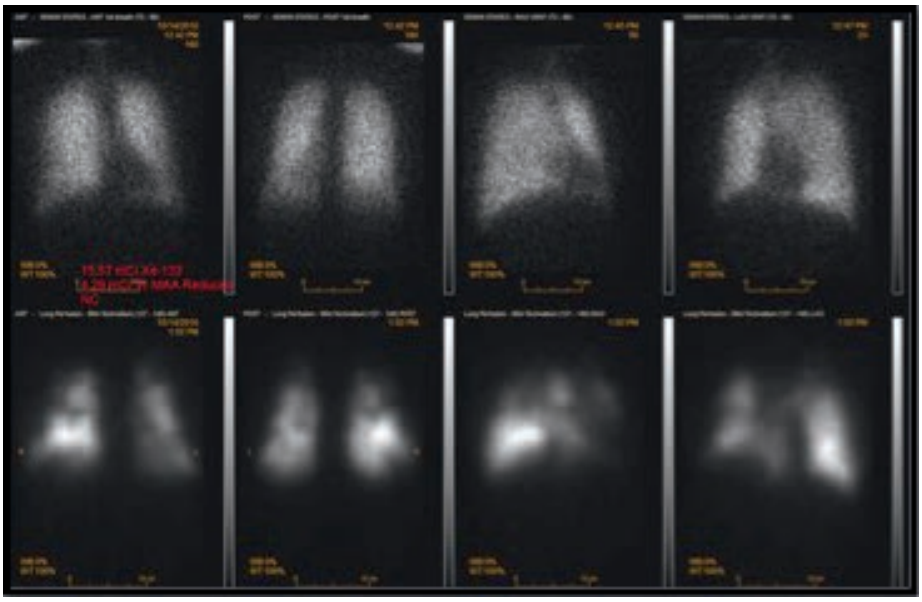

Figure 3: Planar ventilation/perfusion (V/Q) scan images demonstrating bilateral unmatched, wedge-shaped perfusion defects.

Table 2. Right Heart Catheterization

RHC variable	Value
RAP	4 mm Hg
RVP	41/2 mm Hg
PAP	42/18 mm Hg
mPAP	27 mm Hg
PCWP	6 mm Hg
CO (Fick)	4.2 L/min
CI	2.8 L/min per m^2
PVR	5.0 Wood units
SaO_2 sat	94.7%
PAO_2 sat	70.4%

Abbreviations: RHC indicates right heart catheterization; RAP, right atrial pressure; RVP, right ventricular pressure; PAP, pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary edge pressure; CO, cardiac output as measured by Fick equation; CI, cardiac index; PVR, pulmonary vascular resistance; SaO_2 sat, systemic oxygen saturation; PAO_2 sat, pulmonary artery oxygen saturation.

thoracoscopic surgery lung biopsy, which provided a definitive diagnosis.

DISCUSSION AND CLINICAL REASONING

Though there was no evidence by history or on exam of a systemic autoimmune process, we checked both autoimmune and myositis antibody panels. These panels returned negative as did a hypersensitivity pneumonitis antibody panel. Considering her unremarkable aero-allergen exposure history and that her pulmonary function tests demonstrated normal estimates of lung volume by spirometry and plethysmography, we felt reassured that an interstitial lung disease was unlikely. However, the isolated D_LCO on her pulmonary function tests continued to keep occult pulmonary vascular disease on the list of differential diagnoses. With her degree of hypoxemia and noting the peripheral and vascular distribution of the pulmonary opacities, we pursued a V/Q scan to evaluate for any possible microvascular pulmonary thromboembolic disease. The identification of at least two mismatched segmental perfusion defects (perfusion defects noted in areas of the lung with normal ventilation) on planar imaging is considered "high probability" for PE by the Prospective Investigation of Pulmonary Embolism Diagnosis study's criteria.[1] In patients with suspected chronic thromboembolic PH (CTEPH), a V/Q scan is more "sensitive" as it can detect distal and subsegmental perfusion defects that can often be missed on contrast-enhanced chest CT imaging.[2]

