

A PEER-REVIEWED ARTICLE

Aspergillosis: an unusual pathogen in HIV

Ronald D. Wilcox, MD, FAAP

Aspergillosis is a term used to describe infection with one of the pathogenic species of *Aspergillus*, a fungus found in environmental material such as soil or decaying vegetation. When a person has a normal immune system, the fungus is controlled by the immune cells and rarely causes disease. If a patient has a problem with his/her immune system, *Aspergillus* acts as an opportunistic infection and can cause a variety of disease states. The clinical presentation of the disease may differ, though, depending on the type of immune compromise present. Most commonly, aspergillosis occurs in patients who have received transplantation or those with leukemia or lymphoma, but *Aspergillus* species can also cause infections in patients with other causes of low neutrophil counts, such as patients with advanced AIDS. The three species of *Aspergillus* most commonly associated with pathogenesis in humans include *A. fumigatus*, *A. flavus*, and *A. niger*.

Risk factors for aspergillosis include prolonged neutropenia (a low count of neutrophils), high dose or prolonged use of corticosteroids, broad-spectrum antibiotic therapy, diabetes mellitus, marijuana smoking, underlying lung disease, and the presence of other opportunistic infections. When immunocompromised patients are in areas where construction is occurring, an increased incidence is seen. Invasive aspergillosis is a relatively unusual infection in HIV but should be considered in the right setting; the Adult and Adolescent Spectrum of HIV Disease Project by the CDC showed an incidence among 35,252 HIV-infected patients of 3.5 cases per 1000 person-years. The incidence was highest in patients ≥ 35 years of age and those with CD4 counts < 100 cells/mm³.

Aspergillus usually first enters the body by inhalation of spores; therefore most infections involve either the sinus or pulmonary tract. The five pulmonary manifestations of aspergillosis in an HIV-infected patient include allergic bronchopulmonary aspergillosis, fungal ball or mycetoma in a pre-existing cavity, invasive aspergillosis, chronic necrotizing aspergillosis, and tracheitis.

A. Allergic bronchopulmonary aspergillosis occurs most commonly in HIV-infected patients with a history of asthma or atopic dermatitis and is manifested by wheezing, pulmonary infiltrates, eosinophilia, and bronchial plugging. The host's immune response to the presence of *Aspergillus* in the airways is the pathogenesis of this disease, therefore the treatment is steroids to suppress the immune response rather than treatment of the fungus itself.

B. A mycetoma or fungal ball usually develops in a pre-existing lung cavity, such as from prior tuberculosis, when the spores lodge in the cavity and subsequently grow. The fungus is rarely invasive in this form of disease and the pathogenesis of this form of disease is usually related more to the underlying pathology that created the cavity. Radiography may exhibit an "air crescent sign" within the cavity. Treatment is usually surgical intervention for the affected area.

C. Invasive aspergillosis develops when the fungus disseminates into the lung tissue itself, leading to chronic cough, rarely hemoptysis, shortness of breath, and chest pain, and is frequently accompanied by systemic complaints such as weight loss and high fever. Hyphae of the fungus can invade into blood vessel walls, resulting in inflammation

of the vasculature with resultant hemorrhage, thrombosis, and necrosis of the tissue. Radiologically, invasive aspergillosis presents as a consolidation with a haziness extending into surrounding tissue, sometimes referred to as a “halo sign.” Invasive disease may also disseminate, with the manifestations reported later in this article. Treatment requires long-term antifungal therapy and may require surgical intervention.

D. Chronic necrotizing aspergillosis is a semi-invasive form of pulmonary disease seen predominantly in patients with underlying lung pathology, such as bronchiectasis or COPD, or diseases causing immune suppression such as AIDS or alcoholism. In AIDS patients, it may be diagnosed at autopsy and may not be the primary cause of death but an incidental finding. The clinical presentation usually includes several months of productive cough, fever, and weight loss. Only 10% of patients present with hemoptysis.

E. Tracheitis with *Aspergillus* is a rare manifestation of infection and is found predominantly in patients with AIDS but there are increasing reports of incidence in patients with hematologic diseases. The patient may present with cough, fever, chest pain, dyspnea, and upper airway obstruction. Diagnosis is usually via bronchoscopy with visualization of white patches on the airway tissue and histologic examination of biopsy.

In patients with AIDS and severe neutropenia, the aspergillosis may cause disease outside the pulmonary tract. The most common site of extrapulmonary disease is the central nervous system. The infection may present as a ring-enhancing lesion that appears like an abscess in the brain on radiologic examination, found in a patient with new onset seizures, focal neurologic deficits, mental status changes, or headache. The *Aspergillus* can be more invasive into the tissue and lead to hemorrhagic or mycotic aneurysms. Reports of other sites of invasive aspergillosis include sinusitis, skin abscesses, endocarditis, myocarditis, renal abscesses, pancreatic abscesses, esophagitis, osteomyelitis, and endophthalmitis with resultant glaucoma.

Diagnosis of aspergillosis can be very difficult and care must be taken to differentiate colonization versus pathogenic infection when cultured in patients with AIDS. *Aspergillus* seen on biopsy should be considered pathogenic and isolation from otherwise sterile sites such as cerebrospinal fluid, blood, bone marrow, or extra-pulmonary organs should also always be considered pathogenic. The clinical picture must be considered, though, when *Aspergillus* species are isolated on sputum cultures or cultures obtained from broncho-alveolar lavage. To complicate matters more, only 10-30% of patients with invasive pulmonary aspergillosis actually have isolation on sputum culture of the organism. Ideally a transbronchial biopsy is the most conclusive evidence that invasive aspergillosis is occurring in a patient with AIDS.

