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A Rapid Change in Pressure

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Abstract

A 74-year-old woman presented with a 6-week history of progressive dyspnea on exertion. Eight weeks before this presentation, she had been traveling in Italy and had been walking up to 4 miles per day. Progressive dyspnea on exertion had developed after she returned to the United States. She also noted a nonproductive cough, fatigue, loss of appetite, and an unintentional weight loss of 9 kg over the previous 6 months. She had no fevers, chills, night sweats, hemoptysis, wheezing, chest pain, palpitations, orthopnea, paroxysmal nocturnal dyspnea, swelling of the legs or feet, abdominal pain, nausea, vomiting, melena, or hematochezia. Four weeks before this presentation, she had presented to an emergency department at another institution, where imaging was performed. Chest radiography showed no pneumonia, and venous ultrasonography of both legs showed no deep venous thrombosis. A 5-day course of prednisone and azithromycin was prescribed; however, her symptoms continued to worsen, and she began to have dyspnea when she was at rest.

Dyspnea has a broad differential diagnosis and could be attributed to pulmonary causes (e.g., infections, obstructive or restrictive lung disease, or pleural disease), pulmonary vascular causes (e.g., pulmonary hypertension or pulmonary embolism), cardiac causes (e.g., congestive heart failure, myocardial ischemia, arrhythmias, or pericardial effusion), hematologic causes (e.g., severe anemia), or metabolic causes (e.g., acid–base disturbances or oxidative myopathies). The patient's recent travel history arouses concern for pulmonary embolism, and computed tomographic (CT) pulmonary angiography should be pursued despite the negative results of the venous ultrasonography. Heart failure seems unlikely in the absence of associated orthopnea, paroxysmal nocturnal dyspnea, and edema of the legs

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or feet. Chronic progressive processes such as interstitial lung disease, chronic obstructive pulmonary disease (COPD), and pulmonary hypertension should be considered. The unintentional weight loss arouses concern for a malignant condition. The most common cancers among women in this age group are breast, colon, and lung cancers. Colon cancer in particular can lead to progressive anemia that results in dyspnea.

The patient had a medical history of cough-variant asthma (reactive airway disease that manifests as a nonproductive cough), hypertension, and hyperlipidemia. Her medications included albuterol administered through an inhaler, amlodipine, budesonide–formoterol administered through an inhaler, and lovastatin. She had a smoking history of 15 pack-years but had quit smoking entirely 40 years earlier. Her family history was notable for colon cancer in her father and pulmonary hypertension of unclear cause in her mother at the age of 70. There was no family history of autoimmune disorders.

It would be helpful to know how and when the diagnosis of cough-variant asthma was made. A new diagnosis of asthma is unusual after 40 years of age, and cough-variant asthma can be particularly challenging to diagnose. It is possible that she has an alternative chronic pulmonary disease such as COPD, given the remote smoking history. The family history of colon cancer in addition to the unintentional weight loss also suggests a malignant condition; it would be helpful to know whether the patient has had age-appropriate cancer screening. Finally, the history of pulmonary hypertension in the patient's mother arouses concern for an inherited cause of pulmonary arterial hypertension, such as germline mutations in *BMPR2* (encoding bone morphogenetic protein receptor type 2), *ACVRL1* (encoding activin receptor–like kinase 1), or other genes, although it would be unusual for such an inherited condition to manifest for the first time at this age.

On physical examination, her temperature was 37°C, blood pressure 113/69 mm Hg, pulse 108 beats per minute, respiratory rate 24 breaths per minute, oxygen saturation 88% while she was breathing ambient air, and body-mass index (the weight in kilograms divided by the square of the height in meters) 23.5. The mucous membranes were moist, and the nasopharynx and oropharynx had no ulcerations or exudates. The jugular venous pressure was estimated at 6 cm of water. Cardiac examination revealed tachycardia, prominent P2 (the pulmonic component of the second heart sound), and a regular rhythm with no appreciable murmurs. Tachypnea without the use of accessory muscles was noted. Inspiratory crackles were present in the base of both lungs. No wheezing or rhonchi were present. No clubbing, cyanosis, or edema of the arms, hands, legs, or feet was noted. Results of abdominal, neurologic, musculo-skeletal, and cutaneous examinations were normal.

