Successful treatment of larynx-tracheobronchial-pulmonary aspergillosis in an immunocompetent host

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Received May 27, 2013
Accepted October 23, 2013
Published February 14, 2014
DOI http://dx.doi.org/10.4238/2014.February.14.8

ABSTRACT. Immunocompromised individuals are susceptible to pulmonary Aspergillus infections, whereas invasive Aspergillus infection is extremely rare in the presence of normal immunity. A case of larynx-tracheobronchial-pulmonary aspergillosis in an immunocompetent 57-year-old female host who was successfully treated with amphotericin-B and voriconazole is reported here.

Key words: Immunocompetent host; Invasive pulmonary aspergillosis; Larynx-tracheobronchial-pulmonary aspergillosis; Pneumonia
INTRODUCTION

The majority of cases of invasive pulmonary aspergillosis (IPA) are seen in immunocompromised patients. The risk factors are prolonged neutropenia, transplantation, corticosteroid therapy, AIDS, hematological malignancy, and cytotoxic therapy (Gerson et al., 1984; Schaffner, 1985; Denning et al., 1991; Minamoto et al., 1992; Hibberd and Rubin, 1994; Soubani and Chandrasekar, 2002). The majority of IPA patients have hematological immunosuppressive conditions; only 14% of patients have non-hematological immunosuppressive conditions (Vandewoude and Vogelaers, 2007). In addition, other factors predispose patients to fungal infection in general, such as parenteral nutrition, use of multiple antibiotics, and prolonged hospitalization (Soubani and Chandrasekar, 2002). Rarely, IPA, especially larynx-tracheobronchial-pulmonary aspergillosis, is reported in apparently immunocompetent patients or in individuals who are mildly immunocompromised, such as patients with alcoholism, chronic liver disease, diabetic ketoacidosis, or chronic obstructive pulmonary disease (COPD) (Levitz and Diamond, 1984; Karam and Griffin Jr., 1986; Clancy and Nguyen, 1998; Ali et al., 2003). In a review of 545 patients with IPA, underlying risk factors were not identified in 2% of patients (Patterson et al., 2000). Because the diagnosis is often delayed for such patients, the mortality rate has been reported at 100% (Ali et al., 2003). We here present a rare case of larynx-tracheobronchial-pulmonary aspergillosis in an immunocompetent host. This patient was successfully treated with amphotericin B and voriconazole.

