Case Report

Fatal hemoptysis from invasive *Aspergillus niger* in a patient with cavitary lung disease and *Mycobacterium avium complex* infection

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Invasive aspergillosis typically afflicts immunocompromised patients, whereas pulmonary aspergilloma is a recognized complication of pre-existing cavitary lung disease in immunocompetent hosts. In both cases, the most prevalent pathogens are *Aspergillus fumigatus* and *Aspergillus flavus*. We describe a case of fatal hemoptysis from invasive *Aspergillus niger* infection in the setting of bullous lung disease, steroid-treated sarcoidosis, and *Mycobacterium avium complex* infection. This report highlights the potential for *A. niger* to cause invasive disease in conjunction with other pathologic processes in the lung.

**Keywords** Mycobacterium avium complex, Aspergillus niger, hemoptysis, aspergillosis, sarcoidosis

Invasive pulmonary aspergillosis typically afflicts patients with profound immune compromise such as that caused by bone marrow transplantation [1]. In contrast, pulmonary aspergilloma is a recognized complication of cavitary disease of the lung resulting from mycobacterial disease and sarcoidosis in immunocompetent hosts [2,3]. In each instance, *Aspergillus fumigatus* and *Aspergillus flavus* are the most prevalent pathogens. We report a case of invasive pulmonary aspergillosis caused by *Aspergillus niger* in a young female smoker with *Mycobacterium avium complex* (MAC) infection of the lungs, sarcoidosis, and immunosuppression from steroids given for obstructive lung disease. Fatal hemoptysis from *A. niger* in the setting of cavitary MAC disease has never been reported previously. This report underscores the importance of having a high level of clinical suspicion for invasive aspergillosis from *A. niger* in patients with cavitary lung processes, even when immunocompromise is relatively modest.

**Case report**

A 42-year-old female with chronic bronchitis and sarcoidosis diagnosed on the basis of granulomata identified on mediastinal lymph node biopsy nine years previously came to the emergency department with one month of progressive exertional dyspnea, cough, fevers, wheezing, and scant hemoptysis on the night before evaluation. She had received between 40 mg and 60 mg of prednisone daily in one-week courses four times in the five months preceding presentation, most recently 38 days prior to presentation. Recent pulmonary function testing showed a forced expiratory volume in 1 second (FEV₁) of 0.95 (36% predicted), forced vital capacity (FVC) of 1.49 (44% predicted), FEV₁/FVC 64%, and a diffusing capacity of carbon monoxide (DLCO) of 8.6 (37% predicted). She had a 40 pack-year smoking history.

On admission, oxygen saturation was 95% on air, and temperature was 37.6°C. Severe wheezing was
audible bilaterally. The white blood cell count was 19,200/μl with 82% neutrophils. A chest radiograph showed a new round, air-filled opacity with surrounding edema in the left lung superimposed on chronic bilateral interstitial thickening and apical emphysematous changes compared to a film 6 months earlier. Chest computed tomography is shown in Fig. 1. Sputum Gram stain showed many white blood cells and moderate Gram positive cocci in pairs and grew *Mycobacterium avium* complex (MAC) as well as *A. niger*. At bronchoscopy, a moderate amount of purulent drainage originated from the superior segment of the left upper lobe. Acid-fast staining of lavage fluid showed 1+ concentrated organisms later characterized in culture and by PCR as MAC. Fungal culture of lavage fluid grew moderate *A. niger*. Clarithromycin, ethambutol, and rifabutin were started. The patient defervesced, regained a normal white blood cell count, and was discharged after receiving 6 days of antibiotic therapy. Treatment with an antifungal agent was deferred at this time given her clinical improvement on a MAC treatment regimen, and the suspicion by some clinicians that *A. niger* was not the etiologic agent in this case.

One week later, the patient presented with worsening cough, wheezing, chills, and exertional dyspnea. Temperature was 38.4°C and oxygen saturation at rest on air was 89%. Laboratory studies revealed a leukocytosis of 24,000/μl with 84% neutrophils and 7% band forms. A repeat chest CT showed interval development of left lower lobe airspace disease and intracavitary necrosis. She was hospitalized and continued on clarithromycin, ethambutol, and rifabutin, and had piperacillin/tazobactam added for a presumptive diagnosis of nosocomial pneumonia. Bronchoscopy with lavage of the superior segment of the left upper lobe and transbronchial biopsies of the cavity wall were performed. No bacteria were identified on Gram stain or culture, but acid-fast staining of the BAL fluid showed 2+ concentrated organisms, and *A. niger* was grown in fungal culture after 6 days. Transbronchial specimens were sent for histopathology, fungal stain and culture, and acid fast stain. The patient had a negative HIV test.