The patient has tachycardia, tachypnea, and hypoxemia, which are suggestive of respiratory distress. The prominent P2 component suggests pulmonary hypertension; however, it is important to rule out causes of a less prominent A2 (the aortic component of the second heart sound), such as mitral or aortic regurgitation, although these are less likely in the absence of an audible murmur. The normal jugular venous pressure makes volume overload resulting from congestive heart failure less likely; therefore, the inspiratory crackles in both lungs are most likely due to atelectasis or small-airway disease caused by alveolar or interstitial processes.

Clinical chemistry values and the complete blood count were within normal ranges. Results of arterial blood gas analysis performed while the patient was breathing ambient air showed a pH of 7.51, a partial pressure of carbon dioxide of 30 mm Hg, and a partial pressure of oxygen of 61 mm Hg, for a calculated alveolar–arterial gradient of 51.2 mm Hg (on the basis of the patient's age, the expected gradient would be approximately 23 mm Hg). The d-dimer level was 1392 ng per milliliter (reference value, <500 ng per milliliter). An electrocardiogram showed sinus tachycardia with T-wave inversions in leads III, aVF, V₁, V₂, and V₃. Testing of pulmonary function performed 3 days before admission showed normal results on spirometry and normal lung volumes but a mildly reduced diffusion capacity for carbon monoxide.

The blood gas measurements were obtained when the patient was at rest; therefore, the elevated alveolar–arterial gradient suggests ventilation–perfusion mismatch or intrapulmonary shunt, which could be the result of alveolar collapse, alveolar filling, or interstitial or vascular changes that impair gas exchange, such as interstitial fibrosis or pulmonary hypertension. The blood gas measurements have shown acute respiratory alkalosis, which indicates that hyperventilation has been present for a brief period (perhaps a few days). Although the elevated D-dimer level is nonspecific, it arouses concern for venous thromboembolism; however, an elevated D-dimer level may also be seen in other conditions, such as cancer, congestive heart failure, or infection. T-wave inversions in the right precordial and inferior leads can be seen in ischemia, right ventricular strain, and metabolic abnormalities, among other conditions. The combination of right precordial and inferior T-wave inversions, sinus tachycardia, and reduced diffusion capacity for carbon monoxide with normal results on spirometry and normal lung volumes could be consistent with right ventricular strain resulting from acute pulmonary embolism or from other causes of pulmonary hypertension. The differential diagnosis remains broad, but given the acute presentation, pulmonary embolism is the most likely diagnosis. Pulmonary arterial hypertension and interstitial lung disease are also possibilities, and further imaging, including CT pulmonary angiography of the chest and transthoracic echo-cardiography, should be performed.

CT pulmonary angiography showed no evidence of pulmonary embolism; mild bibasilar atelectasis, enlargement of the right ventricle, and multiple sclerotic lesions within the vertebral bodies were noted (Fig. 1A and 1B). A transthoracic echo-cardiogram showed a left ventricular ejection fraction of 70%, moderate dilatation of the right ventricle with moderately impaired systolic function, insufficient tricuspid regurgitation to calculate a right ventricular systolic pressure, and no pericardial effusion (Fig. 2; see also the Supplementary Appendix, available with the full text of this article at [NEJM.org](https://www.nejm.org)).

