

Successful management of cerebral and pulmonary mucormycosis with liposomal amphotericin B in a 28 year-old woman with acute lymphoblastic leukemia

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Abstract. A 28-year-old woman with acute lymphoblastic leukemia developed fever and unilateral pleural based pulmonary infiltrate during prolonged chemotherapy induced neutropenia. CT-guided lung biopsy confirmed the diagnosis of pulmonary mucormycosis and liposomal amphotericin B therapy was started. A few days after the initial symptoms, the patient developed convulsions and a brain abscess was detected in computerized tomography and magnetic resonance imaging. Fungal hyphae detected in histopathological examination of a brain biopsy had identical morphology with those seen in previous lung biopsies. The patient was treated with liposomal amphotericin B for five months and cytotoxic chemotherapy was successfully completed during antifungal therapy. Pulmonary infiltrates and the brain abscess resolved and the patient received an allogeneic bone marrow transplantation from a matched, unrelated donor. Antifungal therapy was continued for one additional month after bone marrow transplantation to prevent a relapse of invasive mucormycosis. Follow-up of the patient revealed no signs of relapse of invasive mucormycosis but two months after successful bone marrow transplantation the patient developed lethal cytomegalovirus pneumonitis which was confirmed by autopsy. No signs of mucormycosis were detected at post-mortem. (www.actabiomedica.it)

Key words: Mucormycosis, acute lymphoblastic leukemia, neutropenia, brain abscess

Introduction

Mucormycosis (zygomycosis) is an invasive fungal infection caused by moulds belonging to the Order Mucorales (1). It is the third most common invasive fungal infection after candidosis and invasive aspergillosis in patients with hematological malignancies in Finland (2, 3). The clinical picture of mucormycosis in these patients resembles that of invasive aspergillosis. The most common foci of infection are the sinuses and the lungs, but occasionally mucormycosis disseminates and can involve any organ. Similar to *Aspergillus* species the agents of mucomycosis have a pro-

pensity to invade blood vessels and cause thrombotic as well as hemorrhagic complications (4).

The diagnosis of mucormycosis has to be confirmed by histopathological evidence of fungal invasion in deep organ biopsies together with positive fungal culture. Unfortunately, many high risk patients with a propensity to acquire these infections have previously received empirical antifungal therapy before the clinical diagnosis is suspected. Thus, fungal cultures may remain negative and the diagnosis has to be based on histopathology alone. Until recently different formulations of amphotericin B at the maximum tolerated dose have been the gold standard in treatment of mu-

cormycosis (1). Many new antifungal agents like voriconazole and caspofungin, which are useful in treatment of invasive aspergillosis, have no role in treatment of mucormycosis (5, 6). The newest triazole agent, posaconazole, have been shown in animal models and in vitro studies to be active against causative agents of mucormycosis (7, 8), but the clinical experience with this drug is still limited.

Since the mortality rate of mucormycosis exceeds 50% (1) early diagnosis and prompt initiation of effective antifungal therapy is necessary for successful outcome. Another important factor for successful treatment of mucormycosis is resolution of predisposing neutropenia. In the rhinocerebral form of mucormycosis, which is sometimes associated with diabetic ketoacidosis, surgical débridement of necrotic tissue is usually necessary. Differentiation of these infections from invasive aspergillosis is especially important in patients with hematological malignancies, since most drugs used against *Aspergillus* species are not effective against mucormycosis. In the present report, we describe a case of disseminated mucormycosis, which was successfully treated with a long course of liposomal amphotericin B.

Case report

Acute lymphoblastic leukemia (ALL) was diagnosed in a previously healthy 28 year-old woman in August 1997. ALL was treated according to the 1994 treatment protocol of Finnish Leukemia Group. The induction chemotherapy consisted of a combination of intravenous cytarabine, mitoxantrone and etoposide followed by four consolidation courses consisting of different combinations of intravenous daunorubicin, vincristine, asparaginase, dexamethasone, cytarabine, teniposide, methotrexate, mercaptopurine and cyclophosphamide.

