Pulmonary Tumor Embolism as an Initial Manifestation of Pancreatic Adenocarcinoma

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Introduction

Pulmonary tumor embolism is a rare syndrome caused by migration of tumoral emboli into the pulmonary arteries. These tumor emboli may form a fibrin-platelet thrombi, resulting in pulmonary-artery hypertension and subsequent right-heart failure. Establishing this diagnosis can be very difficult, and most cases are diagnosed during autopsy,[1] although a history of cancer may be a predictor.

We report a case of pulmonary tumor embolism as the initial presentation of pancreatic adenocarcinoma, which developed into pulmonary-artery hypertension and fatal right-heart failure.

Case Summary

A 35-year-old Ecuadorian female presented to the emergency department complaining of dyspnea and fever. Over the previous month she had experienced nocturnal dry cough, and she had no improvement after antibiotics, and 5 kg of weight loss. During the last 2 weeks she had non-specific chest pain that improved with pain relievers. On the day prior to medical evaluation she developed rapidly progressive dyspnea on minimal effort, and fever as high as 39°C.

She had been living in Spain for 7 years, as a hospitality worker. She had no family history of neoplasms. Her medical history was unremarkable except for tonsillectomy as a child. She had never smoked and did not drink alcohol or use illicit drugs. Her only medication at evaluation was oral contraceptives, for the last 5 years.

Her vital signs were notable for heart rate 136 beats/min, blood pressure 129/74 mm Hg, temperature 36.8°C, and respiratory rate 28 breaths/min. Physical examination revealed normal coloration of the skin and mucous membranes, without jugular venous distention. She was tachycardic, but without murmurs. Auscultation showed fine inspiratory crackles at both lung bases. Abdominal examination revealed hepatomegaly, but no ascites. She also had pitting edema of the legs, but no signs of deep venous thrombosis.

Table 1 shows the laboratory findings. Serology for autoimmune disorders was negative. Microbiology cultures were negative. Electrocardiogram showed sinus tachycardia of 140 beats/min, with no ischemia or right-ventricle-overload signs. Troponin T was < 0.01 ng/mL on 3 sequential measurements. Chest radiograph (Fig. 1) showed a bilateral interstitial pattern. Computed tomography (CT) (Fig. 2) showed: a bilateral interstitial centrilobular micronodular pattern, predominantly in the lower lobes; dilated and beaded peripheral pulmonary arteries,and tree-in-bud pattern on subsegmentary pulmonary arteries; substantial lymphadenopathy of the paratracheal, left para-aortic, subcarinal, left axillary, and bilateral hilar stations; a small pericardial effusion; and enlargement of the pulmonary arteries, with no central intravascular filling defect.

Twenty-four hours after hospital admission she rapidly deteriorated, with increasing dyspnea, peripheral cyanosis, and syncope, and she was admitted to the intensive care unit. She was in respiratory distress, with dyspnea at rest and an increasing oxygen requirement. Echocardiography revealed a right-ventricular diameter of 33 mm (reference range 20–28 mm) and tricuspid insufficiency, with an estimated systolic pulmonary artery pressure of 93 mm Hg (normal value < 40 mm Hg). Her left-ventricular ejection fraction was within the normal range.

She had poor response to initial management with oxygen and continuous positive airway pressure, and she

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Table 1. Laboratory Results

White blood cells (cells/μL)	13.6×10^3
Hemoglobin (g/dL)	13.6
Platelets (cells/μL)	383,000
D-dimer (ng/L)	1,948 (normal 68–494)
International normalized ratio	1.2
Sodium (mmol/L)	136
Potassium (mmol/L)	4.8
C-reactive protein (IU/mL)	141.0
Lactate (mg/dL)	8
Total bilirubin (mg/dL)	0.8 (normal 0.3–1.2)
Amylase (IU/L)	27 (normal 15–55)
Lypase (IU/L)	36 (normal 13–60)
pH*	7.50
P_{aCO_2} (mm Hg)*	30
P_{aO_2} (mm Hg)*	56
$P_{(A\text{-}a)O_2}$ (mm Hg)*	54

* Values from arterial blood sampled while the patient breathed room air.
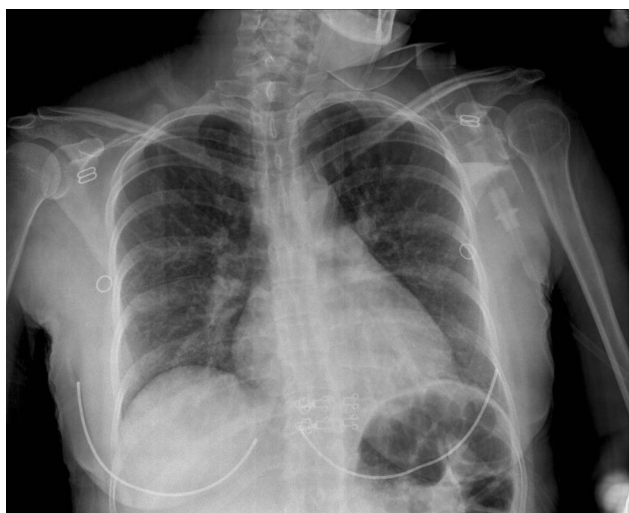$P_{(A\text{-}a)O_2}$ = alveolar-arterial oxygen difference