Evidence of right ventricular strain on echocardiography accompanied by normal left ventricular function suggests precapillary or capillary causes of pulmonary hypertension, such as idiopathic pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. The multiple sclerotic lesions in the vertebral bodies suggest metastatic cancer, which is a major risk factor for venous thromboembolism and can be associated with a rare condition called pulmonary tumor thrombotic microangiopathy. In chronic thromboembolic pulmonary hypertension, CT pulmonary angiography has very high

specificity but only moderate sensitivity because occlusions in small vessels may be missed. Similarly, in pulmonary tumor thrombotic microangiopathy, CT pulmonary angiography often does not show pulmonary emboli because the tumor microemboli lodge in small peripheral subsegmental vessels. Therefore, ventilation-perfusion scintigraphy should be performed in this case. Catheterization of the right side of the heart should also be performed to determine the severity of pulmonary arterial hypertension and to guide targeted therapies. At this point, chronic thromboembolic pulmonary hypertension and pulmonary tumor thrombotic microangiopathy cannot be differentiated without further evaluation. Cytologic examination of blood aspirated from a pulmonary-artery catheter when it is in the wedge position can potentially confirm a diagnosis of pulmonary tumor thrombotic microangiopathy, although false negative results can occur.

Ventilation-perfusion scintigraphy showed multiple areas of Ventilation-perfusion mismatch, which suggests a high probability of pulmonary embolism (Fig. 1C). Catheterization of the right side of the heart showed a right atrial pressure of 15 mm Hg (normal value, 5), right ventricular diastolic pressure of 19 mm Hg (normal range, 0 to 5), mean pulmonary arterial pressure of 47 mm Hg (normal value, 20), pulmonary-capillary wedge pressure of 9 mm Hg (normal value, <15), pulmonary vascular resistance of 1050 dyn • sec • cm⁻⁵ (normal value, <250), cardiac output (as determined with the Fick principle) of 3.11 liters per minute (normal range, 4 to 8), and no response to inhaled nitric oxide. Cytologic testing of a blood sample obtained when the pulmonary artery catheter was in the wedge position showed no evidence of malignant cells. Positron-emission tomography and CT (PET-CT) showed uptake of ¹⁸F-fluorodeoxyglucose (FDG) in multiple scattered sclerotic osseous lesions; in multiple lymph nodes in the chest, abdomen, and pelvis; in the left adrenal gland; and in the fundus of the gallbladder (Fig. 1D).

The combination of a mean pulmonary arterial pressure of higher than 20 mm Hg and a normal pulmonary-capillary wedge pressure is consistent with increased resistance within the pulmonary vasculature, which is most commonly the result of precapillary pulmonary hypertension but can also be seen in disorders specific to the pulmonary capillaries (e.g., pulmonary-capillary hemangiomatosis) and pulmonary venules (e.g., pulmonary veno-occlusive disease). In contrast, pulmonary hypertension that results from left ventricular dysfunction or fibrosing mediastinitis is associated with an elevated pulmonary-capillary wedge pressure. The Ventilation-perfusion scintigraphy shows multiple areas of abnormal perfusion in the lungs but normal ventilation, findings that are highly suggestive of thromboembolic disease and particularly pulmonary tumor thrombotic microangiopathy, given the evidence of widely metastatic disease on PET-CT. Cancers of the breast, lung, thyroid, and kidney commonly metastasize to bone, but the abnormal FDG uptake in the fundus of the gallbladder arouses concern for cholangiocarcinoma. Biopsy of a vertebral sclerotic lesion or the metastases in the adrenal gland would be the next diagnostic test of choice, since treatment of the underlying disease is fundamental to management.

Before a tissue diagnosis could be obtained or empirical chemotherapy started, progressive hypoxemia developed, and 100% oxygen was administered through a high-flow nasal cannula. Systemic glucocorticoids, intravenous heparin, and inhaled epoprostenol, followed by intravenous treprostinil, were administered but had no effect. After a discussion with the

patient's family, a do-not-resuscitate–do-not-intubate order was written. The hypoxemia worsened and ultimately led to a cardiac arrest and death. An autopsy revealed multiple tumor deposits in the vertebrae, lymph nodes, and left adrenal gland, as well as in the fundus and biliary tree of the gallbladder (Fig. 3). Microscopic examination confirmed metastatic, poorly differentiated adenocarcinoma, most likely due to a primary tumor in the gallbladder or cystic duct (Fig. 3C). Most notably, diffuse tumor microemboli, consisting of organizing and recanalized fibrin thrombi that were frequently clustered with aggregates of malignant cells, were present throughout the vasculature of both lungs, which confirmed a diagnosis of pulmonary tumor thrombotic microangiopathy (Fig. 3A).