On the second hospital day, the patient experienced two episodes of hemoptysis totaling approximately 5 ml, and her respiratory distress worsened. Given her clinical decline, liposomal amphotericin B (AmB) was initiated. Biopsy results returned, showing no fungal mycelia or acid-fast bacilli in technically adequate core sections. Macrophages were described as being laden with intracellular crystalline refractile material. A galactomannin test was not performed. The patient endured a night of prominent wheezing and chest tightness for which intravenous methylprednisolone was given, followed by 40 mg of prednisone daily. The patient was receiving antibiotic, antifungal, and anti-MAC therapy at this juncture. Hypoxemia, wheezing, coughing, and fevers improved dramatically in the ensuing few days. AmB was stopped again after five days of treatment as her clinical rebound was attributed by some clinicians to the introduction of corticosteroids and the use of piperacillin/tazobactam.
for bacterial superinfection of pre-existing cavitary lung disease. However, on hospital day 11, she experienced cardiac arrest in the context of massive hemoptysis. Emergent selective pulmonary arteriography with embolization of multiple arteries was done, but despite this intervention, she died from massive hemoptysis on hospital day 12.

At autopsy, sections through the left upper lobe revealed a thick-walled, lobulated cavity containing coagulated blood, *Aspergillus* fruiting bodies, and conidia (Fig. 2). Visualization of acute-branching, nonpigmented, septate hyphae surrounded by necrotic lung tissue and growth of the organism in culture supported invasive disease [4]. The paraesophageal lymph nodes, liver, spleen and lung contained non-caseating granulomata devoid of any microorganisms by special staining, suggestive of a diagnosis of sarcoidosis.

**Discussion**

*Aspergillus* species cause a spectrum of disease in humans, ranging from airway colonization to mycetoma to life-threatening tissue invasion. Aspergilloma and chronic necrotizing pulmonary aspergillosis (CNPA) are known sequelae of cavitary tuberculous infection of the lungs, occurring with a frequency of 11–72% [1,5]. *Aspergillus* superinfection of cavitary lung disease caused by non-tuberculous mycobacteria including MAC has also been described [6,7], although never involving *A. niger*. Here we report a case of fatal massive hemoptysis due to invasive pulmonary *A. niger* in a patient with MAC infection, obstructive lung disease, and sarcoidosis.

The combination of *A. niger* and MAC is unusual: we identified one case report of CNPA from *A. niger* and MAC [8], and one report of *A. niger* mycetoma in an elderly man with chronic obstructive pulmonary disease and treated MAC lung infection [9]. In the latter case, however, cultures and staining of bronchoalveolar lavage and sputum were negative for mycobacteria, and instead *Pseudomonas maltophilia* was isolated later in the clinical course.

As further support of the likely pathogenicity of *A. niger* in our case, intracavitary tissue sections revealed crystals that polarized in a fashion suggestive of calcium oxalate. *A. niger* infection is associated with the production of the mycotoxin oxalic acid, which forms calcium oxalate and may exert its toxicity through the formation of reactive oxygen species at membrane surfaces [10]. Fatal pulmonary oxalosis linked to *A. niger* has been documented in a patient with *Mycobacterium tuberculosis* infection and pneumoconiosis [11], but not in the setting of MAC infection. When conidia and material consistent with calcium oxalate are noted on BAL fluid without the presence of fungal hyphae, *A. niger* infection and non-colonization should be considered [12].

This case demonstrates that *A. niger* can be an invasive pathogen in cavitary lung disease, including that caused by MAC. The finding of calcium oxalate on bronchial washings can be, in the appropriate clinical scenario, a clue to infection with *A. niger*. In selected cases of suspected *A. niger* infection of nontuberculous...
cavitary lung disease, empiric therapy should be considered while seeking a tissue diagnosis.

References