Fig. 1. Chest radiograph shows bilateral interstitial pattern, predominantly in the lower lobes.

rapidly deteriorated during her first 3 hours in intensive care and required endotracheal intubation and mechanical ventilation. Repeat echocardiography showed severe dilatation of the right ventricle, with low right-ventricular ejection fraction and elevated systolic pulmonary artery pressure. She progressed to cardiogenic shock and had no improvement with vasoactive drugs. She had persistent hypoxemia despite mechanical ventilation. Eight hours after intensive-care admission she died from refractory right-heart failure caused by pulmonary-artery hypertension.

At autopsy, both lungs macroscopically contained a few small nodules in the parenchyma. The liver showed a nutmeg pattern of vascular congestion. The right cardiac ven-tricle was severely dilated. Microscopy revealed an infiltrating ductal adenocarcinoma in the body of the pancreas. It was formed by atypical ductal proliferation of cells with large nuclei, wide cytoplasm, pleomorphism, and lymphatic and vascular spread. The bilateral subsegmental pulmonary arteries had multiple neoplastic emboli composed of cells similar to those found in the pancreas. Thromboses were often associated with the tumor emboli, many of which had progressed to the organizational phase, with extensive intimal fibrosis consistent with pulmonary tumor thrombotic microangiopathy (Fig. 3). Some tumor emboli were also found in renal and coronary arteries.

Discussion

Pulmonary tumor embolism is the occlusion of pulmonary vessels by neoplastic cells, and results in cor pulmonale.[2] Autopsy series indicate that the incidence of pulmonary tumor embolism ranges from 3% to 26% among patients with solid tumors, although only 8% of patients with pathology evidence of tumor emboli have documented morbidity or mortality attributable to the pulmonary tumor embolism.[1] Adenocarcinoma is the most common tumor associated with pulmonary tumor embolism, and usually is located in the breast, stomach, lung, colon, or liver.[1,2] Pancreatic origin is unusual.[1,3,4]

Tumor cells can embolize to the lungs via 3 potentially related mechanisms[1]: proximal macrovascular emboli, distal microvascular emboli, and lymphatic dissemination (lymphangitic carcinomatosis). Two hypotheses attempt to explain the rapid onset of pulmonary-artery hypertension due to pulmonary tumor embolism. The first suggests that occlusion of the vascular lumen by neoplastic cells raises vascular pulmonary resistance.[4] The second argues that endothelial interaction with neoplastic cells activates inflammatory and coagulation pathways, inducing an organization phase, with epithelial neoplastic cells emboli that either completely or partially occlude the vessel lumen, with vascular remodeling phenomena,[2] as we saw in the histopathology of our patient. The latter hypothesis is called pulmonary tumor thrombotic microangiopathy, and it has been suggested that it should be considered an independent disorder.[5]

The typical presentation is subacute dyspnea, pulmonary-artery hypertension, and right-heart failure that mimics massive pulmonary embolism,[1] as in our case. At presentation the most common symptom is dyspnea (57–100% of cases). Others complaints can include cough and chest pain. Classic signs of right-heart failure are reported in only 15–20% of cases.[1] Patients with proximal emboli may have a rapid onset and severe clinical deterioration similar to that with massive pulmonary embolism.[2] Microvascular and lymphatic injury is subacute, which may
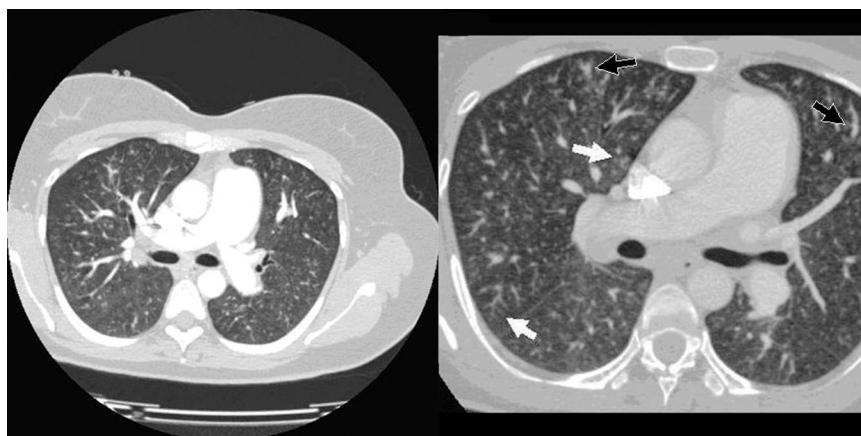
Fig. 2. Thoracic computed tomogram with intravenous contrast reveals (A) dilatation of main pulmonary arteries by >3 cm, and (B) interstitial micronodular pattern, with dilated and beaded vessels (black arrows) and tree-in-bud pattern (white arrows).
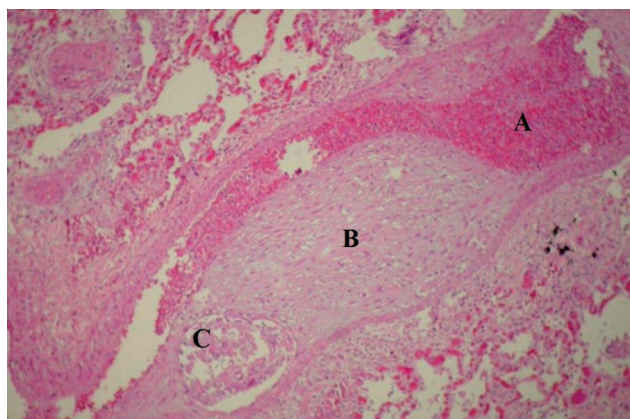

