A 70-year-old man was evaluated for fever and progressive respiratory distress. Fifteen months earlier, he had been successfully treated for a B-cell lymphoma limited to bone marrow. The therapy, which included chlorambucil, prednisone, and vincristine, had resulted in complete remission. A recent evaluation of fever and fatigue revealed recurrence of lymphoma. The patient was admitted for consolidation therapy with cyclophosphamide, adriamycin, vincristine, prednisone, and granulocyte-colony stimulating factor.

Three days after chemotherapy, the patient became neutropenic with a total leukocyte count of 200/μl. Five days later, therapy with vancomycin and ceftazidime was begun in response to fever. The following day, blood cultures were positive for yeast forms, which prompted treatment with intravenous amphotericin B. After 2 days of antifungal therapy, the patient developed progressive respiratory distress.

Physical Examination

Vital signs: temperature, 101°C; respirations, 32/min; pulse, 120 beats/min. General: moderate respiratory distress. Cardiac: no murmurs. Chest: marked inspiratory and expiratory wheezing, which appeared to originate in the trachea and major bronchi.

Laboratory Findings

Hematocrit, 25 percent; WBC, 150/μl; platelets, 50,000/μl. Chest radiograph: widened mediastinum, unchanged during previous months (Fig 1). Room air arterial blood gas values, pH, 7.48; PaCO₂, 30 mm Hg; PaO₂, 74 mm Hg. Special stains of sputum: yeast forms.

What is the most likely diagnosis? What is the mechanism of dyspnea and wheeze? What is the most helpful diagnostic procedure? What are the treatment options?
Aspergillus species can initiate a wide spectrum of pulmonary diseases. The clinical form of disease expressed depends greatly on host factors. For instance, aspergillosis of the lung can be classified into allergic, saprophytic, and invasive disease. The association of allergic bronchopulmonary aspergillosis and bronchocentric granulomatosis in the asthmatic patient is well known. Saprophytic colonization may remain asymptomatic or cause mucoid impaction of the bronchi in patients with asthma or may generate bronchial casts in patients with AIDS. Acute invasive pulmonary or disseminated aspergillosis in the immunocompromised host with severe neutropenia is a recognized and dreaded form of aspergillosis. Recent reports have described tracheobronchitis secondary to aspergillosis as a less well-recognized form of invasive disease that is potentially lethal and requires early clinical detection.

Descriptions of tracheobronchitis secondary to infection by Aspergillus species date back to the 1970s. The term “aspergillar bronchitis” was used to describe bronchial casts formed by mucus and mycelia that line the tracheobronchial tree. Although usually noninvasive, this form of aspergillosis occasionally results in superficial erosions that may progress to extensive ulceration and black membrane formation. Respiratory insufficiency secondary to airway obstruction may result in the patient's death.

There are several reports of immunocompromised patients, including those with AIDS, who have Aspergillus tracheobronchitis characterized by intraluminal growth of the organism with pseudomembrane formation and varying depths of tissue invasion. It has been proposed that the type and extent of immunosuppression may play a role in the magnitude of tracheal and bronchial invasion and possibly progression to pneumonitis and infiltration of vascular structures. Heart-lung and lung transplant recipients appear to be at increased risk for developing tracheobronchial aspergillosis, particularly at the airway anastomotic site.

Cough, upper airway wheezes, and progressive dyspnea that may result in respiratory failure are present in most patients. Cough may not occur, however, in patients after heart-lung or lung transplantation because of the absence of cough reflexes distal to the anastomotic site. Hemoptysis occurs in about 15 percent of patients, with rare reports of massive hemoptysis occurring during bronchoscopic removal of necrotic airway membranes. This complication supports the concept that Aspergillus tracheobronchitis ranges from airway colonization with membrane formation to frankly invasive disease with
have no chest radiographic abnormality. Nearly 20 percent of patient deaths have been attributed to airway obstruction secondary to tracheobronchial necrosis and pseudomembrane formation.

Limited information is available on preventive and therapeutic options in Aspergillus tracheobronchitis. Clinical trials of prophylactic aerosolized amphotericin B, in doses varying from 5 mg to 100 mg, and/or oral itraconazole in high-risk patients demonstrate good patient tolerance and efficacy in preventing disseminated and tracheobronchial aspergillosis. Intranasal amphotericin B has been reported to reduce the frequency of invasive aspergillosis in neutropenic patients. Various formulations of liposomal amphotericin B and newer drugs, such as fluconazole and itraconazole, appear promising in improving the prognosis of patients predisposed to invasive aspergillosis and those with established disease.

The present patient underwent bronchoscopy that revealed extensive pseudomembrane formation of the mucosa of the trachea and mainstem bronchi. The pseudomembrane formed a thick cast that concentrically narrowed the tracheobronchial lumens. Bronchoscopic removal of large pieces of the pseudomembrane resulted in immediate relief of wheezing and respiratory distress (Fig 2). The underlying mucosa revealed extensive shallow ulceration and denudation of the mucosa. Special stains of the pseudomembrane showed hyphal structures with the typical morphology of Aspergillus species.

The patient received topical antifungal therapy (amphotericin B, 5 mg administered by aerosol nebulization four times daily), in addition to the continuation of intravenous amphotericin B. Repeat bronchoscopy 3 days later revealed no progression of the pseudomembrane formation. The patient died 3 days later (18 days following reinduction chemotherapy). Autopsy confirmed pseudomembranous necrotizing tracheobronchitis secondary to Aspergillus fumigatus and Aspergillus flavus infection (Fig 3).

**Clinical Pearls**

1. **Immunocompromised patients with neutropenia are at increased risk for pseudomembranous (necrotic) tracheobronchial aspergillosis in addition to the better known invasive pulmonary form of the disease.**

2. Neutropenia, cough, progressive dyspnea, and wheezing originating in the upper airways in an immunocompromised patient suggest the diagnosis of pseudomembranous (necrotic) tracheobronchial aspergillosis.

3. Bronchoscopy is both diagnostic and initially therapeutic in relieving dyspnea by the removal of obstructing pseudomembranes.

4. Prophylactic use of aerosolized amphotericin B and newer oral antifungal agents in patients at risk may decrease the incidence of both invasive pulmonary and tracheobronchial aspergillosis.

**Suggested Reading**


Conneally E, Cafferkey MT, Daly PA, Keane CT, McCann SR. Nebulized amphotericin B as prophylactic against invasive aspergillosis in granulocytopenic patients. Bone Marrow Transplant 1990; 5:403-06.

