A rare, fatal case of invasive spinal aspergillosis in an antiretroviral-naïve, HIV-infected man with pre-existing lung colonization

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Infection of the central nervous system (CNS) is a rare but devastating complication of invasive aspergillosis. We report a case of invasive aspergillosis with spinal involvement in a human immunodeficiency virus (HIV)-infected patient without neutropenia. A 42-year-old, antiretroviral-naïve, HIV-infected man presented with progressive weakness in the lower limbs and urinary and faecal incontinence for 2 weeks. The patient had been prescribed broad-spectrum antibiotics and prednisone. He had upper motor neuron signs and a sensory level at T1, with accompanying neck stiffness on flexion. Magnetic resonance imaging revealed diffuse abnormal signals of the vertebral bodies in the lower cervical and thoracic areas, with cord compression in the C2 and C3 region and signal distortions of the T2 and T3 vertebral bodies. Chest X-ray and computerized tomography demonstrated post-tuberculous apical cavities with suspected fungal colonization. Histopathology of an extradural spinal lesion at T1/T2 suggested invasive aspergillosis. The patient was started on fluconazole in response to the histopathological evidence of *Aspergillus* infection, but died within 3 weeks. Post-mortem analysis of the biopsy sample by PCR identified the infectious agent as *Aspergillus fumigatus*. Atypically, his CD4+ T-cell count was 239 cells mm−3 and he had no evidence of neutropenia. Invasive aspergillosis should be considered as part of the differential diagnosis among HIV-infected patients with non-specific, focal CNS symptoms, even among those without classical risk factors such as neutropenia, and aggressive antifungal therapy should be instituted as early as possible.

Introduction

*Aspergillus* species are the most frequently isolated moulds among human immunodeficiency virus (HIV)-infected patients (Enoch et al., 2006), but invasive aspergillosis is very uncommon in this population (<1%) (Cornet et al., 2002). Despite this low incidence, it is of particular importance because the case-fatality rate associated with disseminated infection or central nervous system (CNS) involvement is reported to be 88% (Lin et al., 2001). Among HIV-infected persons, invasive aspergillosis usually occurs in patients with a CD4+ T-cell count of <50 cells mm−3 and in those with neutropenia or on corticosteroids (Mylonakis et al., 1998). However, CNS aspergillosis has also been described in immunocompetent patients and following epidural steroid injections (Harcol & Chandy, 1993; Larson Kolbe et al., 2007; Saigal et al., 2004; Sundaram et al., 2006). Aspergillosis generally affects the lungs, but can also spread to other organs, including the CNS. Based on a large, randomized–controlled trial, the drug of choice for invasive aspergillosis is voriconazole (Herbrecht et al., 2002). However, a diagnosis of invasive aspergillosis is often only made post-mortem, and a definitive diagnosis requires both microscopic analysis of tissue and identification of the organism by culture (Walsh et al., 2008).

*Aspergillus* infection in the CNS is rare, but appears to be becoming more common (Kleinschmidt-DeMasters, 2002;
We describe a case of spinal cord compression in an HIV-infected man due to invasive aspergillosis.

Case report

History

A 42-year-old, antiretroviral-naive, HIV-infected man, previously treated for pulmonary tuberculosis (TB), was referred to the neurosurgery service with progressive weakness in the lower limbs and urinary and faecal incontinence for 2 weeks. The patient, who was a farm worker, had been prescribed broad-spectrum antibiotic therapy for suspected bacterial pneumonia and low-dose prednisone prior to referral.

Examination

He had widespread, soft, non-tender, subcutaneous nodules, with blue discoloration of the nodules on the thighs. These were not investigated further. During hospitalization, he developed dyspnoea at rest, a productive cough and fever. He had upper motor neuron signs and a sensory level at T1, with accompanying neck stiffness on flexion.

Magnetic resonance imaging of the spine revealed diffuse abnormal signals of the vertebral bodies in the lower cervical and thoracic areas (Fig. 1). Cord compression was obvious in the C2 and C3 region, with contrast enhancement and signal distortions of the T2 and T3 vertebral bodies. Bilateral apical lung changes with pleural thickening were seen. Blood cultures were negative for fungi or other pathogens. A Ziehl–Neelsen stain of sputum was negative for acid-fast bacilli.

Discussion

This case report describes an HIV-infected man with fatal spinal aspergillosis. He had focal neurological signs suggestive of spinal cord compression, bilateral lung cavities (from previous pulmonary TB) with radiological evidence of fungal colonization and an extradural spinal lesion at the T1/T2 region. The spinal lesion was histopathologically suggestive of an Aspergillus infection; A. fumigatus was confirmed by PCR. This patient had the following risk factors that may have predisposed to invasive aspergillosis. First, he was HIV-infected and antiretroviral-naive. In 2007, only 28% of HIV-infected South Africans who were eligible for antiretroviral treatment had accessed treatment (WHO, 2010). Spinal aspergillosis in an HIV-infected man due to invasive aspergillosis.

A subsequent chest X-ray and a computerized tomography scan revealed bilateral post-tuberculous apical cavities with suspected fungal colonization, with the left lesion being larger than the right lesion.