Fig. 3. Pulmonary biopsy obtained during autopsy shows a longitudinal section of a pulmonary arteriole with organized thrombi (A), with intimal fibrosis reaction (B) occupying two thirds of the vascular lumen. There is also a tumor emboli (C).

lead to right-ventricular claudication,[5] as in our patient. The clinical symptoms are similar to pulmonary embolism, although a higher incidence of cough has been reported.[6] In most cases hypoxemia appears with normal chest radiograph.[7] Electrocardiogram may show right bundle branch block, and echocardiography may show right-ventricular dilatation and elevated systolic pulmonary artery pressure.[1]

Usually, CT is non-diagnostic, but may show:

• Dilatation of the main pulmonary arteries[2]

• Wedge-shaped interstitial opacities related to lymphatic infiltration and pulmonary infarction[8]

• Dilated and beaded subsegmentary pulmonary arteries, associated with vascular dilatation and perivascular interstitial infiltration[7]

• Tree-in-bud pattern, consisting of small centrilobular

nodules of soft-tissue attenuation connected to multiple branching linear structures of similar caliber that originate from a single stalk[8]

That radiographic pattern was originally reported in cases of endobronchial spread of *Mycobacterium tuberculosis*, but now it is recognized as a CT manifestation of several peripheral airway diseases, including certain infections, obliterative bronchiolitis, immunologic disorders, and aspiration of foreign substances.[6]

Positron emission tomography may help determine the origin of vascular filling defects. In contrast to those of thrombotic origin, vascular filling defects of tumoral origin show areas of increased standardized uptake value, which correspond to the pulmonary emboli sites detected on CT.[9] Pulmonary perfusion gammagraphy can show multiple perfusion defects at a subsegmental level,[3] and it also may be reported as normal.[1]

Definitive diagnosis is via pathology, which can be obtained via: pulmonary microvascular cytology through a wedged pulmonary-artery catheter[10]; transbronchial or open-lung biopsy[11]; or autopsy. The rapid clinical deterioration in our patient raised an ethical dilemma about ordering diagnostic procedures,[12] but if the clinical situation allows it, pulmonary-artery catheter is relatively benign and may help make the diagnosis.

Usually pulmonary tumor embolism occurs in an advanced stage of a known cancer, although it can occur any time with a malignant neoplasm.[1] Rarely, pulmonary tumor embolism can be the initial manifestation of an occult cancer, which makes the diagnosis more difficult. Pulmonary tumor embolism has been reported as the presenting symptom of esophageal,[2] breast,[13] and liver cancer.[14] To our knowledge there has been only one previous case report of pulmonary tumor embolism as the initial manifestation of pancreatic cancer, in which, as in our patient,

primary tumor symptoms were absent.[4] The present case emphasizes the importance of considering pulmonary tumor embolism in the differential diagnosis of subacute dyspnea, pulmonary-artery hypertension, and right-heart failure, even in the absence of cancer history or primary tumor symptoms.

Given the finding of nodular interstitial pattern in our patient, an infectious etiology (including atypical bacteria, mycobacteria, or fungus) was the most likely diagnosis. Other entities, including cryptogenic organizing pneumonia, hypersensitivity pneumonitis, and vasculitis, were also on the differential diagnosis. But with no oncologic history, pulmonary tumor embolism was not considered.

Mean survival time with pulmonary tumor embolism, after the onset of symptoms, is 4–12 weeks.[2] Chemotherapy might mitigate the overall process causing the respiratory symptoms, but few cases of successful treatment have been described.[5] Corticosteroids and anticoagulants have shown no benefit.[5] Accepted or unproven therapies[15] were not performed in our patient because of the rapid clinical course.

Teaching Points

Pulmonary tumor embolism should be considered in a patient with subacute dyspnea, pulmonary-artery hypertension, and right-heart failure, especially if the patient has a cancer history, but pulmonary tumor embolism may be the first manifestation of a malignancy, so absence of cancer history should not exclude it from the differential diagnosis.

Pulmonary tumor embolism occurs most frequently in adenocarcinoma of the breast, stomach, lung, colon, and liver. Pancreatic origin is unusual. Pulmonary tumor embolism is difficult to diagnose and requires a high index of suspicion. Definitive diagnosis usually occurs during autopsy. Overall prognosis is poor; most patients die within few weeks of the onset of symptoms.

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