Malignant External Otitis Due to *Aspergillus flavus* with Fulminant Dissemination to the Lungs


Malignant external otitis secondary to aspergillus infection is rare, and only 10 cases have been reported in the literature. Nine of 10 patients responded to therapy and survived their infection. There have been no previous reports of dissemination of *Aspergillus* species from the ear to other organs. We describe a case of malignant external otitis due to *Aspergillus flavus* that disseminated hematogenously to the lungs. The result was an overwhelming, miliary pulmonary infection, which progressed very rapidly to respiratory failure and death. Pathological examination of lung tissue revealed multiple microabscesses and hyphal elements that had invaded the lung parenchyma from small pulmonary arteries.

Disseminated aspergillosis involves two or more noncontiguous organs. Since *Aspergillus* spores are usually acquired via inhalation, the lungs generally are the primary focus of infection from which dissemination occurs. Therefore, the lungs are involved in 94% of cases of disseminated infection and are the organ most commonly affected by aspergillosis [1]. Malignant external otitis secondary to aspergillus infection is rare and is seen primarily, but not exclusively, in severely immunocompromised individuals. We describe a case of malignant external otitis due to *Aspergillus flavus*; miliary spread to the lungs caused fulminant disease and death from respiratory failure within 2 days.

Case Report

A 20-year-old male with acute lymphocytic leukemia was hospitalized for induction chemotherapy with daunomycin, vincristine, prednisone, and L-asparaginase. He was febrile on admission, and treatment with vancomycin and cefazidime was begun; he subsequently defervesced. After 6 days of neutropenia (absolute neutrophil count, <500/μL), the patient’s fever recurred and he developed pain and erythema in the right pinna and external ear canal.

Five days later, palsy in the right facial nerve was noted. Surgical debridement of the ear canal revealed invasion of tissue by septate hyphae; cultures of the surgical specimens yielded *A. flavus*. The patient had worked on a tobacco farm and reported carrying moldy tobacco leaves against the right side of his face before he was admitted to the hospital. Treatment with amphotericin (1.0 mg/[kg ⋅ d]) was begun and the patient’s condition improved clinically; however, he continued to have significant ear pain that required administration of narcotic analgesics. Because of a rising level of serum creatinine the dose of amphotericin was decreased to 0.7 mg/kg every other day after the neutropenia resolved.

A second round of consolidation chemotherapy was begun 4 weeks after induction chemotherapy was begun. The patient once again became neutropenic, at which time a cumulative amphotericin dose of 911 mg had been given. Despite an increase in the daily dose of amphotericin to 1.0 mg/kg, the erythema and pain in the right ear became progressively worse. After 5 days of neutropenia, the patient abruptly developed bilateral diffuse pulmonary infiltrates involving all lung fields (figure 1) and he required intubation. Despite intense ventilatory support (FiO₂, 100%; positive end-expiratory pressure, 5 cm H₂O), the patient became progressively hypoxemic with a Po₂ of 33 torr and died 1 day later.

At autopsy hundreds of 2-3 mm nodules were present as pleural plaques on the lung surface and as yellow-white lesions throughout the parenchyma; all lobes were involved (figure 2). Microscopic examination revealed multiple thrombomycotic emboli that occluded the vascular lumina of small pulmonary arteries. The hyphae in the vessels had invaded the surrounding lung tissue (figure 3). Many of the infected areas had associated infarction and/or perivascular hemorrhage. Cultures of lung tissue obtained at autopsy yielded *A. flavus*. The autopsy was limited to the lungs so the head and neck were not examined.

Discussion

*Aspergillus* species are frequently isolated from soil and decaying vegetation. Large numbers of *Aspergillus* conidia have been found in hay and straw enriched with leaf and grass compost [2]. An association between invasive pulmonary aspergillosis (IPA) and the smoking of marijuana has been previously documented by Kagen [3], who reported that culture of 12 of 13 marijuana cigarettes yielded *Aspergil-
lus species. Our patient may have been infected by direct cutaneous exposure of his ear to moldy tobacco leaves. *A. flavus* and other *Aspergillus* species have been isolated from cured tobacco [4]. Several cases of primary cutaneous aspergillosis have been reported among both healthy and immunocompromised patients [5]. The most common predisposing condition among these patients was hematologic malignancy, and *A. flavus* has been predominant among isolated species.

