

Disseminated invasive aspergillosis in a patient with acute leukaemia

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Abstract. A 46 year old previously healthy woman was diagnosed with acute lymphoblastic leukaemia. The induction phase was complicated by α -haemolytic streptococcal bacteremia which responded to antibacterial therapy. Subsequently, the patient developed pneumonia due to *Chlamydia pneumoniae* which responded to macrolides. Following this infection the patient developed recurrent fever and new pulmonary infiltrates were noted. Bronchoscopy was performed and treatment was administered with liposomal amphotericin B (L-AmB, AmBisome) for two days, but was complicated by acute renal failure. *Aspergillus fumigatus* was cultured from bronchoalveolar lavage fluid. L-AmB was discontinued and voriconazole and caspofungin were administered. Despite aggressive antifungal therapy the patient developed progressive invasive infection, with central nervous system involvement as well as lesions appearing in the kidneys and liver. The patient died one week following the diagnosis of aspergillosis. (www.actabiomedica.it)

Key words: Invasive aspergillosis, liposomal amphotericin B, voriconazole, caspofungin, combination antifungal therapy

Introduction

Immunocompromised patients are at increased risk of infection. In particular, patients with prolonged neutropenia, such as those with acute leukaemia and allogeneic bone marrow transplant recipients are at high risk of developing both bacterial and fungal infections. Historically, candidiasis has been the most frequently encountered fungal infection in this population, but advances in prophylactic and pre-emptive uses of antifungal agents with activity against *Candida* have caused a shift towards other fungal infections, such as invasive aspergillosis (IA) (1). IA can be extremely hard to diagnose early and treatment responses are low (average, 37%) (2). Patients with neutropenia and persistent fever despite treatment with broad-spectrum antibacterial agents, are usually started on antifungal agents, most commonly amphotericin B

deoxycholate, or more recently, liposomal amphotericin B (L-AmB), due to its superior safety profile (3). We report a case of a patient with acute leukaemia, complicated by prolonged neutropenia, bacteraemia, pneumonia due to *Chlamydia pneumoniae*, and ultimately disseminated aspergillosis.

Case report

A 46 year old previously healthy woman was diagnosed with acute lymphoblastic leukaemia (L3, precursor B-cell type). Induction treatment was started with serial doxorubicin and vincristine administrations for 5 weeks as well as intrathecal methotrexate, with good morphological response. During the induction phase the patient became neutropenic and febrile, with bacteremia due to α -haemolytic strepto-

coccus. Good therapeutic response to ceftazidime, penicillin and gentamicin was noted. Due to severe mucositis prophylactic treatment with fluconazole (200 mg/day) was begun. Subsequently, the patient developed dyspnoea and infiltrates were noted on chest X-ray. A polymerase chain reaction (PCR) test on sputum was positive for *Chlamydia pneumoniae* and treatment with erythromycin and then azithromycin was administered, with good initial clinical response. Ten days later, after 33 days of neutropenia, the patient developed fever, increasing dyspnoea, hypoxemia and new pulmonary infiltrates. Bronchoscopy was performed and treatment was begun with L-AmB (AmBisome) i.v. at 5 mg/kg/day. Hyphal elements were seen in microscopy and culture of bronchoalveolar lavage fluid was positive for *Aspergillus fumigatus*. The following day, the chest X-ray showed minimal improvement in infiltrates. The patient's renal function declined, however and progressive oliguria developed after only two days after initiation of therapy. L-AmB was discontinued and treatment was switched to voriconazole. Continuous veno-veno-hemofiltration (CVVHF) was initiated and two days later caspofungin was added to the antifungal regimen. The patient remained intubated and sedated, but when the level of sedation was decreased she remained unconscious and unresponsive. A computed tomographic (CT) scan of the brain, chest and abdomen was performed. Diffuse low-density lesions were seen in the brain, including bilateral frontal lesions, diffuse cortical lesions and a single cerebellar lesion with surrounding oedema (Figure 1). This was considered to be consistent with cerebral aspergillosis. In addition, new wedge-shaped lesions were noted in both kidneys and liver (Figure 2), consistent with diffuse invasive disease. Due to progressive cerebral infection and poor outlook, despite aggressive treatment it was decided to terminate further treatment: the patient died 6 hrs later. Autopsy was not performed.

Discussion

We report a case of diffuse IA in a patient with ALL. The epidemiology of IA has been well studied

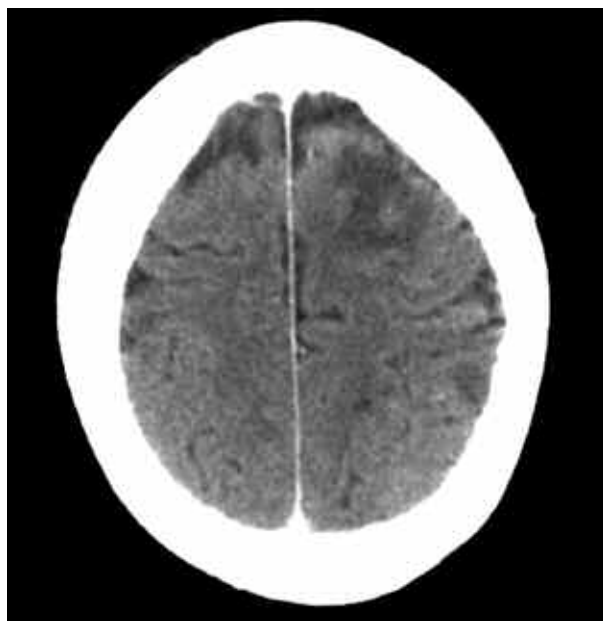


Figure 1. A CT scan of the brain showing bilateral frontal and cortical lesions, consistent with central nervous system disease

