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Subacute Dyspnea in a Young Woman with Newly Metastatic Breast Cancer

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Case Vignette

A 42-year-old woman with a history of BRCA-positive invasive ductal carcinoma presented with a 2-week history of progressive dyspnea, dry cough, and epistaxis.

The patient was diagnosed with ductal carcinoma *in situ* 4 years before presentation and underwent a bilateral partial mastectomy. Three years later, she was diagnosed with recurrent disease and was started on neoadjuvant chemotherapy with docetaxel, carboplatin, and trastuzumab. Six months before presentation, she underwent a completion mastectomy, revealing axillary lymph node involvement. Three weeks before presentation, she was started on neratinib, which was discontinued 2 weeks later because of nausea.

On presentation, the patient appeared in mild respiratory distress and was tachycardic and hypoxemic. Her physical examination was otherwise unremarkable. Her chest radiograph was within normal limits, and initial labs were notable for platelets of 10,000/μl (normal months before) with normal hemoglobin and renal function. She was placed on 2 L/min oxygen supplementation.

Chest computed tomographic (CT) pulmonary angiogram was negative for emboli, though lung windows showed multifocal ill-defined ground glass opacities (Figure 1). Restaging imaging showed extensive metastases to the liver and bone. She was started empirically on antibiotics; however, an extensive infectious workup was unrevealing. An arterial blood gas revealed a Pa_{O_2} of 50 mm Hg, with an A–a gradient of 94. A transthoracic echocardiogram (TTE) with bubble study revealed an enlarged right ventricle with reduced right ventricular function, septal flattening, and a pulmonary arterial systolic pressure (PASP) of 60 mm Hg (TTE five months before had normal right ventricular size and function with PASP of 10 mm Hg). The bubble study was suggestive of a small transpulmonary shunt. B-type natriuretic peptide was 188 pg/ml, and troponin peaked at 0.25 ng/ml.

In the following days, her hemoglobin dropped from 13.5 g/dl to a nadir of 9, and platelets remained below 10,000/μl. Peripheral blood smear showed slight schistocytes, lactate dehydrogenase (LDH) was 987 U/L, and D-dimer more than 20,000 μg/ml. The prothrombin time (PT) and partial thromboplastin time (PTT) were normal, but fibrinogen slightly decreased from 170 to 158 mg/dl.

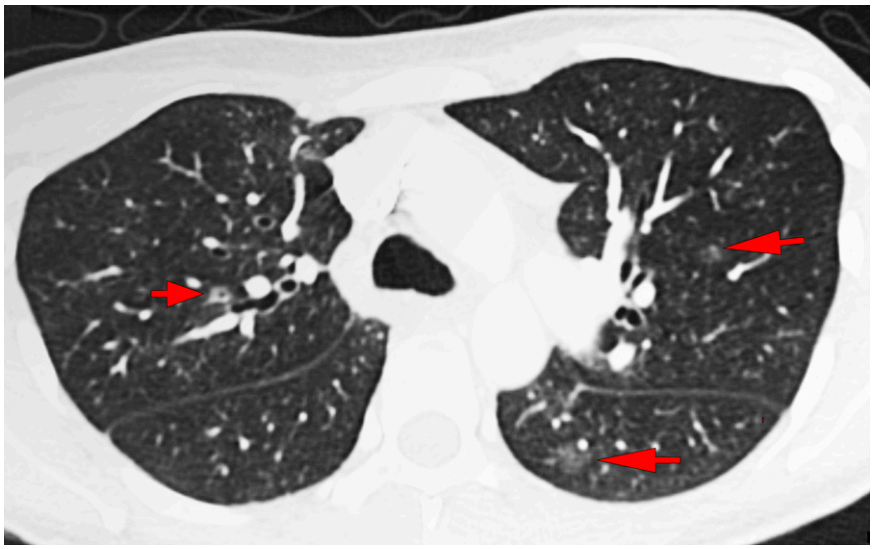

Figure 1. High-resolution computed tomographic angiography of the chest axial image. Arrows depicting bilateral scattered ground glass opacities.