Malignant external otitis secondary to aspergillosis infection has been documented in 10 other patients [6–13]. Five of these patients were neutropenic, two had AIDS, and three had no apparent risk factors. One of the patients died during the course of his acute infection, and an autopsy revealed pulmonary involvement with *Aspergillus* species; however, too little information was reported to determine whether his pulmonary involvement was due to hematogenous spread or to concomitant primary infection in the lung [8].

Radiographic findings in the case described herein were unusual. All lobes of the lung were involved in a diffuse process, and the interval from the first pulmonary symptoms to death was only 2 days. The temporal sequence strongly suggested that the infection began in the ear and spread to the lung because the patient had severe otitis for 1 month before he developed any pulmonary symptoms and before chest radiographs revealed abnormalities. Likewise, the last operative debridement of the ear canal took place 3 weeks before his death and thus did not appear to contribute to dissemination of *Aspergillus* species. In any event, we suspect that *A. flavus* invaded a large vein in the head or neck, which caused a massive shower of aspergillus emboli into the lung. Since the patient’s autopsy was limited to the chest, we could not obtain direct evidence that *Aspergillus* species had invaded a vein in the neck. However, the gross and microscopic pathology supported this conclusion because examination showed multiple lesions of the same age and size: the lesions consisted of fungus that was plugging and growing out of small pulmonary arteries.

Both neutropenia and impaired cell-mediated immunity increase the risk of IPA in patients with leukemia. IPA usually presents as a patchy bronchopneumonia, as a wedge-shaped pleural-based density, or as a discrete walled-off mass sometimes referred to as a mycotic lung sequestrum [14]. Rapid development of diffuse lung disease in a patient with impaired cell-mediated immunity usually suggests infection with pathogens such as *Pneumocystis carinii*, cytomegalovirus, and other viruses; tuberculosis; histoplasmosis; or strongyloidiasis. Radiographs of patients with noninfectious processes such as leukemic infiltration, congestive heart failure, lung injury from use of cytotoxic drugs, and adult respiratory distress syndrome also usually show diffuse changes. Miliary

Figure 1. Chest roentgenogram of a patient who had disseminated aspergillosis following malignant external otitis reveals bilateral infiltrates that involve all lobes of the lung.

Figure 2. *A:* Cut section of the patient’s right lung at autopsy demonstrates multiple miliary abscesses secondary to Aspergillus infection. *B:* External surface of the right lung shows numerous pleural plaques secondary to Aspergillus infection.
microabscesses have been described as part of the spectrum of IPA but may be due to hematogenous spread from other pulmonary sites [1, 5]. Widespread acute pulmonary dissemination, as was seen in our case, is highly unusual and has not been documented in patients with malignant external otitis.

Recurrence neutropenia was temporally associated with and probably contributed to the abrupt deterioration in our patient's condition. It is possible that invasion of a large vein in the head or neck was the critical event associated with his death. Although the patient's infection stabilized somewhat after amphotericin therapy and surgical debridement, he still had active ear drainage and ear pain that required administration of narcotic analgesics. A recent report describes two healthy hosts in whom therapy with amphotericin for invasive aspergillus otitis failed but in whom itraconazole therapy was successful [10]. Another report describes a case of invasive otitis that relapsed after discontinuation of treatment with amphotericin B. The patient was then treated with itraconazole and had a complete response [6]. Itraconazole has also performed well in treatment of small numbers of other bone infections caused by Aspergillus species [15]. Therefore, itraconazole could be considered as alternative or adjunctive therapy for this condition. Regardless, aggressive antifungal therapy is clearly indicated in patients with invasive aspergillus otitis since this condition may be associated with severe complications, as was illustrated by the findings in this case.

References