Invasive *Aspergillus fumigatus* associated with liver and bone involvement in a patient with AIDS

A 39-year-old male who had emigrated from Malawi to the UK presented to his general practitioner with an eight-week history of an intermittent non-productive cough. He had no hemoptysis or constitutional symptoms and was a non-smoker. He reported having been hospitalized for two months in Malawi for pulmonary *Mycobacterium tuberculosis* infection (PTB) eighteen years previously. He was referred to the hospital outpatient clinic for further evaluation.

Examination findings included decreased air entry at the left apex of the lung. A chest radiograph (CXR) showed left apical opacification and cavitation with associated volume loss (Figure 1). Sputum analysis for bacteria and acid-fast bacilli (AFB) were negative on special staining and culture. These findings were interpreted as representing previously treated PTB infection. The patient consented to HIV testing and was found to be HIV-1 antibody positive with a CD4 count of 21/10⁶ cells/l (2%) and HIV viral load of 233 000 copies/ml. Co-infection with hepatitis B was confirmed by serology: HBsAg positive and HBeAg positive. Co-trimoxazole was started for *Pneumocystis* prophylaxis.

Four weeks later he re-presented to hospital with a one-week history of severe frontal headache and general malaise, but no fevers, photophobia or nuchal rigidity. Clinical examination was unremarkable except for the previously noted findings in the left lung field. A serum cryptococcal latex agglutination test (CrAg) was positive at a titer of 1:20. Lumbar puncture evaluation revealed an opening pressure of 18 cmH₂O and microscopy confirmed the presence of *Cryptococcus* on India ink staining, a white cell count (WCC) of 2550 cells (95% mononuclear cells, 5% polymorphs), and fewer than five red blood cells. Cerebrospinal fluid (CSF) protein was 1266 mg/l (normal range 250—450 mg/l). The CSF glucose:plasma glucose ratio was 1:2. CSF CrAg was positive at a titer of 1:40. The patient was commenced on intravenous amphotericin B and flucytosine. *Cryptococcus neoformans* was cultured from the CSF. Abnormal results were also obtained for: hemoglobin (Hb) 7.9 g/dl (normal range 13.0—16.5 g/dl); mean cell volume (MCV) 75.5 fl (normal range 79—96.0 fl); WCC 3.95 × 10⁹ cells/l (normal range 4.00—11.0 × 10⁹ cells/l); and lymphocytes 0.85 × 10⁹ cells/l (normal range 1.30—4.00 × 10⁹ cells/l). Neutrophils were 2.60 × 10⁹ cells/l (normal range 2.50—7.50 × 10⁹ cells/l).

During treatment for cryptococcal meningitis, the patient complained of a productive cough of yellow sputum and pleuritic chest pain. A repeat CXR revealed cavitation in the apex of the left lung, unchanged from the investigations of four weeks previously. A fibreoptic bronchoscopy was normal and staining and cultures of bronchoalveolar lavage (BAL) fluid were negative for bacteria, *Pneumocystis jirovecii* (*Pneumocystis pneumonia, PCP*) and mycobacteria. Six further sputum samples were negative for bacteria and mycobacteria on stain and culture. A course of oral co-amoxiclav was prescribed for a presumed bacterial chest infection, which resulted in an improvement in his respiratory symptoms. Prior to discharge the patient was converted to oral fluconazole 400 mg daily. Two weeks following discharge he was clinically well and commenced on anti-retroviral therapy consisting of zidovudine, lamivudine and efavirenz.

Five months after diagnosis of cryptococcal meningitis the patient presented with a productive cough and pleuritic chest pain localized to the left apex. He denied any hemoptysis. On examination he was afebrile and decreased air entry was again noted in the left upper lobe. Investigations showed a WCC 3.72 × 10⁹ cells/l, Hb 9.3 g/dl, MCV 87.9 fl, platelets 573 × 10⁹/l (normal range 150—450 × 10⁹/l), neutrophils 1.98 × 10⁹ cells/l, and lymphocytes 0.65 × 10⁹ cells/l. C-Reactive protein (CRP) was elevated at 192.1 mg/l (normal range 550 Letters to the Editor

![Figure 1](image-url)
range < 5 mg/l) and the erythrocyte sedimentation rate (ESR) was 82 mm/h (normal range 1–10 mm/h). After 18 weeks on antiretroviral therapy the CD4 count was $1 \times 10^6$ cells/l and the viral load had fallen to < 50 copies/ml. Intravenous co-amoxiclav was commenced empirically to treat suspected community-acquired pneumonia. Routine and mycobacterial blood cultures were negative.