At the end of October 1997 the patient developed high fever ($>39^{\circ}\text{C}$) during deep and prolonged neutropenia (neutrophils $<100/\mu\text{l}$ for 2 weeks) 11 weeks after initiation of cytotoxic chemotherapy. The C-reactive protein (CRP) was also highly elevated (300 mg/l). Since the fever was not responding to broad spectrum antibacterial therapy, empirical treat-

ment with conventional amphotericin B (cAmB) was started at dose of 0.8 mg/kg/day. Two days later a pulmonary infiltrate was seen in the chest radiograph and high resolution computerized tomography (HRCT) revealed a large pleural based infiltrate in the upper lobe of the left lung suggesting invasive mold infection. The antifungal therapy was changed to liposomal amphotericin B (LAmB) at a dose of 300 mg/day (3.5 mg/kg/d), since the patient had elevated creatinine values. During febrile neutropenia *Aspergillus* galactomannan antigen was tested in serum specimens twice a week (Platelia[®], *Aspergillus*, Bio-Rad). Also bronchoscopy was performed and the bronchoalveolar lavage (BAL) specimen was cultured and tested for *Aspergillus* antigen (9). All these tests gave negative results.

Concomitant with detection of pulmonary infection the patient developed convulsions. A brain abscess (Figure 1) with a diameter of 3 cm was suspected on the basis of CT and magnetic resonance imaging (MRI). A CT-guided biopsy was done to examine the etiology of the pulmonary infection. Fungal culture remained negative, but histological examination by an experienced mycologist revealed broad, non-septate fungal hyphae with branches occurring at right angles. The morphology of hyphae was suggestive for moulds belonging to the Order Mucorales and causing mucormycosis. Two weeks later histological examination of a brain biopsy revealed fungal hyphae identical to those detected in the previous lung biopsy. *Aspergillus* antigen testing of serum specimens was performed weekly after resolution of neutropenia but all the results remained negative.

The patient received a 150 days long course of LAmB from the end of October 1997 to the end of March 1998. The total cumulative dose was 38 g. During the antifungal therapy the pulmonary infiltrates and brain abscess started to resolve. CRP values normalized and the remaining courses of cytotoxic chemotherapy were completed fulfilled by the end of March. The underlying acute lymphoblastic leukemia was in remission and the patient received an allogeneic bone marrow transplantation (BMT) from a matched unrelated donor after total body irradiation and high-dose cyclophosphamide at the end of March 1998. LAmB therapy was continued for an additional 5