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Questions

1. *What is the cause of this patient's subacute pulmonary hypertension?*

2. *What imaging may help narrow the differential?*

3. *How is the patient's thrombocytopenia and hemolytic anemia explained by the clinical presentation?*

[Continue onto next page for answers]

Clinical Reasoning

The differential diagnosis for a patient with acute to subacute progressive dyspnea, hypoxemia, and pulmonary hypertension (PH) includes pulmonary embolus (PE), drug-related PH, acute lung injury (ALI), or acute respiratory distress syndrome (ARDS)-related PH, acute on chronic PH, and in a patient with active malignancy, pulmonary tumor thrombotic microangiopathy (PTTM). The CT pulmonary angiogram ruled out PE as the diagnosis. The patient's only relevant recent medications were neratinib, a tyrosine kinase inhibitor (TKI), docetaxel/carboplatin, and trastuzumab, all part of her breast cancer treatment regimen. As TKIs and certain chemotherapeutic drugs have been implicated as a cause of PH (i.e., dasatinib) (1), as well as used in its treatment (i.e., imatinib) (2), we also entertained the possibility of drug-induced PH. However, PH owing to TKI or chemotherapy would not explain the pulmonary ground glass opacities, hemolytic anemia, and the low-level disseminated intravascular coagulation (DIC) with profound thrombocytopenia. Furthermore, docetaxel has shown promise in animal models as a possible therapy for PH with its ability to reverse pulmonary vascular remodeling (3). There is no compelling evidence implicating carboplatin as a causative drug in PH. In postmarketing studies, HER2-targeted agents (i.e., trastuzumab) have rarely been associated with PH (<1%) (4). Given that the chest imaging was inconsistent with ALI or ARDS, and the lack of a prior history of PH (normal TTE 5 months before), these etiologies were considered less likely.

With the subacute and rapidly progressive nature of her dyspnea and hypoxemia, as well as the presence of a dry cough with new PH in the setting of metastatic malignancy, there was significant concern for PTTM. To further investigate this possibility, a radionucleotide perfusion scan of the lungs was performed, which showed multiple subsegmental bilateral peripheral perfusion defects (Figure 2). The clinical history, classic findings on CT and nuclear perfusion scan of the lungs, as well as the laboratory findings of microangiopathic hemolytic anemia (MAHA) and low-grade DIC, was consistent with the diagnosis of PTTM. Confirmation of the diagnosis with more invasive procedures such as right heart catheterization or lung biopsy was discussed, but the patient was deemed too high risk owing to worsening thrombocytopenia and rapidly progressive hypoxemia.

In discussion with the patient regarding the likely diagnosis and its devastating prognosis, she was clear that her goal was to spend her remaining time at home with family. She agreed to an empiric trial of sildenafil in an attempt to improve pulmonary pressures, as well as a course of glucocorticoids in hopes of gaining time with family. Although our patient's rapid decline precluded pathologic confirmation, the aforementioned clinical features strongly supported the diagnosis of PTTM.

Discussion

PTTM is difficult to establish antemortem and is a diagnosis more often made at autopsy. In two autopsy case series of patients with carcinoma, PTTM was found in 1.4% and 3.3% of cases respectively (5, 6). The most common malignancy associated with PTTM is gastric adenocarcinoma, with an estimated prevalence of 16.7% and 26.8% in two autopsy series (6, 7). Other commonly associated malignancies include those of the breast, lung, and pancreas (8).

Clinical manifestations of PTTM are often nonspecific and include symptoms such as fatigue, dry cough, and progressive dyspnea. In one systematic review of patients with PTTM, dyspnea (94%) and cough (85%) were the most common presenting symptoms (8). Dyspnea and hypoxemia are typically noted to be subacute and rapidly progressive over weeks to months.

The pathophysiology of PTTM begins with tumor cells shedding into the bloodstream from a solid tumor focus, which embolize into the pulmonary arterioles. In the pulmonary vasculature, tumor cells induce endothelial injury activating the coagulation cascade, platelet aggregation, and release of cytokines, often manifesting as DIC and MAHA (6, 8, 9). Intimal arterial thickening and remodeling ensues and is mediated by growth factors released from tumor cells (9). Typical findings on histopathology include tumor microemboli, microthrombi, and intimal fibroblastic proliferation in the distal pulmonary arterioles and venules (Figure 3) (6–8).

Common lab abnormalities include elevated D-dimer, anemia, thrombocytopenia, and elevated LDH. Anemia and elevated LDH are likely a result of erythrocyte shearing while passing through the damaged pulmonary vascular endothelium. Thrombocytopenia is likely consumptive in the setting of DIC. These lab abnormalities may develop over a variable time course, and thus absence of all or some of these abnormalities should not preclude the diagnosis of PTTM (8).

