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Case Report

Disseminated invasive aspergillosis in an apparently immunocompetent host

Nadeem Sajjad Raja, Nishi Nihar Singh

Department of Medical Microbiology, University of Malaya Medical Center, Kuala Lumpur, Malaysia

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Aspergillosis is a spectrum of diseases caused by members of the genus *Aspergillus* that continues to pose a significant threat to immunocompromised, organ transplant, neutropenic and cancer patients. In view of increasing risk factors leading to invasive aspergillosis, it is imperative for clinicians to be familiar with the clinical presentation, diagnostic methods and management of the disease. We describe a 34-year-old immunocompetent male patient receiving chemotherapy for *Aspergillus fumigatus* infection that had disseminated to lung, liver and spleen. A computed tomogram of thorax and abdomen showed thick-walled cavities of different sizes with air fluid levels, consolidation in both lungs and involvement of liver and spleen. His broncheoalveolar lavage and sputum specimens yielded *A. fumigatus*. Successful treatment of this infection was achieved with amphotericin B and itraconazole.

Key words: Antifungal agents, aspergillosis, *Aspergillus fumigatus*, diagnosis, fungal lung diseases

Introduction

Invasive aspergillosis remains the most invasive fungal infection worldwide despite ongoing improvements in medical therapy. A 14-fold increase in invasive aspergillosis cases has been reported in a teaching hospital in Germany [1]. Invasive aspergillosis has been reported in patients with profound neutropenia or patients with any form of immunodeficiency. However, invasive aspergillosis is rarely found in immunocompetent patients. Disseminated aspergillosis is a life-threatening rapidly fulminant illness, which involves 2 or more vital organs of the body [2-8]. It has been on the rise over the last decade. We report a case of disseminated invasive aspergillosis caused by *Aspergillus fumigatus* in an apparently immunocompetent host from the University of Malaya Medical Center, Kuala Lumpur, Malaysia.

Case Report

A 34-year-old male blacksmith presented with a 1-week history of intermittent fever, shortness of breath, cough with sputum and loss of appetite and weight. There was no significant past tuberculosis history or other medical illness. The patient did not drink alcohol. He had been a chronic smoker (10 cigarettes/day). On examination, the patient was afebrile with a pulse rate of 90/min, blood pressure 117/75 mm Hg and respiratory rate 24/min. He produced copious amount of green-colored sputum. Bilateral generalized crepitations and occasional rhonchi were noted on auscultation. Oxygen saturation was 93%. Chest radiograph illustrated widespread haziness bilaterally and bullae in the right mid-zone. Other laboratory investigations were: hemoglobin, 121.2 mg/L and platelet, 615×10^9/L. Serum levels of electrolytes were decreased (sodium, 133 mmol/L; chloride, 97 mmol/L), while potassium was within normal limits. Liver function tests were abnormal [albumin, 25 g/L; alkaline phosphate, 629 IU/L (normal range, 50-136 IU/L); total bilirubin, 19 μmol/L; lactate dehydrogenase (LDH), 218 IU/L]. Erythrocyte sedimentation rate (135) and C-reactive protein [CRP; 14.2 mg/dL (normal range, 0.05-0.8 mg/dL)] were markedly increased. On the basis of the chest X-ray and an increased white blood cell (WBC) count of 19.9×10^9/L (neutrophils 90%, lymphocytes 6%), a diagnosis of bronchopneumonia was made. Amoxicillin-clavulanic acid was started initially, but discontinued

Corresponding author: Dr Nadeem Sajjad Raja, Department of Medical Microbiology, University of Malaya Medical Centre, Kuala Lumpur 59100, Malaysia.
E-mail: rajanadeem@um.edu.my

after 3 days as it was unsuccessful. Later, anti-tuberculosis therapy without steroids was administered for 2 weeks. The patient did not show clinical response and remained in the hospital. Cultures of sputum, liver biopsy, bone marrow aspirate and blood (bacterial, viral and mycobacterial) were negative. Serological test for melioidosis was also negative. Computed tomography (CT) scan of thorax and abdomen revealed multiple anterior mediastinal and pretracheal lymph nodes, multiple thick-walled cavities of different sizes with air fluid levels and surrounding consolidations in both lung fields. The spleen and liver were enlarged with multiple small low attenuation areas. These findings were suggestive of systemic fungal infection. Bronchial washings were collected at bronchoscopy. Both washings and sputum grew *A. fumigatus* on Sabouraud dextrose agar. Human immunodeficiency virus results were negative. Clinical laboratory result showed T cell count (1464 cell/μL) within normal range (i.e., 928-2379 cells/μL). Histopathology of bone marrow revealed no obvious granulomas or abnormal clump of cells seen. Reticulous fibers were not increased.