in neutropenic patients. A study by Nosari and colleagues showed that 7.1% of patients with acute leukaemia develop IA, with the vast majority of patients (92%) being neutropenic at the time of diagnosis (4). Although major improvements have been made in the treatment of IA, the case fatality rate of immunocompromised patients with this infection remains extremely high (5). L-AmB was initiated in this case due to persistent fever, despite treatment with broad-spectrum antibacterial agents. This decision was based on the fact that she had previously been treated with fluconazole, which is commonly used in our hospital as a prophylactic agent in patients with acute leukaemia and neutropenia. Second, when used empirically in this setting, L-AmB is better tolerated than the “conventional” amphotericin B deoxycholate (3). Unfortunately, following this intervention the patient developed renal failure necessitating CVVHF and termination of L-AmB. Three large randomised studies on patients with fever and neutropenia suggest that renal toxicity affects 5.5-18.7% of patients who receive L-AmB (3, 6, 7).

Bronchoscopy was performed at the time of initiation of empiric L-AmB. Subsequently, *Aspergillus*

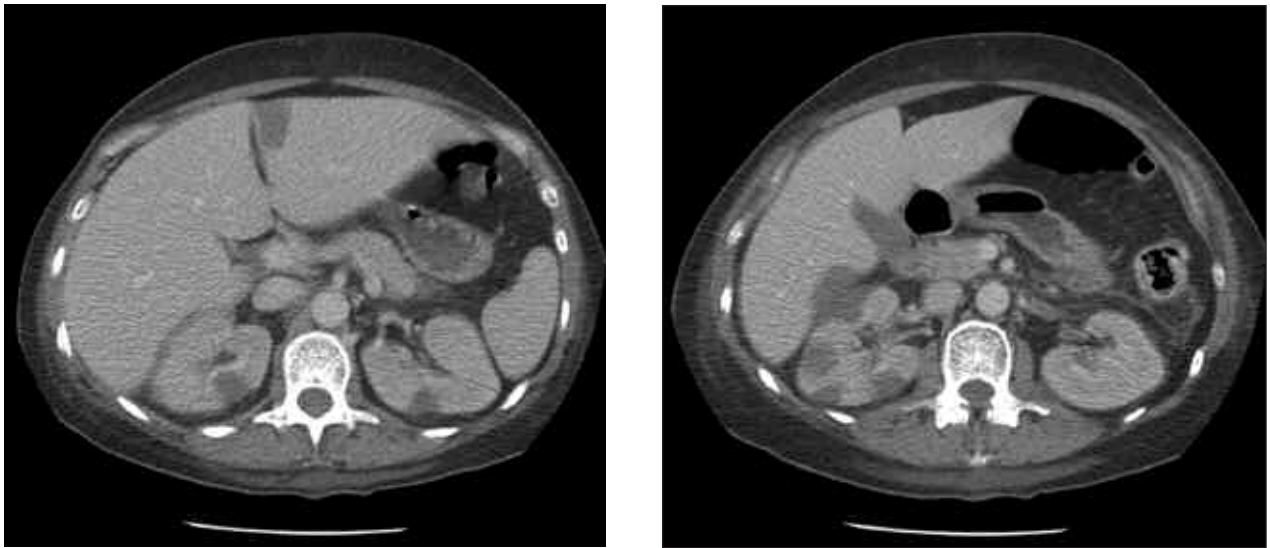


Figure 2. A CT scan of the abdomen showing multiple wedge-shaped lesions in the liver and kidneys

fumigatus grew from the bronchoalveolar lavage fluid. Antifungal therapy was switched to voriconazole, which has been shown to be superior to amphotericin B deoxycholate in the management of invasive aspergillosis (5). Although no trials have compared L-AmB and voriconazole in the management of aspergillosis, the study by Herbrecht and colleagues has prompted many authorities to recommend voriconazole as the primary antifungal agent for this infection. Updated treatment guidelines for IA, by the Infectious Diseases Society of America and due to be published in the summer of 2006, may clarify the status of voriconazole. Despite this therapeutic intervention, the patient's condition worsened, prompting us to add caspofungin as a salvage therapy, which has been approved for this indication. Nevertheless, a catastrophic central nervous system infection developed, virtually precluding further therapy. Although no randomized studies have compared the combination of voriconazole and caspofungin to the more conventional approach of L-AmB or voriconazole monotherapy, observational studies suggest that solid organ transplant recipients with IA and renal failure have improved prognosis when the combination is compared to L-AmB alone (8).

It is possible that the diagnosis of IA may have been delayed due to a positive PCR for *Chlamydia pneumoniae*, which prompted us to treat accordingly

with macrolides. The initial therapeutic response however, suggests that the fungal infection had not become established at that time. We did not measure the *Aspergillus* galactomannan antigen in our patient, since the incidence of IA has traditionally been low at our institution.

In summary, we present a case of IA which did not respond to any antifungal therapy, including L-AmB, voriconazole or caspofungin. Clearly, despite clear advances in diagnosis and management of aspergillosis in the past decade, improved and early detection and still more effective therapy, including antifungal combinations, are the key to future success in the management of these devastating infections.

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