Angioinvasive Pulmonary Aspergillosis: Presentation as Massive Pulmonary Saddle Embolism in an Immunocompromised Patient

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A 33 year old woman with chronic myelogenous leukemia presented with clinical symptoms and hemodynamic signs suggestive of pulmonary embolism. Initial angiographic studies supported the diagnosis of a massive saddle pulmonary embolus, and an inferior vena cava filter was inserted. However, subsequent autopsy revealed unsuspected angioinvasive pulmonary aspergillosis with secondary in situ thrombosis. The clinical features and diagnostic considerations in immunocompromised patients presenting with the clinical picture of pulmonary embolism are discussed.

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Case Report

A 33 year old woman with chronic myelogenous leukemia was admitted for evaluation of dyspnea and syncope. One year earlier, she had presented with leukocytosis, which was treated with intermittent busulfan. Eight months earlier, a lymphoid “blast crisis” stage was treated with a single course of vincristine, prednisone, hydroxyurea and adriamycin chemotherapy. Subsequent bone marrow examinations revealed extensive myelofibrosis and hypocellularity without malignant cells. A right subclavian Hickman catheter was inserted for chronic platelet and red blood cell transfusions. Several days before admission, she developed weakness and dyspnea and had a syncopal episode while walking.

Clinical features. On admission, she was afebrile, and in respiratory distress. Blood pressure was 90/60 mm Hg without pulsus paradoxus, pulse was 140 beats/min and respirations were 44 breaths/min. The neck veins were distended. The lungs were clear. There was accentuation of the pulmonary valve closure sound and a parasternal impulse. The liver was enlarged and tender. Mild right leg weakness was present. A right subclavian Hickman catheter was in place. The hematocrit was 28.8% and the white blood cell count was 1,400 mm$^3$ with 35% neutrophils, 3% bands, 50% lymphocytes, 6% monocytes, 5% basophils, 1% eosinophils and no malignant cells. The platelet count was 8,500. Arterial blood gases on room air were partial pressure of oxygen (Po$_2$) 63 mm Hg, partial pressure of carbon dioxide (Pco$_2$) 23 mm Hg and pH 7.48. Chest roentgenogram showed a small chronic right mid-lung infiltrate unchanged.
from prior studies. An electrocardiogram showed sinus tachycardia and a new "S_Q,T" pattern (a pronounced S wave in lead I with an associated Q wave and inverted T wave in lead III). Computed tomographic studies of the pulmonary outflow tract with contrast medium showed no evidence of mediastinal adenopathy or masses. A technetium-99 radionuclide lung scan suggested complete absence of perfusion to the right lung (Fig. 1).

**Catheterization and treatment.** Emergency cardiac catheterization was performed. The hemodynamic measurements (Table 1) showed the presence of right ventricular failure with marked elevation of both right heart filling and pulmonary artery pressures. The pulmonary artery venous oxygen saturation was reduced, consistent with systemic hypoxemia and low cardiac output. Pulmonary angiography showed a large filling defect extending from the main pulmonary artery into the right pulmonary artery with no flow to the right lung (Fig. 2). There was slow flow into the left pulmonary artery around the filling defect in the main pulmonary artery with no evidence of peripheral left lung emboli. Superior vena cava venography showed no evidence of subclavian Hickman catheter thrombosis.

Massive pulmonary saddle embolism was the presumptive diagnosis. Therapy with intravenous heparin, intravenous streptokinase or surgical embolectomy was considered but rejected because of thrombocytopenia. A Greenfield inferior vena cava filter was placed with difficulty and it subsequently migrated into a renal vein. Broad spectrum antibiotic agents and high-dose parenteral corticosteroids were administered. Blood, urine and sputum cultures were negative for bacteria, fungi and acid-fast bacilli. The patient became progressively hypoxic, and died on the sixth hospital day.

**Autopsy findings (Fig. 3).** A massive organizing, saddle thrombus obstructed and conformed to the main (90% obstruction) and right (100% obstruction) pulmonary arteries, with propagation into the secondary and tertiary branches of the right pulmonary artery. The thrombus was packed with myriad, septate, 5 to 10 mm thick, acutely branching filaments characteristic of *Aspergillus fumigatus*. The right pulmonary artery showed evidence of vasculitis with hyphal invasion and vessel destruction. There were multiple small recent right lung infarcts. The heart was enlarged (390 g) with moderate right ventricular dilation and hypertrophy. An area of invasive aspergillosis was noted in the right upper pulmonary lobe (2 cm diameter) and most likely represented the primary focus of *A. fumigatus* infection. In addition, multiple (left-sided) cerebrocortical lesions of invasive as-

**Figure 1.** The technetium-99 radionuclide lung perfusion scan in the anterior (A), posterior (P) and left lateral (L Lat) views shows complete absence of perfusion to the right lung, consistent with the presence of a massive pulmonary embolus obstructing flow to the right main pulmonary artery.