Progressive dyspnea on exertion, a decreased 6-minute walk distance, and an isolated low D_LCO in concert with a chest CT negative for acute PE should prompt consideration of pulmonary vascular disease. Chronic thromboembolic disease (CTED) and CTEPH are two causes of pulmonary vascular disease due to thromboembolic events. CTEPH can occur in 0.4% to 8.8% of patients who develop an acute PE.[3] One-half of patients with CTEPH do not recall ever having had a diagnosis of PE.[4] A diagnosis of CTEPH becomes obvious typically following 6 months after the index PE event. CTED is diagnosed in patients who have imaging evidence of embolic burden in the pulmonary vasculature but do not have RHC-documented PH.[5] Both CTEPH and CTED are diagnosed by means of a V/Q scan and can reportedly be associated with normal-appearing pulmonary arteries on contrasted chest CT imaging in a significant number of patients. Our patient's V/Q scan was positive for multiple perfusion defects (Figure 3) but contrasted CT imaging did not reveal any filling defects in the pulmonary arteries. An RHC is also important for the diagnosis of CTEPH. Despite this patient's echocardiogram being normal, an RHC was pursued (Table 2). This was followed by a dedicated fluoroscopic pulmonary angiogram to determine the pulmonary vascular thrombotic burden contributing to her PH. The findings of mildly elevated pulmonary pressures, moderately elevated pulmonary vascular resistance, and the absence of a significant clot burden on pulmonary angiography were inconsistent with a diagnosis of significant CTEPH. Her pulmonary hemodynamics and unremarkable venous-phase emptying noted on the pulmonary angiogram were also inconsistent with PVOD, another diagnosis which was considered.[6]

While the diagnosis remained elusive, the patient continued to have a functional decline with increasing oxygen requirement. As her clinical picture remained concerning for a pulmonary vascular disease, we revised our list of differential diagnoses to include atypical vasculitis, an embolic or malignant phenomenon, and although less likely, we left PVOD on the differential. Considering that there was no evidence of an infectious source by exam or blood work, septic PE was also considered an

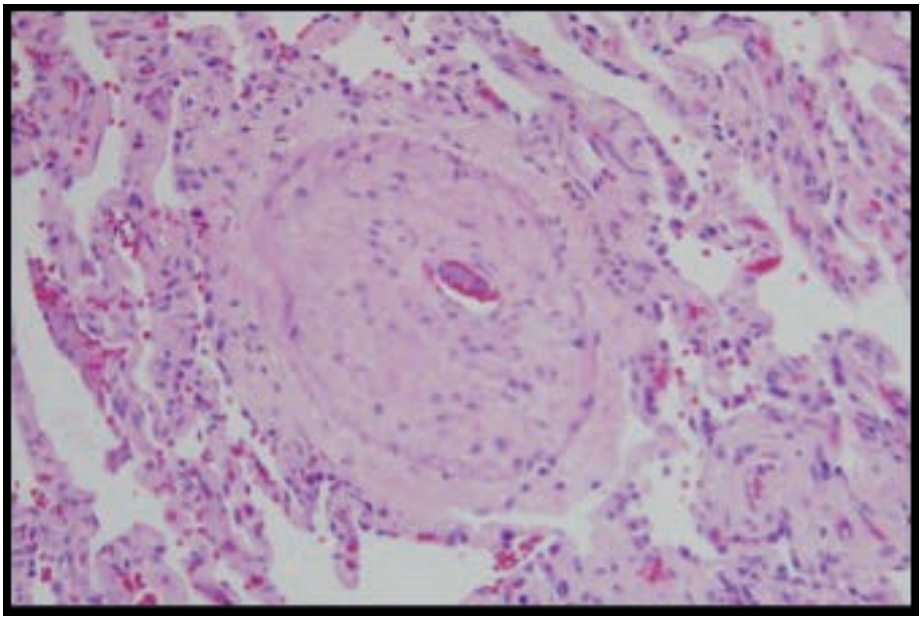

Figure 4: Pulmonary artery, with intimal proliferation and intraluminal lymphoma cells. The lumen is severely narrowed due to the lymphomatous cell burden in the vessel.

unlikely diagnosis. As previously mentioned, there was no serologic evidence supporting the diagnosis of a rheumatologic disorder or pulmonary vasculitis. Other conditions that may result in pulmonary perfusion abnormalities and had previously been described in the extant literature included fat emboli, pulmonary capillary hemangiomatosis, pulmonary vasculitis, and pulmonary tumor emboli.[7]

Ultimately, the patient underwent a surgical lung biopsy via video-assisted thoracoscopic surgery to get a definitive diagnosis. The pathology was consistent with a primary pulmonary intravascular large B-cell lymphoma (IVLBCL) (Figure 4).