Pulmonary tumor thrombotic microangiopathy is almost universally fatal. There is no specific treatment except for chemotherapy targeted at the underlying cancer, which was not possible in this case because of the rapid progression of the disease.

COMMENTRY

Rapidly progressive pulmonary hypertension with cor pulmonale (heart failure on the right side resulting from underlying pulmonary disease) caused by tumor microemboli in the pulmonary vasculature is an extremely rare process that is challenging to identify early. By the time of diagnosis, the disease is often fulminant and has a very poor prognosis, as seen in the patient we describe.

As shown in case reports and small case series, patients with pulmonary tumor thrombotic microangiopathy typically present with dyspnea on exertion and hypoxemia, which usually develop over the course of 3 weeks to 6 months; the mean time from the onset of symptoms to death is 1 month.^{1–3} Histologically, pulmonary tumor thrombotic microangiopathy is characterized by tumor microemboli associated with fibrointimal proliferation, which progressively occludes the pulmonary vessels and results in increased pulmonary vascular resistance.¹ Tumor cells are thought to spread hematogenously or through the lymphatics and enter into the venous system through the thoracic duct.² The attachment of cancer cells is hypothesized to cause endothelial damage, which results in activation of the coagulation cascade because of the expression and release of tissue factor and leads to in situ thrombosis.¹ Tumor cells also express cytokines, including vascular endothelial growth factor (VEGF), platelet-derived growth factor, and osteopontin, which results in macrophage recruitment and fibrointimal proliferation.¹ This process leads to progressive luminal narrowing, which causes subacute pulmonary hypertension and right ventricular dysfunction (Fig. 4). In a small autopsy series, 70% of patients had medial hypertrophy of the muscular pulmonary arteries that was suggestive of subacute pulmonary hypertension, and 45% had right ventricular hypertrophy and dilatation.³

The diagnosis of pulmonary tumor thrombotic microangiopathy is challenging owing to the rarity of the disease and the nonspecific initial findings associated with it. Electrocardiography may show evidence of right ventricular strain. Tests of pulmonary function may show a reduction in the diffusion capacity for carbon monoxide with relatively normal lung volumes and normal spirometry results. Laboratory analysis may reveal microangiopathic hemolytic anemia and disseminated intravascular coagulation.⁴ Because

the tumor microemboli are tiny and lodge in distal vessels, CT pulmonary angiography typically shows no evidence of pulmonary emboli, and radionuclide Ventilation-perfusion scintigraphy shows multiple peripheral subsegmental perfusion defects accompanied by normal ventilation.⁴ Echocardiography generally shows right ventricular strain, and catheterization of the right side of the heart shows precapillary pulmonary hypertension, which is defined by an elevated mean pulmonary arterial pressure (>20 mm Hg) and normal pulmonary-capillary wedge pressure (<15 mm Hg). The diagnosis of pulmonary tumor thrombotic microangiopathy can be made on the basis of cytologic examination of aspirated blood from the wedged pulmonary-artery catheter, although false negatives can occur (a sensitivity up to 80 to 88% was reported in a single small case series).¹ Although PET-CT shows sites of metabolically active metastatic disease, diffuse metabolic activity is not typically seen in the lungs because the tumor cells in the small vessels are occlusive but not rapidly proliferating.

Owing to its rapidly progressive and typically fatal natural history, pulmonary tumor thrombotic microangiopathy has historically been a postmortem diagnosis in patients with metastatic disease. In autopsy series of patients with known metastatic carcinomas, the estimated prevalence is 1 to 3%, which suggests that the phenomenon may be clinically underdiagnosed.^{1,5} Pulmonary tumor thrombotic microangiopathy is most commonly associated with adenocarcinomas — in particular, gastric carcinoma. Pulmonary tumor thrombotic microangiopathy was identified on autopsy in 16 to 27% of patients with gastric carcinoma (more commonly in mucinous, signet-ring, and poorly differentiated sub-types).¹ Other associated cancers include adenocarcinoma of the breast, lung, and gallbladder, as well as ovarian clear-cell carcinoma and urothelial carcinoma.