CASE REPORT

A 57-year-old previously healthy woman presented at the hospital with a chief complaint of pharynx itching, watery nasal discharge for 23 days, fever, and dyspnea for 19 days prior to admission. She had no significant medical history. She was not taking any medications prior to her illness, she had never smoked or consumed alcohol, her family history was negative, and she did not have chronic liver disease, diabetes mellitus, or COPD. She was a housewife and had never worked in any other employment. She came from a low socioeconomic background. She had a temperature of 40°C and crackles at the bases of both lungs. Her computed tomography (CT) scan revealed a cavity in the upper lobe of the left lung and mucoid impaction along the bronchus (Figure 1). Her white blood cell count was 13.3 x 10^9 cells/L with 87.7% neutrophils. Arterial blood gas values with nasal cannula oxygen at 2 L/min were: pH 7.52; PaCO_2 33 mmHg; PaO_2 59 mmHg. All other laboratory tests, including liver function tests and urinalysis, were normal. The results of initial sputum and blood cultures and sputum stains for acid-fast bacteria were negative. Empirical treatment with intravenous Tienam and Avelox was initiated because of the initial diagnosis of severe community-acquired pneumonia, and supplemental oxygen was administered by nasal cannula at 2 L/min. After 72 h, the patient was still febrile. Gram stain of her sputum revealed fungal hyphae and spores, and the sputum culture was positive for *Aspergillus fumigatus*. This indicated that she may have invasive pulmonary aspergillosis, but we needed confirmed evidence. She deteriorated, and a repeat CT scan showed progression. Fiber optic bronchoscopy was performed on the fourth day of hospital admission, and large white moss was observed in the airway (Figure 2). Tissue histopathology showed that the hyphae (Figure 3) and bronchoalveolar lavage culture were positive for *A. fumigatus*. Her antibiotic treatment was ceased, and 1 mg amphotericin
B was initiated on the third day of hospital admission, and the dose was gradually increased. During the period of application of amphotericin B, she had severe vomiting, renal tubular acidosis, and phlebitis, and therefore the treatment was stopped; the total cumulative dose of amphotericin B was 1850 mg. Subsequently, we chose 200 mg voriconazole twice a day until the end of her treatment. Subsequent cultures were negative for mycobacteria. Malignant cells were not detected in the bronchoalveolar lavage. At 14 days after the initiation of antifungal therapy, the patient’s temperature was 37°C and there was no evidence of white moss in the airway (Figure 4). However, the patient had body temperature fluctuations multiple times in the course of treatment, where the temperature could rise again to over 38°C, while in other instances, her body temperature dropped to normal, even without special treatments such as those combined with other antibiotics or antipyretic drug treatment; her temperature rose for less than 2 h each time. Clinical and radiological improvement was observed, and total therapy was continued for 4 months. A repeat CT scan of the chest at the end of the 4-month period was normal (Figure 5). A variety of tests was performed to exclude underlying immunosuppression. Neutrophil counts had returned to normal. Peripheral smear, lactate dehydrogenase, blood glucose, glutamate oxaloacetic transaminase (GOT), glutamate pyruvic transaminase (GPT), albumin, and globulin levels were all normal. The HIV test was negative. She received pulmonary function tests twice. Interestingly, the first pulmonary function test on the third day of hospital admission showed obstructive ventilatory disorder and the bronchial dilation test was negative; however, during treatment of *Aspergillus*, her condition improved, and her bronchial dilation test was positive in the second pulmonary function test.

![Figure 1](image1.jpg)

**Figure 1.** Initial CT demonstrating cavity in the upper lobe of left lung and mucoid impaction along the bronchus.

![Figure 2](image2.jpg)

**Figure 2.** Fiber optic bronchoscopy demonstrating large white moss in the airway.
DISCUSSION

Invasive pulmonary aspergillosis usually occurs in immunocompromised hosts following inhalation of *Aspergillus*. Our case highlights that larynx-tracheobronchial-pulmonary aspergillosis can also occur in immunocompetent individuals and can be successfully treated with amphotericin B and voriconazole. The number of reported cases of invasive pulmonary aspergillosis presenting as acute community-acquired pneumonia in apparently immunocompetent hosts is small. Clancy and Nguyen (1998) reported one such patient and described 11 other cases of invasive aspergillosis that were previously reported in the English language literature. Nine patients were previously healthy, one had COPD, one had cirrhosis, and one had hypertension. Patients usually presented fever, cough, sputum production, dyspnea, chest pain, and hemoptysis. In the present case, the patient was a housewife without a history of
underlying diseases. She had allergy-like symptoms including pharynx itching and watery nasal discharge in the early disease stage, which was followed by high fever that did not respond to conventional antimicrobial therapy. Our detailed inquiry revealed that the patient had cleaned her old house before the onset of this disease. Because we found large white moss in her airway by fiber optic bronchoscopy, we considered that the disease of this patient might be associated with the inhalation of large amounts of *Aspergillus*. The radiological appearance of IPA includes rounded densities and pleural-based infiltrates. Typical chest CT findings are multiple nodules with or without a halo sign or an air crescent sign. However, in this case, the earliest indications that it may have been an *Aspergillus* infection were mucoid impaction along the bronchus, referred to as finger-in-glove sign, and bilateral multiple rounded infiltrates and a cavity in the upper lobe of left lung. Based on these signs, we looked for further evidence of *Aspergillus* infection. The diagnosis of invasive pulmonary aspergillosis is often difficult. Sputum cultures may be negative. Furthermore, the presence of *Aspergillus* in a smear or culture of sputum or respiratory secretions is not necessarily indicative of invasive infection since these organisms are ubiquitous in the environment and can colonize the respiratory tree. The diagnosis of IPA is definite when tissue histopathology shows the hyphae, with or without a positive culture for *Aspergillus* from the same site, a positive culture following percutaneous needle aspiration, or open lung biopsy (Denning et al., 1994). Bronchoscopy or bronchoalveolar lavage is safe and sensitive, and is particularly useful in high-risk patients when the organism has to be identified quickly by smear. In this case, we conducted a repeated sputum fungal culture and bronchoscopy. Sputums and bronchoalveolar lavage fluid culture as well as biopsy all confirmed *A. fumigatus* infection. In the study of Clancy and Nguyen (1998), the diagnosis was delayed in all patients. Among the patients for whom the diagnosis was made antemortem, the median time from onset of symptoms to definite diagnosis was 15 days (range, 10-17 days). This period was 26 days in our patient. Because our patient was not immunocompromised, she was not initially considered with a diagnosis of fungal pneumonia. We considered *Aspergillus* pneumonia when she failed to improve despite therapy and a sputum stain for fungal hyphae was positive.