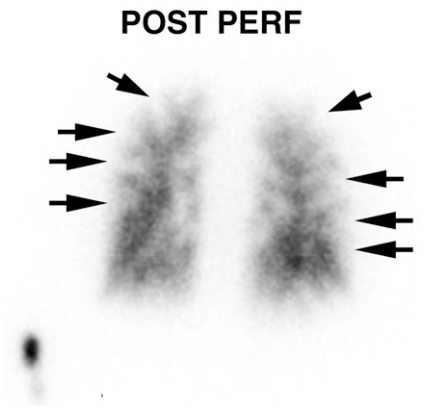

Figure 2. Nuclear medicine perfusion scan (posterior view). Arrows depict multiple bilateral subsegmental perfusion defects. Note: no concurrent ventilation images performed owing to the coronavirus disease (COVID-19) pandemic. PERF = perfusion.

Although standard criteria have not been established to confirm the antemortem diagnosis of PTTM, certain clinical data can aid in substantiating the diagnosis. CT chest imaging often shows ground glass opacities, nodules (often centrilobular), and interlobular septal thickening and may show mediastinal and hilar lymphadenopathy. Radionucleotide ventilation–perfusion ($\dot{V}/\dot{Q}$) imaging may show classic peripheral wedge-shaped unmatched perfusion defects (9–11). Echocardiography demonstrates signs of pulmonary hypertension with variable compromised right ventricular size and function. Common lab abnormalities may further support the diagnosis. The aforementioned clinical history, labs, and imaging findings in a patient with metastatic cancer can be strongly suggestive of PTTM, although pathology is required for confirmation.

A further challenge in the diagnosis of PTTM is differentiating it from disease mimics. Many of the thoracic radiographic features previously noted can also be seen in chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary veno-occlusive disease (PVOD). In general, CTEPH is more commonly associated with aortopulmonary collaterals, wedge-shaped

