suggest that ALD may occur more commonly than we have acknowledged, which emphasizes the importance of considering this disorder in any young man with apparent idiopathic primary adrenal insufficiency. It may be valuable to screen all such patients for ALD.

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Pulmonary Microvascular Cytology for the Diagnosis of Pulmonary Tumor Embolism

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PULMONARY TUMOR EMBOLISM (PTE) occurs when aggregates of tumor cells lodge in the pulmonary microvasculature. PTE can cause various clinical manifestations, including hypoxemia, dyspnea, pulmonary hypertension, acute cor pulmonale, and death in patients with cancer. We report on two patients who had precipitous terminal courses of respiratory failure—the first caused by extensive pulmonary tumor emboli resulting in fulminant cor pulmonale and the second by lymphangitic carcinomatosis. Pulmonary microvascular cytology sampling was an important diagnostic tool in both patients.

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Report of Cases

Patient 1

A 39-year-old woman with a history of breast cancer was admitted with rapidly progressive shortness of breath and hypotension. She was empirically begun on intravenous heparin because of the clinical suspicion of pulmonary emboli.

On physical examination, the patient's vital signs were as follows: pulse 122 beats per minute; blood pressure 89/57 mm of mercury; respiratory rate 44 breaths per minute; and temperature 38.4°C (101.1°F). Physical examination revealed the patient to be in moderate respiratory distress and intermittently confused. Cardiopulmonary examination revealed jugular venous distention, tachycardia, and clear lung fields. Abdominal examination revealed mild right upper quadrant tenderness and hepatomegaly. The extremity exam revealed 2+ pitting edema without clubbing.

A chest radiograph revealed a moderately enlarged heart with right lower lobe patchy consolidation (Figure 1). Her laboratory test results indicated metabolic acidosis, severe hypoxemia, and microangiopathic hemolytic anemia.

An echocardiogram revealed a moderately dilated right ventricle with severe right ventricle failure and no evidence of tamponade. A pulmonary artery catheter was inserted to aid in hemodynamic monitoring and vasopressor therapy. The hemodynamic data revealed a cardiac output of 3.4 liters per minute, central venous pressure of 20 mm of mercury, pulmonary capillary wedge pressure of 10 mm of mercury, and a pulmonary artery pressure of 59/31 mm of mercury. A ventilation-perfusion scan revealed a matched nonsegmental defect in the left lower lobe, which was interpreted as low probability for pulmonary embolism.

With the patient's history of breast cancer, acute right ventricular failure, and microangiopathic hemolytic anemia, pulmonary tumor emboli was believed to be a strong diagnostic consideration. A pulmonary microvascular cytology specimen was obtained from the distal port of the pulmonary artery catheter and revealed carcinoma, confirming the diagnosis of tumor emboli (Figure 2, left).

Despite aggressive hemodynamic support and attempted treatment of the tumor, the patient died of refractory cardiogenic shock within 24 hours of admission. At autopsy, the heart weighed 250 grams and had moderate dilatation of the right ventricle without hypertrophy. The tricuspid valve was dilated at 12 cm. The lungs grossly showed small deposits of metastatic carcinoma in her pleural and parenchymal lymphatics and a recent hemorrhage in the lingula. No pulmonary thromboemboli were present. Through microscopic examination, the majority of small pulmonary arteries showed plugging by nests of carcinoma (Figure 2, right) or neoplastic cells associated with proliferating young fibrous tissue—corresponding to carcinomatous arteriopathy. Extensive metastatic carcinoma was present in the liver; small