Pulmonary IVLBCL is an extremely rare type of extranodal large B-cell lymphoma first described by Pfleger and Tappeiner in 1958.[8] This disease is characterized by a distinct proliferation of lymphomatous cells within the pulmonary microvasculature. Clinical symptoms and signs result from a compromised blood flow in the pulmonary capillaries. Pulmonary capillaries are particularly vulnerable while larger arteries and veins are typically spared, resulting in a significant gas exchange derangement. While lung involvement is common, it is rare for the primary presentation to be isolated to the lungs. Common presenting features include fever, weight loss, and anemia; however, the presentation varies depending on the organ(s) affected.[9] With regard to primary pulmonary disease, dyspnea, cough, and hypoxemia are the most notable symptoms. The CT findings are variable but include ground-glass opacities, centrilobular nodules, and interlobular septal thickening. Tissue biopsy by transbronchial biopsy or surgical lung biopsy remains the "gold standard" for diagnosis. The prognosis for this aggressive lymphoma is typically poor, often due in part to a delay in diagnosis.[10] Unfortunately, in a significant number of cases the diagnosis is often arrived at by autopsy.

For our patient, the persistent and systematic pursuit of a diagnosis despite conflicting data (positive V/Q scan in absence of discernable risk factors for venous thromboembolism) helped us arrive at this diagnosis in a timely fashion. She received 6 cycles of a chemotherapy regimen of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone under the supervision of a malignant-hematology specialist. She responded very well and was weaned off supplemental oxygen quickly following a remission of her disease. Currently, she is over 18 months from her last chemotherapy dose. She reported no physical limitations at her last evaluation. Her lymphoma remains in remission.

CONCLUSION

Primary pulmonary IVLBCL.

Teaching Points

1. A V/Q scan is sensitive for detecting perfusion defects in both PE and CTEPH.
2. A contrast-enhanced CT scan of the chest can be falsely negative in up to 49% of patients with CTEPH.
3. The differential diagnosis for perfusion defects on V/Q scan includes CTEPH, pulmonary vasculitis, pulmonary capillary hemangiamatosis, tumor emboli, and fat emboli.
4. Primary pulmonary IVLBCL is a rare type of B-cell lymphoma. It is characterized by proliferation of lymphomatous cells within the pulmonary microvasculature.
5. Primary pulmonary IVLBCL is a rare condition that can mimic CTEPH due to the tumoral cell occlusion of the pulmonary microvasculature. Lung biopsy is the only definitive way of diagnosis. Early diagnosis can result in a potential remission.

References

1. Sostman HD, Miniati M, Gottschalk A, Matta F, Stein PD, Pistolesi M. Sensitivity and specificity of perfusion scintigraphy combined with chest radiography for acute pulmonary embolism in PIOPED II. *J Nucl Med*. 2008;49(11):1741-1748.
2. Tunariu N, Gibbs SJ, Win Z, et al. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. *J Nucl Med*. 2007;48(5):680–684.
3. Yang S, Yang Y, Zhai Z, et al. Incidence and risk factors of chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. *J Thorac Dis*. 2015;7(11):1927-1938.
4. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with

the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol*. 2009;53(17):1573-1619. doi: 10.1016/j.jacc.2009.01.004.
5. Kim NH, Delcroix M, Jais X, et al. Chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2019;53(1):10.1183/13993003.01915-2018. Print 2019 Jan. doi: 1801915.
6. Scheibel RL, Dedeker KL, Gleason DF, Pliego M, Kieffer SA. Radiographic and angiographic characteristics of pulmonary veno-occlusive disease. *Radiology*. 1972;103(1):47-51. doi: 10.1148/103.1.47.
7. Broaddus VC, Mason RJ, Ernst JD, et al. *Murray and Nadel's Textbook of Respiratory Medicine*. 6th ed. Amsterdam: Elsevier; 2016.
8. Pfleger L, Tappeiner J. On the recognition of systematized endotheliomatosis of the cutaneous blood vessels (reticuloendotheliosis?) *Hautarzt*. 1959(10):359-363.
9. García-Muñoz R, Rubio-Mediavilla S, Robles-de-Castro D, Muñoz A, Herrera-Pérez P, Rabasa P. Intravascular large B cell lymphoma. *Leuk. Res Rep*. 2014;3(1):21-23.
10. Chen Y, Ding C, Lin Q, Yang K, Li Y, Chen S. Primary intravascular large B-cell lymphoma of the lung: a review and case report. *J Thorac Dis*. 2014;6(10):E242-E245.