The efficacy of available therapeutic agents for pulmonary aspergillosis is currently poor. The most widely used drug in the treatment of IPA is amphotericin B (Popp et al., 1999). We started treatment of 1 mg amphotericin B on the third day of hospital admission and then gradually increased the dose. During the time of application of amphotericin B, the patient had severe vomiting, renal tubular acidosis, and phlebitis, and therefore we were forced to stop the treatment; the total cumulative dose of amphotericin B was 1850 mg. After amphotericin B, we chose 200 mg voriconazole twice a day until the end of her treatment. Clinical improvement was achieved on the 14th day of antifungal therapy. Radiological improvement was observed on the 21st day of antifungal therapy. Because the survival of patients with invasive aspergillosis is poor, there is no consensus about the optimal duration of antifungal therapy. Denning (1998) reported that after clinical improvement, antifungal therapy should be continued for 4 weeks. However, every patient should be evaluated individually. The case treatment course was almost 4 months. The patient had body temperature fluctuations multiple times in the course of treatment, in which her temperature could rise to over 38°C, and then drop to normal without any special treatment such as combined with other antibiotics or antipyretic drugs; the temperature rose for less than 2 h each time. We thought that these kinds of illness changes might be related to the inflammatory response caused by *Aspergillus*. In the course of
treatment, we also found an interesting condition change. The patient received two pulmonary function tests, and the first was on the third day of hospital admission, and the result was obstructive ventilatory disorder and the bronchial dilation test was negative. During treatment of Aspergillus, her condition improved, and her bronchial dilation test was positive in the second pulmonary function test. These two different results suggested that before the treatment of Aspergillus, the large white moss obstructed her airway resulting in obstructive airway disorders and the negative bronchial dilation test. However, as the disease was controlled, the white moss disappeared in her airway, and the airway manifested hypersensitivity to Aspergillus, in a manner similar to that observed in asthma, and the bronchial dilation test was positive. Therefore, we can infer that the pharynx itching and watery nasal discharge at the onset of the infection were allergic manifestations to Aspergillus; the high sensitivity to Aspergillus and inhaling large amounts of strong state A. fumigatus can induce invasive pulmonary aspergillosis. In this case, we suggest a hypothesis that if the patient had the correct treatment she may be considered an allergic bronchopulmonary aspergillosis (ABPA) patient and not an IPA patient. ABPA and IPA may represent different stages of the same disease, but this hypothesis needs further validation. In the study of Clancy and Nguyen (1998), all the patients had advanced infections at the time of diagnosis and died a short time after hospitalization. They concluded that acute community-acquired pneumonia due to aspergillosis is a rare infection in immunocompetent hosts, and that it carries a uniformly fatal prognosis (Clancy and Nguyen, 1998).

In conclusion, invasive pulmonary aspergillosis must be considered in immunocompetent patients with pulmonary infiltrates who do not respond to broad-spectrum antibiotics. Fungal hyphae recovered from sputum stains in such a setting cannot be routinely dismissed as contamination.

Conflicts of interest

The authors declare no conflict of interest.

REFERENCES