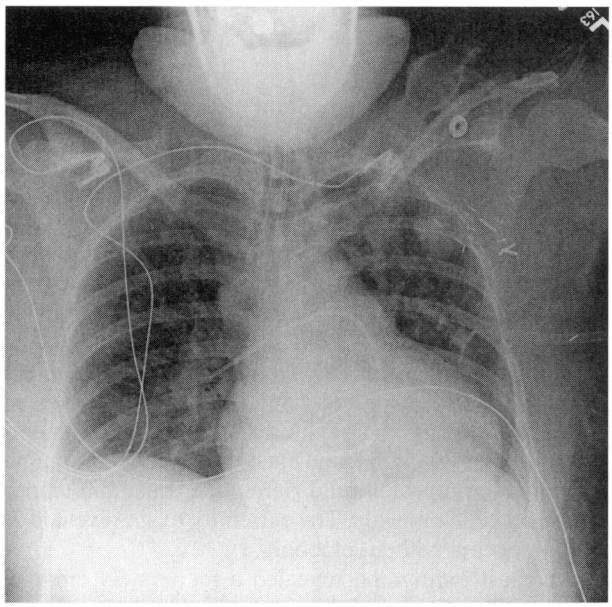

Figure 1.—The chest radiograph shows a moderately enlarged cardiac silhouette with patchy right lower lobe consolidation.

amounts were also present in thoracic lymph nodes and vertebral bone marrow.

Patient 2

A 41-year-old man was admitted to the hospital with three days of chills, fever, and cough. The patient's vital signs were as follows: pulse 105 beats per minute, blood pressure 129/82 mm of mercury, temperature 37.8° C (100° F), and respiratory rate 18 breaths per minute. Physical examination revealed the patient to be in mild respiratory distress and lethargic, but arousable. Cardiopulmonary examination revealed diffuse expiratory rhonchi and bibasilar crackles. An S_3 gallop was not heard. Examination of the patient's extremities revealed clubbing. A chest radiograph showed increased bilateral interstitial markings and right upper lobe consolidation.

The patient was treated for community-acquired pneumonia with intravenous antibiotics. On day 3 of admission, the patient developed increasing respiratory distress and required mechanical ventilation. A chest radiograph showed increasing interstitial markings and Kerley's B lines (Figure 3). A pulmonary artery catheter was inserted; it revealed a pulmonary artery pressure of 62/32 mm of mercury and a normal pulmonary capillary wedge pressure, suggesting cardiogenic pulmonary edema was not the cause of the clinical and radiographic findings.

Computerized tomography of the chest revealed dense consolidation of the right upper lobe and enlarged mediastinal lymph nodes. Mediastinoscopy to obtain a tissue diagnosis was contemplated, but the patient went into cardiogenic shock and the surgery was not performed.

An echocardiogram revealed pericardial tamponade. Pericardiocentesis was performed, removing 50 ml of fluid. The persistent Kerley's B lines on the chest radiograph in the absence of cardiogenic pulmonary edema suggested the possibility of lymphangitic tumor. A pulmonary microvascular cytology specimen demonstrated cells suspicious for malignancy, and the pericardial fluid revealed malignant cells. Despite prolonged resuscitative efforts, the patient died of refractory shock.

