Endocarditis Caused by *Aspergillus* Species in Injection Drug Users

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*Aspergillus* endocarditis is a rare event; a very few cases have been reported in injection drug users (IDUs) and patients infected with human immunodeficiency virus (HIV). We report 2 proven cases and 1 highly suggestive case of *Aspergillus* endocarditis in IDUs, 2 of whom were infected with HIV, and discuss some related clinical and pathogenic aspects.

Invasive aspergillosis is an opportunistic infection with a high mortality rate that usually occurs in the immunocompromised host [1]. Several risk factors have been associated with the acquisition of invasive aspergillosis, including neutropenia, cardiac surgery, organ transplantation, and prolonged treatment with high doses of corticosteroids or antineoplastic and immunosuppressive agents.

Invasive aspergillosis most frequently affects the respiratory tract, the CNS, and the eyes [1]. *Aspergillus* endocarditis is, accordingly, quite rare; it is a very rare manifestation of invasive aspergillosis in injection drug users (IDUs), both those with and those without HIV infection [2, 3]. We describe 3 cases of *Aspergillus* endocarditis in IDUs, 2 of whom were infected with HIV, and discuss some related clinical and pathogenic aspects of the infection.

**Case reports.** Patient 1 was a 35-year-old man, an IDU infected with HIV since 1989 but without prior major opportunistic infections (stage B3, according to the Centers of Disease Control and Prevention classification). He was admitted to our hospital in January 1992 with a 15-day history of fever and weakness. He had never received antiretroviral therapy and he had not been treated with antibiotic therapy before admission to the hospital. At the time of admission his temperature was 38.5°C, and a cardiac 2/6 holosystolic murmur was audible along the left sternal border. The electrocardiogram disclosed a complete right bundle block. A chest radiograph showed multiple areas of consolidation in the middle and upper right lung. A transthoracic echocardiogram (TTE) showed a large (5 cm × 4 cm) and mobile pedunculated mass on the tricuspid valve (figure 1A). All blood cultures were persistently negative for bacteria and fungi. Laboratory tests revealed the following values: WBC count, 4.7 × 10⁹ cells/L, with 66% neutrophils; hemoglobin, 7.7 g/dL; platelet count, 62 × 10⁹ cells/L; erythrocyte sedimentation rate (ESR), 47 mm/h; and CD4⁺ T cell count, 121 cells/mm³.

On the second day of the patient’s stay in the hospital, antibiotic treatment was initiated with penicillin (2 million U daily) and netilmicin (300 mg iv daily), but the patient’s temperature did not decrease and his clinical condition rapidly worsened. On the fourth day, he died of cardiogenic shock. The autopsy confirmed the large pedunculated mass on the tricuspid valve and the multiple septic infarctions in the right lung. Macroscopic examination of other organs and the CNS found no pathologic lesions. Histopathologic examination of a section of the cardiac mass revealed active endocarditis, and staining revealed fungal hyphae (figure 1B). Culture of specimens of the endocardial vegetations grew *Aspergillus fumigatus*.

Patient 2 was a 31-year-old man, an IDU not infected with HIV, and a greengrocer. He was admitted to our hospital in September 2000 with a 1-month history of weakness and fever that were unresponsive to antibiotics. At the time of admission, his temperature was 38.5°C, and an aortic 3/6 diastolic murmur was audible. Laboratory tests revealed the following values: WBC count, 13.5 × 10⁹ cells/L; hemoglobin, 10.2 g/dL; platelet count, 177 × 10⁹ cells/L; and ESR, 90 mm/h. Renal function tests revealed a mildly elevated creatinine level (150.3 μM/L).

A chest radiograph appeared normal. A TTE showed a large vegetation (2 cm × 2 cm; figure 1C) on the aortic valve with moderate to severe aortic insufficiency and dilated left ventricle. Blood cultures were negative for bacteria and fungi. A latex test was negative for *Aspergillus* antigen, and serologic tests were negative for *Aspergillus* antibodies. Empirical treatment was initiated with oxacillin (12 g daily) and netilmicin (150 mg iv daily).

Twelve days after admission, the patient complained of pain in the left lower limb, examination of which revealed pale skin and an absent pulse. An angiograph showed a large embolus occluding the origin of the common iliac arteries. The patient...
underwent embolectomy. *Aspergillus niger* was identified by culture of the embolus.

Treatment was initiated with a lipid formulation of amphotericin B (3 mg/kg iv daily). After 2 days of treatment, the clinical condition of the patient improved and the fever disappeared. He was referred to a cardiothoracic surgery unit for aortic valve replacement. Three days after admission to the unit, before surgery, the patient was found to have left hemiplegia and was in a coma. A CT scan of the brain showed a large hypodense lesion with peripheral enhancement in the right parietal-occipital region. Twelve hours after the onset of coma, the patient died.