A CXR showed progressive changes within the left hemithorax (Figure 2). A thoracic computed tomography (CT) scan showed dense consolidation within the left upper zone associated with marked cavitation and intracavitary material together with marked volume loss within the left hemithorax and a left-sided pleural effusion. Abdominal CT revealed numerous small focal low-density lesions in the liver, spleen and bone (Figure 3). Whilst the diagnosis of an aspergilloma was thought to be reasonable based on the appearances of the chest CT, the additional radiographic findings in the bone and liver strongly suggested disseminated tuberculosis (TB). A whole body bone scan was performed and showed normal uptake of tracer in all parts of the skeleton.

A repeat bronchoscopy was performed: bacteria, PCP and AFB were not identified on staining of the BAL but septated hyphae were stained and the appearance was consistent with Aspergillus. The patient was switched from fluconazole to voriconazole to treat presumptive invasive aspergillosis (IA). Culture of the BAL later grew Aspergillus fumigatus. The aspirate from pleural fluid contained a few reactive mesothelial cells, macrophages, lymphocytes, occasional neutrophils and red blood cells. Culture of this fluid was negative for bacteria, fungi and mycobacteria.

A bone marrow aspirate and trephine were performed prior to commencement of voriconazole. Histology showed a reactive marrow consistent with HIV myelopathy, patchy myelofibrosis and reactive plasma cell infiltration and no granulomas. Multiple echogenic lesions with hyper-echoic centers were noted throughout the liver and spleen on ultrasound examination. Liver biopsy revealed no granuloma or fungal forms. Histology was consistent with a lobular hepatitis of minimal activity and evidence of hepatitis B infection.

In view of the radiographic deterioration and despite the absence of granulomas on bone marrow and liver specimens it was felt that the radiographic pictures remained consistent with disseminated mycobacterial infection. The patient was commenced on quadruple anti-tuberculous therapy consisting of rifampicin, isoniazid, ethambutol and pyrazinamide. Clarithromycin was co-administered to cover suspected Mycobacterium avium intracellulare infection.

Microbiological culture of the bone marrow and liver samples subsequently grew A. fumigatus. Treatment of presumed disseminated mycobacterial and aspergillus disease was continued for four weeks on an inpatient basis. During this time there was normalization of the WCC and neutrophil count. The CRP decreased to 36.3 mg/l and ESR to 22 mm/h.

Improvement of cough and pleuritic chest pain was achieved at discharge. A further CXR showed that parenchymal changes seen within the left lung had improved together with resolution of the pleural effusion. Medication on discharge included co-trimoxazole, rifabutin, ethambutol, pyrazinamide, isoniazid, pyridoxine, tenofovir, emtricitabine, efavirenz and voriconazole.

Aspergillus fumigatus was confirmed on culture of BAL, bone marrow sample and liver biopsy. Aspergillus fumigatus was not isolated from blood culture. The A. fumigatus radio-allergosorbent test (RAST) test was negative but Aspergillus antigen (monoclonal antibody to galactomannan) enzyme-linked immunosorbent assay was positive. TB therapy was discontinued when final TB cultures revealed no growth. Voriconazole treatment for disseminated aspergillosis was continued on an outpatient basis with gradual resolution of the patient’s respiratory and systemic symptoms.

Aspergillus is a spore-forming (conidia) fungus with more than 185 species in the genus and 20 types reported to cause...
invasion in humans. Exposure to infection occurs through inhalation of spores. *Aspergillus fumigatus* is the most commonly isolated species.

*Aspergillus* spp are infrequently implicated in disease in healthy hosts. Protection from infection depends on granulocyte function as phagocytes kill the conidia. Prolonged neutropenia is the predominant risk factor for developing IA.1,3–7 Thus immunosuppression, corticosteroid use and parenteral antibiotic use are cited as major risk factors for the development of invasive disease.

Aspergillosis is not included in the list of AIDS-defining conditions produced by the Centers for Disease Control,4 and IA is uncommon in HIV-infected individuals with an incidence of less than 1%.5–7 The definition of disseminated IA requires the demonstration of *Aspergillus* spp at two or more non-contiguous sites.8 Our patient had a number of predisposing risk factors for IA as a consequence of HIV infection. These included neutropenia,1–3 CD4 lymphocytopenia,9 and a previous AIDS opportunistic infection.1,6,9

Pulmonary infection by *Aspergillus* is most common in HIV-infected patients.1,2,6 In our patient we isolated *A. fumigatus* from bronchoalveolar lavage. The specificity of the isolation of *Aspergillus* spp is high for invasive disease in immunocompromised hosts.10 Our patient also had pre-existing pulmonary cavitation as a result of old PTB, this being an independent risk factor for the development of IA.11

Pulmonary aspergillosis is well documented in the literature12 and dissemination by hematogenous spread has been observed. Hematogenous seeding of the axial skeleton, intervertebral discs and vertebral bones frequently complicates IA.8 Osteomyelitis was confirmed by positive culture of a posterior iliac crest bone marrow trephine. Abdominal CT identified the presence of small low-density bone lesions. Lesions were also visualized in the liver and *Aspergillus fumigatus* was cultured from percutaneous liver biopsy. Our patient had chronic hepatitis B infection, which has also been proposed as a risk factor for IA.13 To our knowledge, hepatic infection by *Aspergillus spp* in HIV co-infected patients has not been documented previously in the literature.