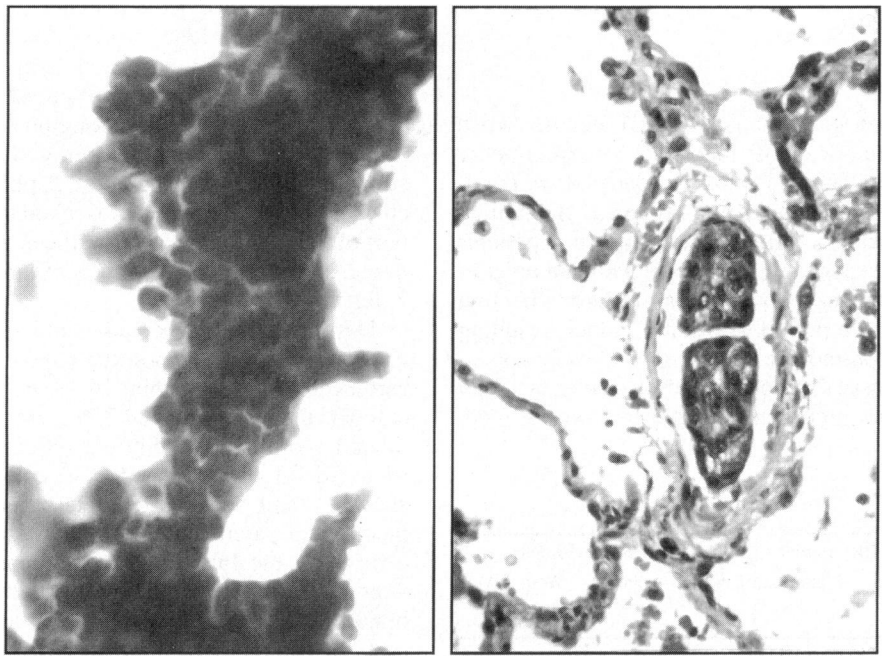

Figure 2.—The pulmonary microvascular cytology (left) shows a large clump of cohesive carcinoma cells (Papanicolaou's stain, X170). The lung section at autopsy (right) shows two clumps of breast carcinoma cells in a small muscular artery (hematoxylin-eosin, X150).

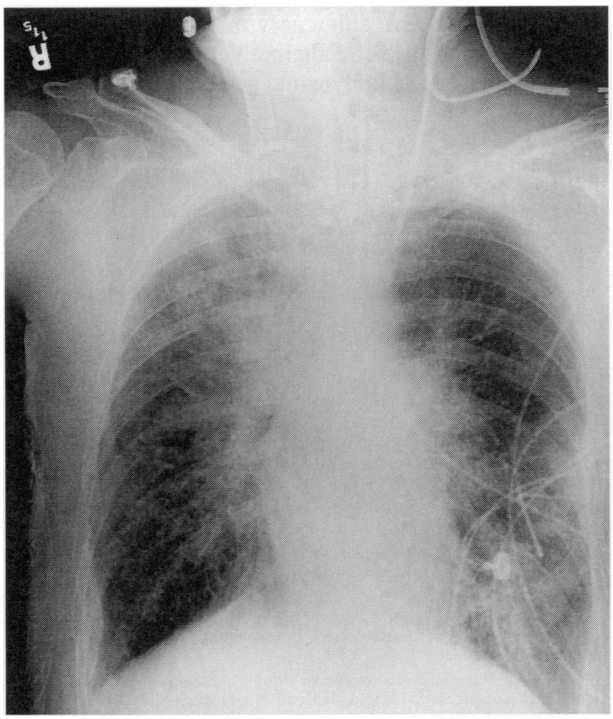

Figure 3.—The chest radiograph shows Kerley's B lines and mediastinal widening.

An autopsy revealed a 10-cm ulcerated gastric adenocarcinoma with extensive pulmonary metastasis, including diffuse lymphangitic carcinomatosis that had spread to the mediastinal lymph nodes and pleura. Focally, neoplasm was intravascular in pulmonary veins.

Discussion

Pulmonary tumor embolism is considered to be a rare clinical entity. PTE is believed to arise from solid tumors that invade the systemic circulation, are filtered, and then lodge in the pulmonary microvessels. The first detailed clinical description of this disease was in 1897[1]; in recent years, however, a number of reports have focused on this topic.[2,3] A large number of retrospective autopsy studies have documented how surprisingly common PTE is, but even in patients with known cancer, the diagnosis of PTE antemortem is made in as little as 6% of such cases.[4,5] Several studies[4,6] have reported four types of pulmonary vascular involvement by tumor emboli: large vessel embolism; microvessel embolism involving small arteries and arterioles; pulmonary microvascular invasion as a part of lymphangitic carcinomatosis; and combinations of the above mechanisms. The first patient in this report had extensive microvessel tumor embolism, which resulted in acute right ventricular failure; the second patient had diffuse lymphangitic carcinomatosis, which led to respiratory failure.

These two cases document aspects of the presentation of PTE. Patients experience an explosive, rapidly fatal outcome due to acute cor pulmonale that mimics massive pulmonary thromboembolism. Patients also have lymphangitic carcinomatosis leading to progressive respiratory failure. The use of a pulmonary microvascular cytology specimen was crucial in both cases; it is a valuable alternative to lung biopsy in critically ill, unstable patients. In our first patient, it made possible a rapid antemortem diagnosis.