In the rare cases of antemortem diagnosis of pulmonary tumor thrombotic microangiopathy, treatment of pulmonary hypertension includes supportive care with pulmonary vasodilators and targeted chemotherapy for the underlying cancer, although most patients eventually die from metastatic cancer.⁶ Although the primary disease-modifying treatment is chemotherapy for the underlying cancer, many patients do not have adequate performance status to be able to receive chemotherapy at the time of diagnosis. Case reports have described survival of 6 to 12 months among patients with gastric carcinoma who were treated with a combination of a tyrosine kinase inhibitor (imatinib) and an endothelin-receptor antagonist (e.g., bosentan or ambrisentan)^{7,8} or with a combination of chemotherapy, dexamethasone, warfarin, and aspirin.^{1,9} Another case report described 12-month survival in a patient who had colorectal carcinoma and was treated with the VEGF inhibitor bevacizumab in combination with imatinib, bosentan, and tadalafil.^{1,10}

The current case illustrates the difficulty in the diagnosis and management of pulmonary tumor thrombotic microangiopathy, especially in a patient without a known malignant disease. In patients with metastatic cancer who present with symptoms of pulmonary venous thromboembolism but have negative results on CT pulmonary angiography, the diagnosis of pulmonary tumor thrombotic microangiopathy should be considered, and a Ventilation-perfusion scan should be obtained. If the diagnosis is made, early palliative-focused care should be considered, given the very poor prognosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Imaging Studies.

Computed tomographic (CT) angiography of the chest shows enlargement of the right ventricle (Panel A, asterisk), with a ratio of the diameter of the right ventricle to that of the left ventricle of greater than 1 (normal value, 1); sclerotic lesions in the vertebral bodies can also be seen (arrow in Panel B, bone-window setting). Ventilation-perfusion scintigraphy (Panel C) shows multiple moderate-sized areas of decreased perfusion (arrows) that had normal corresponding ventilation (not shown) in the apical and anterior right upper lobe, lateral right middle lobe, anterior left upper lobe, lingula, superior and lateral basal segments of the left lower lobe, and the superior segment of the right lower lobe. A positron-emission tomographic–CT image (Panel D) shows uptake of ^{18}F -fluorodeoxyglucose in multiple scattered sclerotic vertebral lesions; in multiple lymph nodes in the chest, abdomen, and pelvis; in the left adrenal gland; and in the fundus of the gallbladder.

Figure 2. Transthoracic Echocardiogram.

The area of the right ventricle was measured at end diastole (Panel A) and at end systole (Panel B). The fractional change in area was found to be 24% (normal value, >35). The area of the right atrium was 16 cm² (normal value, <18), and the volume index was 38 ml per square meter (normal value, <33).

Figure 3. Histologic Findings.

Histologic sections of the lungs show vascular occlusion by malignant cells with surrounding fibrin and fibrointimal proliferation (Panel A, arrow). Metastatic adenocarcinoma involving an abdominal lymph node can be seen: tumor cells extensively infiltrate the subcapsular sinuses and show central necrosis (Panel B, arrow). Diffuse involvement by adenocarcinoma can be seen in the gallbladder wall (Panel C). The gallbladder and cystic duct are the most likely primary sites of cancer in this case. (Hematoxylin and eosin staining was used in all panels.)

Figure 4. Proposed Pathophysiology of Pulmonary Tumor Thrombotic Microangiopathy.

Tumor cells spread hematogenously, through the lymphatics, or both, and enter into the venous system through the thoracic duct. The interaction between cancer cells and the blood-vessel wall causes endothelial damage, which leads to expression and release of tissue factor and activation of the coagulation cascade. Tumor cells express cytokines, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and osteopontin, which results in macrophage recruitment and fibrointimal proliferation. This causes progressive luminal narrowing and, subsequently, pulmonary hypertension.