Galactomannans (GM) have been measured in serum and broncho-alveolar lavages (BAL) to determine the positive predictive value of isolation of *Aspergillus* species and invasive disease. Pasqualotto *et al* found that a cut-off BAL GM level of 1.5 improved the sensitivity (100%) and specificity (90.4%) of the assay as compared to a level of 0.5 when studied in lung transplant patients. Caution must be exercised when interpreting a positive galactomannan level in serum because false positives have been reported when a patient is receiving piperacillin/tazobactam and amoxicillin/clavulanate; other fungal infections seen in HIV such as cryptococcosis, penicilliosis, and histoplasmosis can also raise galactomannan levels. Galactomannan levels have been proposed as a means of following response to therapy for fungal infections.

Treatment for invasive aspergillosis can be very challenging but newer medications have been shown to have better efficacy. The current drug-of-choice for the treatment of invasive aspergillosis is voriconazole. When voriconazole was compared to standard

amphotericin B at 12 weeks, the voriconazole group had a greater likelihood of complete or partial response (53% vs 32%), a lower mortality rate (29% vs 42%), less likelihood of need to change to another antifungal because of poor response or intolerance (36% vs 80%), and a lower overall rate of severe adverse reactions. However, a direct comparison of lipid formulation amphotericin versus voriconazole has not been reported in the literature. Central nervous system *Aspergillus* infections seem also to have a lower mortality rate when treated with voriconazole. The recommended dose is 6 mg/kg IV twice daily on day one followed by 4 mg/kg twice daily on subsequent days. Because HIV medications may alter the levels of voriconazole, trough levels should be monitored with the goal of a trough between 1.0-5.5 mg/L. When the patient is ready to be placed on po medications, dosing can either be at 200 or 300 mg twice daily. There have been reports of isolates of *A. fumigatus* with resistance to voriconazole.

Alternative possible agents for therapy include posaconazole, itraconazole, amphotericin B (conventional formulation and lipid formulations), and the echinocandins. Retrospective studies comparing the combination of echinocandins with either azoles or amphotericin B suggest possibly an improvement in mortality or efficacy in patients with hematologic malignancies or transplantation but larger prospective studies are needed before this can become common clinical practice.

Surgical intervention is often required, in addition to medical management, for treatment of invasive disease, such as in cases of sinusitis, pericardial infection, empyema, chest wall invasion from pulmonary lesion, necrotic cutaneous lesions, pulmonary nodules in close proximity to the pericardium or major vessels, endocarditis, persistent hemoptysis, osteomyelitis, and central nervous system lesions.

Although aspergillosis is a rare complication of AIDS, the HIV care provider must consider the organism in the differential of an apparent infectious complication, especially in the setting of pulmonary disease or central nervous system lesions in those with low CD4 counts. Diagnosis can be challenging and different modalities, including galactomannans, histology, and culture, may need to be used to diagnose the disease. The drug of choice for treatment, voriconazole, has many drug interactions with HAART, so the HIV care clinician needs to explore possible interactions when prescribing voriconazole or when making a change in the antiretroviral regimen.❖

BIBLIOGRAPHY

- Holding KJ, Dworkin MS, Wan PCT *et al.* Aspergillosis among people infected with human immunodeficiency virus: incidence and survival. *Clin Inf Dis* 2000;31:1253-7
- Huang YT, Hung CC, Liao CH *et al.* Detection of circulating galactomannan in serum samples for diagnosis of *Penicillium marneffei* infection and cryptococcosis among patients infected with human immunodeficiency virus. *J Clin Microbiol* 2007 Sep;45(9):2858-62
- Lin CY, Sun HY, Chen MY *et al.* Aetiology of cavitary lung lesions in patients with HIV infection. *HIV Medicine* 2009;10:191-8
- Oosten AW, Sprenger HG, van Leeuwen JTM *et al.* Bilateral renal aspergillosis in a patient with AIDS: a case report and review of reported cases. *AIDS Patient Care STDs* 2008;22(1):1-5.
- Paula JS, Junior AB, Filho AL, Romao E. Secondary glaucoma associated with bilateral *Aspergillus niger* endophthalmitis in an HIV-positive patient: case report. *Arq Bras Oftalmol* 2006;69(3):395-7
- Pineau S, Talarmin JP, Morio F *et al.* Contribution of molecular biology and *Aspergillus* galactomannan antigen assay for the diagnosis of histoplasmosis. *Med Mal Infect* 2009 Nov 27, e-pub.
- Prasad R, Garg SR. Progressive increase in cavitation with the evolution of fungus ball: a clue to the diagnosis of chronic necrotizing pulmonary aspergillosis. *Lung India* 2009 Jul;26(3):95-7
- Sugar AM. Treatment of invasive aspergillosis. www.UpToDate.com, accessed 08-11-10. Article last updated June 17, 2010.
- Tauber MG, Lee BL. Aspergillosis (Chapter 6.6). *The AIDS Knowledge Base, 2nd Edition. 1994. Pp. 6.6-1-6.6-6.*

Ronald Wilcox is Project Director/Principal Investigator, Delta Region AETC, and Associate Professor of Medicine, Pediatrics, and Public Health, LSUHSC School of Medicine.