A wide variety of neoplasms are associated with pulmonary tumor embolism. In a review of 164 reported cases[2], hepatoma was the most frequent (29%), followed by carcinoma of the breast (18%), kidney (18%), and stomach (9%). Carcinomas of the prostate, colon and choriocarcinomas have been reported less frequently. The incidence of PTE in solid malignancies at autopsy has been reported to range from 0.9% to 26%.

The clinical features of PTE have been succinctly described by Chan and colleagues.[2] The authors propose a useful clinical profile to aid the clinician in making the diagnosis of PTE. Most cases occur in patients with known malignant disease. A new malignancy, however, will occasionally present as the subacute onset of pulmonary hypertension. The profile for PTE includes a clinical history of documented or suspected malignancy, acute or subacute onset of progressive dyspnea, and signs of cor pulmonale.[2] Dyspnea—often accompanied by chest pain and cough—is the most common symptom. Physical manifestations of PTE include signs of pulmonary hypertension and right ventricular overload, including elevated venous pressures and loud P_2 or right-sided gallop. Generally, dyspnea and pulmonary hypertension are subacute in onset; however, as demonstrated in our first patient, PTE can have an explosive presentation of acute cor pulmonale and shock. From a clinical standpoint, it is important to consider PTE in the differential diagnosis of a patient suspected to have thromboembolic pulmonary embolism. This diagnostic problem can be challenging, because tumor embolisms occur in patients who are at high risk of thromboembolic events, especially those with mucin-producing adenocarcinomas.

Most PTE patients have profound dyspnea and hypoxemia although chest radiographs are typically normal. Nonspecific localized or diffuse interstitial infiltrates have been identified in some cases, which may suggest concomitant lymphangitic carcinomatosis. The clinical presentation of PTE mimics pulmonary thromboembolism in the majority of patients; as a result, ventilation perfusion lung scans have been performed in patients with PTE. The typical pattern revealed involves multiple, small, peripheral, subsegmental perfusion defects, and the ventilation scan is usually normal.[7] Pulmonary angiograms have been performed in patients with PTE, and these can reveal delayed filling of segmental arteries, pruning and tortuosity of vessels, and, rarely, subsegmental filling defects.[8] Pulmonary angiography, however, does not establish a definitive diagnosis of PTE.

The diagnosis of PTE presents clinicians with a challenging problem. Lung biopsy is the procedure of choice to establish the definitive diagnosis and to determine the

extent of PTE and lymphangitic carcinomatosis. It is important to note, however, that in patients who are hemodynamically unstable or severely hypoxemic, this procedure carries significant risks. Recently, Masson and colleagues[9] used a pulmonary artery catheter in the wedge position to sample the pulmonary microvascular circulation in a patient. They demonstrated that after the catheter is wedged, 10 to 15 ml of blood is slowly aspirated and discarded. The next 5 to 10 ml is aspirated into a heparinized syringe for cytologic analysis.

Two important features of pulmonary microvascular cytology specimens must be noted.[10,11] In rare instances, malignant cells can be found in the microvascular cytology specimen without a significant tumor burden in the pulmonary vasculature, which is most likely due to a large tumor burden in the hepatic veins.[10] In addition, false-positive reports are possible because of the large number of megakaryocytes in the pulmonary vasculature. The megakaryocytic nuclei can appear bizarre and resemble malignant cells. It is therefore crucial to interpret a positive pulmonary microvascular cytology result *in conjunction* with the clinical and radiographic data.

PTE should be considered in the differential diagnosis of a patient with carcinoma and dyspnea, hypoxemia and evidence of right heart failure.[12] Placement of a pulmonary artery catheter can aid in hemodynamic management and allow cytological sampling of the lung microvasculature. A pulmonary microvascular cytology specimen can be a useful alternative to lung biopsy in the setting of severe hemodynamic or respiratory distress.

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