Patient 3 was a 39-year-old man, an IDU infected with HIV, who was admitted in July 1994 to a general hospital with a 30-day history of fever and dyspnea. His HIV status was not determined, although he was aware of having been infected since 1993. At the time of admission, his temperature was 39°C, and a 2/6 diastolic murmur was audible along the right sternal border. Laboratory tests revealed leukopenia (2.1 × 10^9 cells/L; 77% neutrophils), normochromic normocytic anemia (hemoglobin concentration, 8.3 g/dL), a low platelet count (18 × 10^9 cells/L). His ESR was 98 mm/h, and his CD4^+ T cell count was 72 cells/mm^3. Measurement of arterial blood gas revealed hypoxemia and hypocapnea. A chest radiograph showed bilateral pulmonary infiltrates and bilateral pleural effusions.

A presumptive diagnosis of *Pneumocystis carinii* pneumonia was made and treatment was initiated with trimethoprim-sulfamethoxazole (trimethoprim, 15 mg/kg/day; sulfamethoxazole, 80 mg/kg/day), but the patient’s clinical condition did not improve. Ten days after admission, cultures of 4 blood samples were positive for *Candida parapsilosis*. A TTE showed a mobile mass attached to the aortic valve that was associated with a severe aortic regurgitation. Therapy was initiated with fluconazole (600 mg iv daily), and the patient was referred to our infectious disease institute with the diagnosis of endocarditis caused by *C. parapsilosis*. The patient’s clinical condition progressively worsened, and he died 4 days after admission as a result of cardiogenic shock. Autopsy revealed a dilated left ventricle, a large vegetation on the aortic valve with valve fissuration, and multiple foci of bronchopneumonia in the right lung. Microscopic examination of the endocardial vegetation did not confirm the presence of *Candida* species but revealed an invasive mass of branching and septate hyphae, highly suggestive of *Aspergillus* species (figure 1D).

**Discussion.** Our 3 patients, of whom 2 were IDUs with...
proven *Aspergillus* endocarditis and 1 was an IDU with a fungal infection highly suggestive of *Aspergillus* species comprise a small but interesting series. Few cases of *Aspergillus* endocarditis in IDUs have been described in the literature [2, 3], and some aspects of this entity need further discussion.

Fungal infections may account for 5%–50% of serious infections in IDUs [4], and fungal endocarditis, mostly caused by *non-albicans* species of *Candida*, is uncommon [5]. Although illicit drugs are often contaminated with *Aspergillus* spores [4], the development of invasive aspergillosis, including endocarditis, requires exposure to a critical amount of inoculum that is hard to quantify and may depend upon the immune status of the patient [1].

An interesting feature of our series is the possible link between the work of patient 2, the market greengrocer, and exposure to *Aspergillus* species. In fact, the primary ecological niche of this mold is decomposing vegetable material. In this case, multiple exposures associated with poor hygiene while preparing drugs to be injected may have predisposed the patient to the disease.

The association of *Aspergillus* endocarditis with HIV infection in 2 of our 3 patients is worthy of note. To the best of our knowledge, only 2 such cases have been previously described in the literature [2, 6]. During the course of HIV disease, several aspects of immunological impairment may predispose patients to invasive aspergillosis. Granulocytes are the main source of protection against *Aspergillus* infection. However, during the course of HIV disease, several defects in neutrophil activities have been reported, such as chemotaxis, phagocytosis, and killing of bacteria and fungi, even in patients with a normal granulocyte cell count [7–9]. Regarding monocyte/macrophage-mediated immune responses, it has been shown that HIV infection impairs a number of functions carried out by these cells, resulting in (1) defective phagocytosis of both fungi *Candida albicans* and *Aspergillus fumigatus*, (2) impaired intracellular killing of *Candida pseudotropicalis*, and (3) dysregulation of cytokine production [10].

Other relevant points are the diagnosis and the clinical management of these patients. *Aspergillus* species are rarely isolated from blood culture, and they cannot be isolated until late in the course of infection. Therefore, the diagnosis of *Aspergillus* endocarditis should be strongly pursued for IDUs with negative blood culture results, large valvular vegetations, and evidence of peripheral embolization. In case of embolization, accessible emboli should be cultured and examined histologically to make the diagnosis [1, 5], as we did for patient 2. Microbiological diagnosis of *Aspergillus* endocarditis is difficult; on the other hand, the clinical value of *Aspergillus* antigen or antibody assays and molecular diagnostic techniques still need validation.

The clinical management of endocarditis in IDUs with negative blood culture results should include prompt treatment with amphotericin B, even in the absence of definitive evidence, because any delay in starting therapy is usually fatal [1]. However, in the majority of cases, combined medical and surgical treatments are recommended [1, 5].

In conclusion, this report emphasizes the need to consider a diagnosis of *Aspergillus* endocarditis in IDUs and, especially, in HIV-infected patients with negative blood culture results, and it stresses that the management of endocarditis in IDUs requires considerable clinical skill.

References