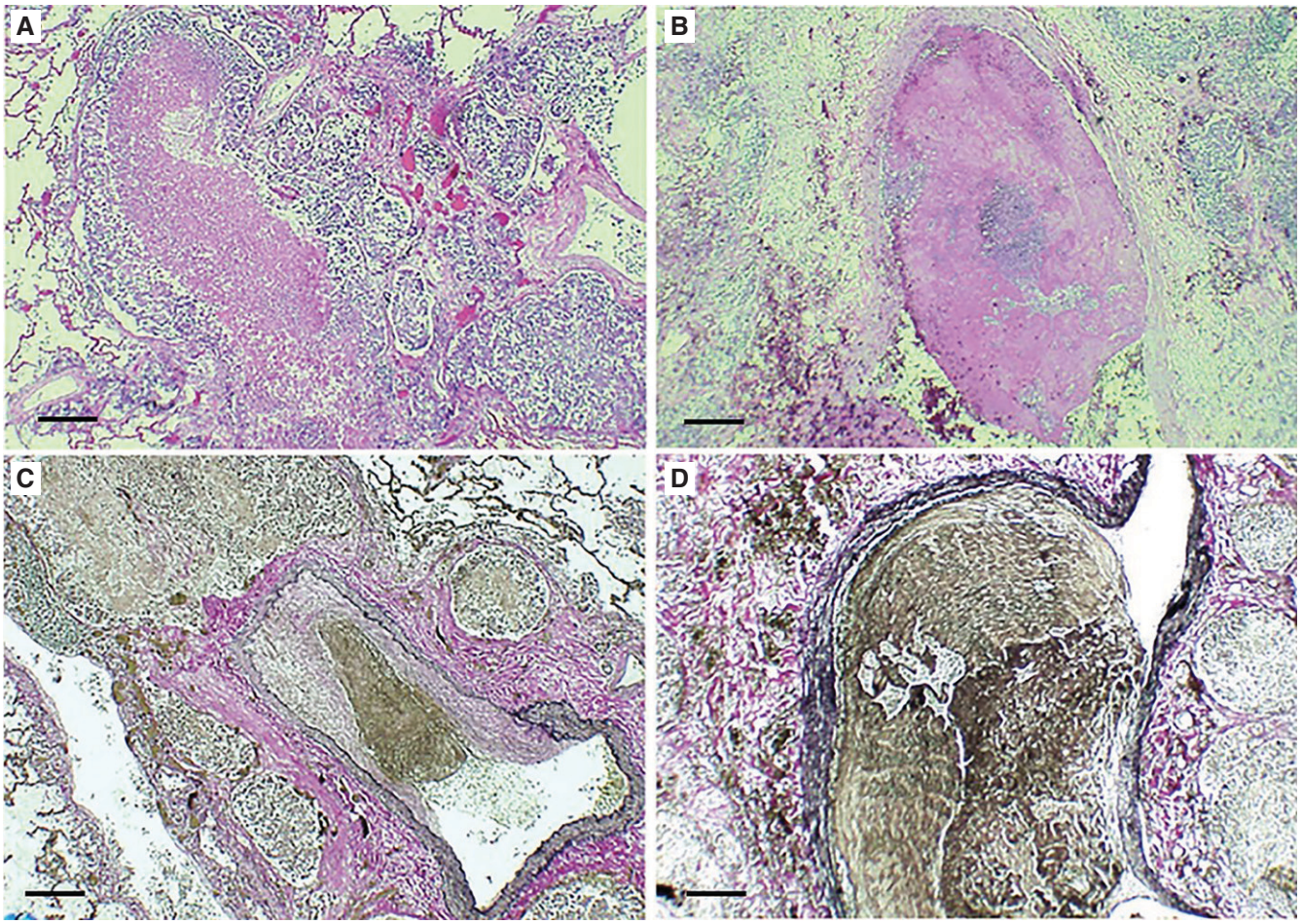

Figure 3. Pathology from a different patient with pathologically confirmed pulmonary tumor thrombotic microangiopathy. (*A*) Medium-sized blood vessels containing tumor emboli. Scale bar, 200 μm. (*B*) A singular blood vessel containing nests of tumor cells surrounded by fibrin debris. Scale bar, 100 μm. (*C*) Tumor thrombus with fibrocellular intimal proliferation within blood vessel. Scale bar, 100 μm. (*D*) The same blood vessel shown in *B* stained with elastin to highlight vessel wall. Scale bar, 40 μm.

infarcts, and mosaicism. Cough is commonly noted in cases of PTTM but is not typical of PVOD or CTEPH. Most notably, the time course of clinical manifestations is more rapidly progressive in PTTM, given the short duration from presentation to death (8).

Antemortem procedures that assist in establishing a diagnosis of PTTM include right heart catheterization with cytologic analysis of pulmonary microvascular samples drawn through a wedged pulmonary arterial catheter and tissue sampling via transbronchial or video-assisted thoracoscopic lung biopsy. Hemodynamically similar to pulmonary arterial hypertension and CTEPH, PTTM has a precapillary pattern, with elevated mean pulmonary arterial pressures and normal pulmonary capillary wedge pressures on right heart catheterization. One study quotes a sensitivity as high as 80–88% for pulmonary microvascular cytology; however, some experts anecdotally report lower success rates (10). Furthermore, the presence of malignant cells on cytologic examination does not conclusively establish a diagnosis of PTTM, as this finding can also be seen with tumor emboli and lymphangitic carcinomatosis. Less commonly, a definitive diagnosis is made via tissue sampling with transbronchial or surgical lung biopsy, both of which are high risk in patients with severe PH and thrombocytopenia (12, 13).

Although there is no strong evidence supporting the use of any particular therapy in PTTM, case reports describe the use of several treatments, including imatinib (TKI), PDE-5 inhibitors, endothelin antagonists, prostacyclins, glucocorticoids, as well as treatment of the primary malignancy, with variable success (8).

Unfortunately, the diagnosis of PTTM portends a very poor prognosis, with the average time to death from onset of symptoms being about 9.5 weeks. Death often results from right heart failure and hemodynamic collapse (8). Improved antemortem diagnosis and a clearer understanding of the pathophysiology is likely to help identify therapeutic targets.

Answers

1. *What is the cause of this patient's subacute pulmonary hypertension?*

The presence of subacute rapidly progressive dyspnea, hypoxemia, dry cough, new pulmonary hypertension, classic pulmonary CT chest and $\dot{V}/\dot{Q}$ scan findings, as well as laboratory evidence of

MAHA and DIC in a patient with metastatic breast cancer is most suggestive of pulmonary tumor thrombotic microangiopathy. This is best classified as pulmonary hypertension World Health Organization group 5.

2. *What imaging may help narrow the differential?*

A $\dot{V}/\dot{Q}$ scan is most likely to help narrow the differential if it shows the classic peripheral wedge-shaped perfusion defects (Figure 2). Only histopathology can confirm the diagnosis.

3. *How is the patient's thrombocytopenia and hemolytic anemia explained by the clinical presentation?*

Hemolytic anemia was caused by erythrocytes shearing while passing through damaged pulmonary vascular endothelium with endoluminal thrombi and tumor emboli. Thrombocytopenia was due to consumption from DIC and likely underproduction with suspected bone marrow infiltration.