Treatment with amphotericin B (1.0 mg/kg/day, total 42 mg/day) was initiated. The fever showed downward trend on day 4 of antifungal therapy. At 1 week, fever subsided and there was reduction in the volume of sputum. Amphotericin B was substituted with itraconazole 200 mg twice daily after 2 weeks. The patient showed clinical improvement and repeated sputum and bronchoalveolar lavage specimens remained sterile. He was ultimately discharged well and received oral itraconazole (200 mg twice daily) maintenance therapy for 1 year.

Discussion

Aspergillus is a spore-forming (conidia) saprophytic thermotolerant fungus, commonly found in soil, organic debris, and dust, spices and decaying vegetable matter. There are approximately 200 species of ubiquitous *Aspergillus* with airborne conidia in the world and *A. fumigatus* is the most commonly isolated pathogen in this group. The conidia are released into the atmosphere and can easily reach the lung alveoli due to their small size (2-3 μm). The most frequent site of human infection is the lung, followed by the liver, spleen, heart, bones, central nervous system, sinuses, ear, eye, oesophagus, urinary tract and lymph nodes [3,9,10]. Aspergillosis disease has 3 well-known forms: 1) pulmonary aspergillosis (bronchopulmonary allergy or aspergillosis), a local form of disease; 2) invasive aspergillosis, a complication of chronic lung disease; and 3) disseminated aspergillosis.

Marked neutropenia is the most common risk factor in disseminated aspergillosis. Nevertheless, patients with acute haematological malignancies or other malignancies and receiving cytotoxic treatment, bone marrow and organ transplant recipient and those receiving high doses of corticosteroids are at risk of acquiring disseminated invasive aspergillosis. Other predisposing features include congenital or acquired immunodeficiency, diabetes, chronic granulomatous disease, cytomegalovirus infection, alcoholism and parental antibiotic therapy.

Invasive aspergillosis is rarely found outside the above-mentioned groups or the immunocompetent and patients who are mildly immunocompromised, such as those with chronic liver disease or diabetic ketoacidosis [2,8-12]. However, invasive aspergillosis has been increasing in patients with advanced chronic obstructive pulmonary disease, particularly when treated with oral corticosteroids [13]. *Aspergillus* spp. cause pulmonary aspergillosis in the presence of already pre-existing lung cavity secondary to bullae, bronchial cyst, neoplasm, tuberculosis, pulmonary infarction and ankylosing spondylitis [9]. In our patient, chest X-rays showed pre-existing pulmonary cavity formed secondary to bullae. Other underlying conditions predisposing to disseminated invasive aspergillosis were also ruled out. He had no T-cell dysfunction and had not received antibiotics. Our patient's laboratory findings revealed no evidence of neutropenia or immunosuppression. However, his smoking history might have contributed to some abnormalities in the pulmonary defense mechanism. This case highlights the fact that aspergillosis can occur in patients with bullae even in the absence of an immunocompromised state, corticosteroid or cytotoxic therapy and neutropenia.

The respiratory tract remains the primary focus of aspergillosis as a result of the inhalation of infectious spores. The common clinical features of fever, cough, malaise, weight loss and dyspnoea are non-variable, nonspecific and consistent with bronchopneumonia. In our patient's case, there was no clinical improvement despite antimicrobial and antituberculosis therapy. Differential diagnosis of aspergillosis should be considered in patients not responding to antimicrobial therapy or antituberculosis therapy. The outcome in invasive aspergillosis is directly linked with early diagnosis and treatment [6]. Elevated levels of bilirubin,

LDH and CRP are occasionally seen — although these are considered as nonspecific findings — while WBC counts are usually normal [14-16]. High levels of LDH, bilirubin, WBC and CRP were observed in our patient.