Pathological findings

The extradural spinal lesion at the T1/T2 region, involving underlying bone in the T2/T3 position, was biopsied. Although this was clinically suspected as either a tuberculous osteitis or a soft-tissue malignancy with extension into the vertebral column, histopathological examination was compatible with Aspergillus infection.

The patient’s CD4+ T-cell count during the time of hospitalization was 239 cells mm−3, with a concomitant white-cell count of 24.13 × 109 l−1. He was slightly anaemic [haemoglobin, 13.2 g dl−1 (normal range, 14.3–18.3 g dl−1)] and had a moderate neutrophil leukocytosis [neutrophils, 94.2 % (normal range, 51–76 %)]. He had hypoalbuminaemia that worsened during hospitalization from an initial 20 g dl−1 to an eventual 14 g dl−1 (normal range, 35–52 g dl−1). Other indicators of liver-function impairment included increased levels of aspartate aminotransferase [45 U l−1 (normal range, 5–40 U l−1)], alanine aminotransferase [75 U l−1 (normal range, 5–40 U l−1)], alkaline phosphatase [195 U l−1 (normal range, 40–120 U l−1)] and gamma glutamyl transpeptidase [199 U l−1 (normal range, 0–60 U l−1)]. The patient also reported a history of excessive alcohol use over weekends.

The patient was started on fluconazole in response to the histopathological evidence of Aspergillus infection and was continued on broad-spectrum antibiotic therapy. The patient died within 3 weeks of the start of fluconazole treatment. The initial biopsy specimen was not sent for culture, and the patient died before a follow-up biopsy could be taken for this purpose. The formalin-fixed sample initially submitted for histopathological examination was sent to the US Centers for Disease Control and Prevention, where the infectious agent was identified as Aspergillus fumigatus by PCR (Muñoz-Cadavid et al., 2010).
2008). HIV infection is a well-described risk factor for invasive aspergillosis; however, most patients have advanced immunosuppression (usually indicated by a low CD4+ T-cell count). Atypically, the patient described here did not have an extremely low CD4+ T-cell count at the time of diagnosis. However, a pan-leukocyte gating method was used to determine the CD4+ T-cell count (Glencross et al., 2002); the concomitant leukocytosis could have influenced the interpretation of the CD4+ T-cell count, falsely elevating it. Second, he had fungal colonization of lung cavities. Given the prevalence of HIV and tuberculosis in South Africa, it is likely that many patients are colonized with Aspergillus. Subsequent dissemination of A. fumigatus from the lungs, either contiguous or haematogenous, is then facilitated by risk factors such as neutropenia. Third, the patient had a history of excessive alcohol use, which has been documented as a risk factor for aspergillosis (Blum et al., 1978; Epling et al., 1984; Smith & Walker, 1982). Fourth, he received prednisone and broad-spectrum antibiotics shortly before the diagnosis of aspergillosis was made. Both have been implicated as risk factors; corticosteroids inhibit the function of pulmonary macrophages (Schorn et al., 1977). Atypically, the patient had slight neutrophil leukocytosis and not neutropenia (Cornet et al., 2002). Elevated neutrophil counts were previously reported in a 33-year-old woman with AIDS who had disseminated aspergillosis affecting the brain and spine (Martinez et al., 2009). Furthermore, HIV-infected patients have defects in neutrophil function as well as activation of neutrophils, contributing to this dysfunction, which may manifest at all stages of HIV disease (Kuritzkes, 2000).

A retrospective analysis of 32 HIV-infected patients with CNS aspergillosis found that all died, regardless of whether they were treated with amphotericin B, lipid formulations of amphotericin B, itraconazole or a combination of amphotericin B and itraconazole (Mylonakis et al., 2000), which were the primary drugs used to treat aspergillosis in the past (Walsh et al., 2008). Fluconazole has very limited activity against Aspergillus; unfortunately, this was the only antifungal drug available at the resource-limited state hospital. Recent reports suggest that treatment of CNS aspergillosis, even among HIV-infected patients, should instead be based on voriconazole (Balasubramaniam et al., 2007; Elter et al., 2006; Gubler et al., 2007; Hidron et al., 2009; Schwartz et al., 2005; Stiefel et al., 2007; Tattevin et al., 2004), which is also recommended as the primary treatment for invasive pulmonary aspergillosis (Walsh et al., 2008).

**Fig. 1.** Magnetic resonance imaging. (a) Axial TW2 view, showing spine and lung involvement. Cavities with aspergillomas are visible, as well as the mass in the spine on the T2/T3 level. (b) Coronal view showing both lungs with apical pathology. (c) Sagittal TW1 view of spine, showing lesion at the T2/T3 level. A, Anterior; R, right; S, superior. On the bars, each small tick represents 1 cm; larger ticks represent 5 cm.
In conclusion, we recommend that invasive aspergillosis be considered as part of the differential diagnosis among HIV-infected patients with non-specific, focal CNS symptoms, even among those without classical risk factors such as neutropenia, and that aggressive antifungal therapy be instituted as early as possible.

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References