Follow-Up

Despite up titration of sildenafil over the 2 days before discharge, the patient continued to deteriorate. On Hospital Day 6, the patient made the decision to return home on hospice while continuing oxygen as well as sildenafil and glucocorticoid therapy. She died soon after arriving home. Her family elected not to pursue autopsy.

Insights

- PTTM should be suspected in patients with adenocarcinoma (especially gastric) who present with acute or subacute progressive respiratory failure, new pulmonary hypertension, and a negative workup for acute pulmonary embolism. Clinical history and labs can further hint at the diagnosis.
- Dyspnea and cough (often dry) are the most common presenting symptoms in patients with PTTM. The most common lab findings include anemia, thrombocytopenia, elevated D-dimer, and LDH with evidence of DIC and MAHA.
- Common CT chest findings in PTTM include ground glass opacities, centrilobular nodules, septal thickening, and sometimes mediastinal and hilar lymphadenopathy. Notably, CT pulmonary angiography rarely demonstrates tumor emboli. $\dot{V}/\dot{Q}$ scan is more sensitive because tumor microemboli are often lodged in distal pulmonary arterioles and venules. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Montani D, Bergot E, Günther S, Savale L, Bergeron A, Bourdin A, *et al.* Pulmonary arterial hypertension in patients treated by dasatinib. *Circulation* 2012;125:2128–2137.
2 Hoeper MM, Barst RJ, Bourge RC, Feldman J, Frost AE, Galié N, *et al.* Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. *Circulation* 2013;127:1128–1138.
3 Ibrahim YF, Shults NV, Rybka V, Suzuki YJ. Docetaxel reverses pulmonary vascular remodeling by decreasing autophagy and resolves right ventricular fibrosis. *J Pharmacol Exp Ther* 2017;363:20–34.
4 Umoru G, Taitano M, Beshay S, Niravath P, Sahay S. Pulmonary arterial hypertension in breast cancer patients on HER2-targeted therapy: a review of FDA Adverse Events Reporting System data. *ERJ Open Res* 2020;6:00199-02020.
5 Uruga H, Fujii T, Kurosaki A, Hanada S, Takaya H, Miyamoto A, *et al.* Pulmonary tumor thrombotic microangiopathy: a clinical analysis of 30 autopsy cases. *Intern Med* 2013;52:1317–1323.
6 von Herbay A, Illes A, Waldherr R, Otto HF. Pulmonary tumor thrombotic microangiopathy with pulmonary hypertension. *Cancer* 1990;66:587–592.
7 Chinen K, Tokuda Y, Fujiwara M, Fujioka Y. Pulmonary tumor thrombotic microangiopathy in patients with gastric carcinoma: an analysis of 6 autopsy cases and review of the literature. *Pathol Res Pract* 2010;206:682–689.
8 Godbole RH, Saggar R, Kamangar N. Pulmonary tumor thrombotic microangiopathy: a systematic review. *Pulm Circ* 2019;9: 2045894019851000.
9 Godbole R, Saggar R, Zider A, Betancourt J, Wallace WD, Suh RD, *et al.* Insights on pulmonary tumor thrombotic microangiopathy: a seven-patient case series. *Pulm Circ* 2017;7:813–820.
10 Price LC, Wells AU, Wort SJ. Pulmonary tumour thrombotic microangiopathy. *Curr Opin Pulm Med* 2016;22:421–428.
11 Toyonaga H, Tsuchiya M, Sakaguchi C, Ajimizu H, Nakanishi Y, Nishiyama S, *et al.* Pulmonary tumor thrombotic microangiopathy caused by a parotid tumor: early antemortem diagnosis and long-term survival. *Intern Med* 2017;56:67–71.
12 Kitamura A, Nishimura N, Jinta T, Suda R, Yamano Y, Ishikawa G, *et al.* A case of pulmonary tumor thrombotic microangiopathy diagnosed by transbronchial lung biopsy and treated with chemotherapy and long-term oxygen and anticoagulation therapies. *Case Rep Pulmonol* 2013; 2013:259080.
13 Takahashi Y, Uruga H, Fujii T, Mochizuki S, Hanada S, Takaya H, *et al.* Antemortem diagnosis of pulmonary tumor thrombotic microangiopathy in a patient with recurrent breast cancer: a case report. *BMC Cancer* 2016;16:666.