The diagnosis of invasive aspergillosis remains difficult even today; a high degree of suspicion is imperative in patients with risk factors. Unfortunately, there is no single test available to establish definitive diagnosis of aspergillosis infections. However, features currently regarded as diagnostic tools in invasive aspergillosis include: 1) histopathologic evidence of disease; 2) positive culture; 3) positive CT scan or magnetic resonance imaging; 4) detection of *Aspergillus* antigen in serum; 5) polymerase chain reaction; and 6) chest X-ray [12,17-20]. The demonstration of the presence of septate, acute, branching hyphae in the lung tissue specimen along with a positive *Aspergillus* culture from the same site provides the most rubust diagnosis [9]. The isolation of *Aspergillus* spp. from respiratory tract specimen is controversial because a patient may aspirate spore and a sample may be contaminated after collection. Also, plate contamination with *Aspergillus* spp. is common in clinical laboratories.

There is a risk that *A. fumigatus* with clinical relevance may be underestimated [21]. Treger et al revealed that repeated isolation of the same species would usually occur only in patients in whom the fungus is growing in the lower respiratory tract [19]. Broncheoalveolar lavage (BAL) specimen for fungal smear and culture is usually helpful in invasive aspergillosis diagnosis in patients with diffuse lung involvement and the specificity of a positive result is very high (i.e., 97%) but sensitivity is approximately 30-50% [22]. Horvath and Dummer found higher sensitivity (77%) in positive cultures of BAL specimens from invasive aspergillosis cases [23]. Blood cultures rarely yield positive results [24].

Chest radiograph shows nonspecific changes. CT scan in the early stages of infection may be the first definitive suggestion of diagnosis and may depict signs of infection like halo due to hemorrhagic necrosis surrounding the fungal lesion [25-28]. In our patient, CT scan provided confirmed diagnosis of disease. *A. fumigatus* was isolated from BAL and sputum specimens later. CT scan showed direct involvement of liver and spleen. Altered liver function results concurred with CT scan findings. Liver biopsy specimen was collected after 2 weeks of antifungal therapy and remained sterile. We hypothesize that intravenous amphotericin B might have arrested the disease progression and interfered with culture results.

Serological diagnosis by enzyme-linked immunosorbent assay test has been established by measuring the presence of antigen in invasive aspergillosis patients [29]. It has shown high sensitivity (89.7%) and specificity (98.1%) in screening of high-risk patients for the establishment of *Aspergillus* infection [30].

Amphotericin B is still widely used and considered as drug of choice for patients with invasive aspergillosis. The favorable outcomes are associated with early diagnosis and aggressive therapy. In 1 study, the overall response rate in patients with aspergillosis to amphotericin B was 30-50%. The recommended dosage of amphotericin B is 0.6 to 1.2 mg/kg/day, but higher dosage up to 1.5 mg/kg/day may be initiated in severely immunocompromised patients. Amphotericin B has considerable side effects, including electrolyte disturbances, nephrotoxicity and hypersensitivity reactions [9,31,32]. Liposomal amphotericin B and lipid complex amphotericin B have been introduced to overcome the adverse effects of amphotericin B. The use of liposomal amphotericin B allows higher doses to be administered in patients who are at high risk for nephrotoxicity during amphotericin B therapy or have a poor response to the therapy [9].

Itraconazole is a reasonable alternative to amphotericin B; it is used for treatment of invasive aspergillosis in less immunocompromised patients. Itraconazole is available in oral, suspension and intravenous formulations. It is also beneficial to use itraconazole (200 mg twice daily) in the late stages of therapy after the initial control of infection with amphotericin B [9,32]. Clinical efficacy has also been demonstrated with voriconazole, posaconazole and other antifungal agents such as ravuconazole, echinocandins, caspofungins, micafungin, anidulafungin and terbinafine [17,32,33].

The recovery was eventful with amphotericin B in our patient, who was switched to itraconazole after 2 weeks, for 1-year maintenance therapy. The optimal duration of treatment must be determined empirically and depends on the extent of invasive aspergillosis, the response to therapy and the immune status of the patient. In general, the less immunocompromised the patient, the longer the time required to evaluate the response to therapy [34,35].

Disseminated invasive aspergillosis is rare in immunocompetent patients. Clinical suspicion of the condition in patients who do not respond to antibiotic

or antituberculosis therapy is imperative for early diagnosis, allowing aggressive antifungal therapy and increasing the chance of a favorable outcome.

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