This man had advanced immunosuppression secondary to HIV infection with a CD4 count at diagnosis of 21 × 10⁶ cells/l. Lortholary et al. described a CD4 cell count of <50 × 10⁶ cells/l as being associated with aspergillosis.9 Prior cryptococcal meningitis may also be an independent risk factor for the development of IA. Staib et al. noted that in one group of patients with AIDS and cryptococcosis, 67% had aspergilli isolated from their respiratory tracts.14 We hypothesize that the accumulation of independent risk factors for IA in this individual accounted for the dissemination of disease.

The diagnosis was initially suspected to be disseminated mycobacterial infection given the clinical and radiographic findings. The eventual diagnosis was proven disseminated IA after isolation of *A. fumigatus* from three non-contiguous sites: lung, liver and bone. Further features suggestive of invasive disease include histopathological evidence from BAL, positive radiological imaging and the presence of serum *Aspergillus* antigen.

Amphotericin B is one of the preferred treatments for invasive disease.15 This patient received exposure to amphotericin B for treatment of cryptococcal meningitis. We hypothesize that the intravenous amphotericin B treatment may have partially treated the pulmonary disease and so interfered with BAL culture results. This resulted in a negative culture of the first BAL sample taken. Fluconazole has little activity against *Aspergillus* hence disease progression after conversion to this agent. After the identification of *Aspergillus* in BAL the patient was treated with oral voriconazole, which resulted in both clinical and radiological improvements.16

Disseminated IA is uncommon in HIV-infected individuals. Symptoms may mimic those of other infections. As illustrated in this case, disease may occur at atypical sites. A high degree of clinical suspicion for IA is necessary for HIV-infected patients with numerous risk factors.

Conflict of interest: No conflict of interest to declare.

References

Abscess of the corpus cavernosum

Localized abscess in an organ is generally treated with surgical drainage and, in some cases, systematic administration of appropriate antibiotics. Removal of an organ impaired by infection is rarely performed except in critical cases. We encountered a patient who required a penectomy for persistent abscess of the corpus cavernosum due to secondary infection with methicillin-resistant Staphylococcus aureus (MRSA).

A 54-year-old man presented with a one-week history of pain in the base of the penis unrelated to urination, with non-systemic symptoms. The patient denied any recent sexually transmitted disease, trauma, voiding symptoms, use of urethral instruments, tuberculosis, and diabetes or other systemic disease. He suffered from erectile dysfunction, which had gone unattended. Physical examination revealed a painful nodule of the right and left corpus cavernosum close to the crus of the penis and a normal prostate. Routine laboratory tests including urinalysis showed no abnormalities. T2-weighted magnetic resonance imaging of the pelvis showed localized bilateral abscess formation in the corpus cavernosum (Figure 1). Exploration of the right base of the penile shaft by lateral approach revealed a sterile abscess of the cavernosum. Moreover, biopsy of the abscess wall showed fibrous tissue but neither tubercular change nor cancerous tissue. Although the patient’s symptoms disappeared temporarily after removal of pus with a Penrose drain and intravenous injection of a broad-spectrum antibiotic for 10 days, the wound ruptured spontaneously after three weeks and discharged new pus, the culture of which yielded MRSA. The drainage volume increased, and the pain in the penis worsened daily. The patient was re-hospitalized after three months due to gait disturbance and a fever of 38°C, and was given injections of vancomycin for seven days. Despite treatment, his condition deteriorated, and a total penectomy and perineal urethrostomy were performed. His condition improved substantially, and he was discharged in good health 14 days later. The surgical specimen revealed various inflammatory infiltrates, granulomatous change, and cell debris in the right and left corpus cavernosum with a few epithelioid cells. Staining by the Ziehl–Neelsen method was negative; however, culture of the surgical specimen for Mycobacterium was not performed.

Abscess of the corpus cavernosum is rare and can develop after trauma,1 as a complication of cavernosography,2 as an unusual presentation of gonorrhea,3 after intracorporeal injections,4 or from undetermined causes,5,6 as in our case. It can usually be managed by drainage and antibiotic therapy;6,7 however, penectomy may be necessary in persistent cases.

Conflict of interest: No conflict of interest to declare.

References