**Figure 2.** Right anterior oblique view of contrast angiogram of the main pulmonary artery. The angiographic catheter tip lies immediately inferior to a large filling defect (white arrows) in the main pulmonary artery. There was sluggish opacification of the left pulmonary artery (LPA) by contrast medium and virtually no opacification in the expected location of the right pulmonary artery (RPA). A subclavian Hickman catheter is present.
Figure 3. *Aspergillus fumigatus* pulmonary artery thrombus. **Left,** Opened proximal main pulmonary artery in situ (arrow) showing complete occlusion at this level. **Center,** Fungal thrombus removed from pulmonary artery tree as a cast of main, left (L) and right (R) pulmonary arteries. **Right,** Septate, acutely branching hyphae characteristic of *Aspergillus* (methenamine silver stain, ×375, reduced by 20%).

pergillosis were noted. There was no systemic venous thrombosis.

**Discussion**

In this immunocompromised patient with leukemia, a diagnosis of subacute cor pulmonale secondary to massive pulmonary saddle embolism was based on hemodynamic and angiographic findings (6). Her progressive debilitation and immobility (7), Hickman catheter (8), repeated platelet transfusions (9) and underlying malignancy increased the risk for systemic venous thrombosis and subsequent pulmonary embolism. However, autopsy revealed that pulmonary vascular obstruction was caused by unsuspected angioinvasive pulmonary aspergillosis with secondary in situ thrombosis.

**Angioinvasive aspergillosis.** In immunocompromised patients, a clinical and hemodynamic syndrome typical of massive pulmonary embolism may be caused by diseases other than systemic venous thromboembolism with differing management strategies and prognoses. Angioinvasive pulmonary aspergillosis should be considered a cause of pulmonary vascular obstruction in immunocompromised patients with leukemia, lymphoma or neutropenia after cytotoxic chemotherapy (10). In several series of patients with acute leukemia, aspergillosis accounted for 12 to 55% of cases of invasive fungal infections, and roughly 40% of patients dying with leukemia had evidence of aspergillosis (11,12). As in our patient, the lung was the probable site of primary infection in more than 95% of the cases, with systemic dissemination occurring in 25% (13). The most common clinical presentation was unremitting fever with patchy bronchopneumonia often evident on roentgenogram but with almost invariably negative blood and cerebral spinal fluid cultures. In fact, the diagnosis was correctly established by sputum culture in only 12 to 34% of patients (13,14), underscoring the need for tissue examination in patients at high risk for aspergillosis.

Pathologic examination of lung tissue usually reveals bronchopneumonia with necrotizing bronchitis and invasion of small blood vessels and pulmonary infarction due to invasion and occlusion of medium- or large-sized pulmonary vessels (15). The angioinvasive properties of aspergillosis have contributed to the development of the superior vena cava syndrome (16), carotid arterial and cerebral occlusions (10), the Budd-Chiari syndrome and coronary artery thrombosis (14). The clinical, gross and histologic data in our patient suggested obstruction of the main pulmonary artery secondary to fungal invasion and injury of the underlying endothelium with secondary thrombus deposition. As our case illustrates, the diagnosis is often unsuspected ante-mortem. This may contribute to the fact that overall mortality is generally greater than 80% in patients with invasive aspergillosis although there are occasional reports of successful therapy with amphotericin B (17).

**Differential diagnosis.** Other causes of pulmonary vascular obstruction should also be considered in patients with dyspnea with underlying malignancy. Spontaneous tumor embolization that results in occlusion of the main pulmonary artery or large segmental branches and acute cor pulmonale is exceedingly rare (2,3,18). More frequently, acute cor pulmonale occurs during operative procedures from embolization of tumors that tend to involve large systemic veins such as renal cell carcinoma (19,20), hepatoma (2), sarcoma (21) and choriocarcinoma (18). Tumor microembolization of small pulmonary vessels can lead to the gradual onset of dyspnea, hypoxemia, right ventricular hypertrophy and severe pulmonary hypertension similar to the findings in our patient (20). This tumor embolization occurs in approximately 2% of all patients with solid malignant neoplasms in whom carcinoma of the breast (2-4,22), prostate (3), liver (2,3) and trophoblastic tissues (2) predominate. Chest roentgenogram, lung scan and angiographic studies are usually nondiagnostic and lung biopsy is often necessary to make the diagnosis.

*Lymphangitic carcinomatosis has been reported to produce a similar clinical picture of subacute cor pulmonale* (4). Both peribronchial and perivascular pulmonary lymphatics become distended by the tumor, resulting in compression of the surrounding arterial system with associated arteriolar...
thrombosis and endarteritis (23). Frequently, the generalized lymphatic involvement in such instances produces an “interstitial infiltrate” pattern on chest roentgenograms. Cardiac catheterization and pulmonary angiography show severe pulmonary hypertension, poor perfusion of peripheral lung parenchyma and absence of proximal large intraluminal filling defects. A definitive diagnosis is usually made by biopsy or at autopsy.

**Conclusions.** These observations suggest that examination of lung tissue to exclude the presence of angioinvasive aspergillosis or malignant cells within the microvasculature and lymphatics should be strongly considered in immunocompromised patients with clinical and hemodynamic evidence of developing cor pulmonale before cardiovascular collapse. Although tissue biopsy must be undertaken with caution in patients with neutropenia and thrombocytopenia, the risks of this procedure may be outweighed by the morbidity of inappropriate administration of streptokinase, heparin or vena caval filter placement in patients with the incorrect diagnosis of systemic venous thromboembolism, and by the possible recovery of occasional patients with the use of anticancer or antifungal chemotherapy.

**References**

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