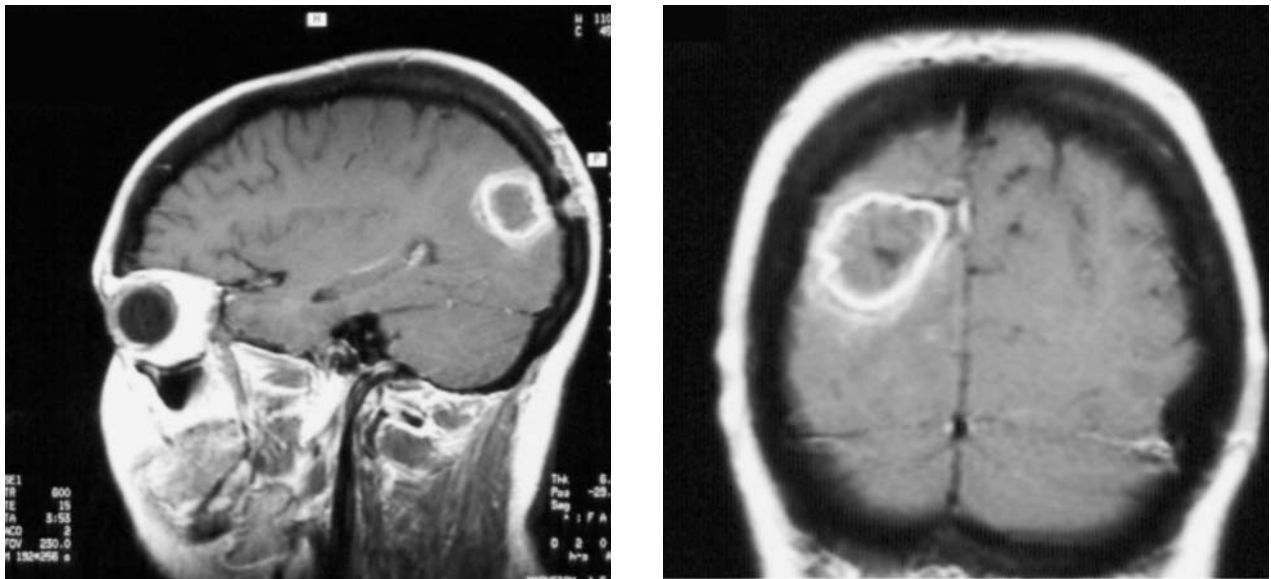


Figure 1. MRI of brain abscess caused by mucormycosis in a patient with acute lymphoblastic leukemia

weeks to prevent relapses of mucormycosis during the chemotherapy induced neutropenia. The patient tolerated the long course of LAmB well. During the antifungal therapy the creatine values normalized but bilirubin and alkaline phosphatase values were temporarily elevated (three and two times over the upper limit of normal, respectively). These values normalized when LAmB treatment was stopped at the beginning of May.

Five weeks after allogeneic BMT the patient was discharged. However, two weeks later she developed high fever and diffuse bilateral pulmonary infiltrates. A cytomegalovirus (CMV) antigen test from blood was highly positive and the patient was taken into intensive care unit for CMV pneumonitis. In spite of specific CMV therapy the patient died one week later. The autopsy confirmed the diagnosis of CMV pneumonitis. However, no signs of mucormycosis could be detected.

Discussion

Isolated cerebral mucormycosis without extension of the fungus from paranasal sinuses and disseminated mucormycosis are rare conditions that occur mainly in patients with hematological malignancies

(1). The mortality in these infections remains extremely high despite appropriate antifungal therapy (1, 10). Successful outcome is dependent on correction of predisposing factors like neutropenia and early initiation of effective antifungal therapy. Since many antifungal agents useful in the treatment of invasive aspergillosis are ineffective against moulds belonging to the Order Mucorales, early diagnosis is essential in choosing appropriate antifungal therapy. The only effective antifungal agents for treatment of mucormycosis are different formulations of amphotericin B and the newest triazole agent, posaconazole (7, 8). The use of cAmB is, however, hampered by the need of high doses and considerable toxicity of this agent with prolonged use (1, 11). Low nephrotoxicity and uncommon infusion related adverse effects make LAmB a promising alternative in the treatment of mucormycosis.

Our patient developed disseminated mucormycosis during chemotherapy-induced neutropenia with a large, pleural-based pulmonary infiltrate and brain abscess. The patient had already received empirical cAmB therapy when the pulmonary infection was detected. This is probably the reason for the negative fungal cultures from the BAL fluid as well as the culture-negative lung and brain biopsies. However, the experienced mycologist was able to detect identical

fungal hyphae from both biopsies and the histopathological findings suggested that diagnosis indeed was mucormycosis and not invasive aspergillosis. The diagnosis was further supported by repeatedly negative *Aspergillus* antigen tests in serum and BAL samples (9).

The patient received a five months long course of LAmB with an exceptionally high cumulative dose of amphotericin B. In spite of that she experienced only mild and reversible hepatotoxicity and elevated creatinine values normalized during the LAmB therapy. In this case LAmB enabled us to fulfill the cytotoxic chemotherapy and even perform a successful allogeneic BMT after resolution of the pulmonary infiltrate and cerebral abscess. By using secondary antifungal prophylaxis with LAmB during the BMT we were able to prevent relapses of mucormycosis. Unfortunately, despite the successful management of mucormycosis our patient developed another lethal opportunistic infection, CMV pneumonitis two months after BMT. Although the final outcome was poor our results show that liposomal amphotericin B is effective and safe choice in treatment of these potentially lethal mould infections in patients with deep and continuous immunosuppression.

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