

Zygomycosis in the immunocompromised patient: a case report

Aspasia Georgala¹, Marc Vekemans¹, Mireille Husson², Nathalie Meuleman³, Hugues Beguin⁴, Nicole Nolard⁴, Mickael Aoun¹

¹Infectious Disease Department of the Jules Bordet Institute in Brussels, Belgium; ²Microbiology Laboratory - Section of Mycology of the Jules Bordet Institute in Brussels, Belgium; ³Hematology Department of the Jules Bordet Institute in Brussels, Belgium; ⁴Institute of Public Health in Brussels, Belgium

Abstract. Zygomycosis is a highly aggressive infection observed in immunocompromised patients, such as those with haematological malignancies. The sites most frequently involved are the sinuses and the lungs. New diagnostic tools and new antifungal treatments are essential in order to diagnose early and treat efficiently infections due to moulds. We report a case of sinusitis due to *Absidia corymbifera* occurring during chemotherapy-induced bone marrow aplasia in a patient with acute leukaemia. The sinusitis was successfully treated with AmBisome[®], and surgical debridement. (www.actabiomedica.it)

Key words: Zygomycosis, haematological malignancy, AmBisome[®]

Introduction

Fungal infections in immunocompromised patients have increased and diversified during the last two decades. Haematological patients, solid organ transplant recipients and patients receiving immunosuppressive therapy are exposed to a great number of fungal pathogens which are ubiquitous, difficult to identify and very often fatal. Zygomycosis is defined as a the blood-vessel involving infection due to fungus of the class of Zygomycetes. The most usual presentations are rhinocerebral, pulmonary, gastrointestinal and cutaneous; other localizations such as brain and kidneys are seldom described. Amphotericin B (conventional Amphotericin B, lipid formulations of Amphotericin B), early surgical debridement and control of predisposing factors are the corner-stone of successful management of zygomycosis. New antifungals such as voriconazole and caspofungin have no activity against molds implicated in zygomycosis; posaconazole is the only new antifungal drug with potential activity against these molds.

Case report

A 52-year old patient newly diagnosed with acute leukaemia was treated with induction chemotherapy comprised of cytosine-arabioside, etoposide and daunorubicine. Antimicrobial prophylaxis included oral ciprofloxacin (500 mg bid), oral fluconazole (400 mg qid) and aerosolized amphotericin B (5 mg qid). On day 6 of chemotherapy the patient developed febrile neutropenia. Broad-spectrum antibiotics were prescribed; a transient response was observed, but a few days later the patient presented with a new fever which didn't respond to antibacterials. On day 14 of chemotherapy the patient was still febrile and he reported pain in the right eye. Periorbital erythema was present (Figure 1) and a sinus CT scan demonstrated a significant right sinusitis with bone erosion (Figure 2). Non-septate hyphae with right-angled branching were seen in a sinus aspiration stained with Calcofluor white (Figure 3). Culture of the sinus aspirate on Sabouraud agar incubated at 37°C yielded woolly, olive grey colonies without any pigment production (Figure



Figure 1. Periorbital and facial cellulitis in the first day of presentation

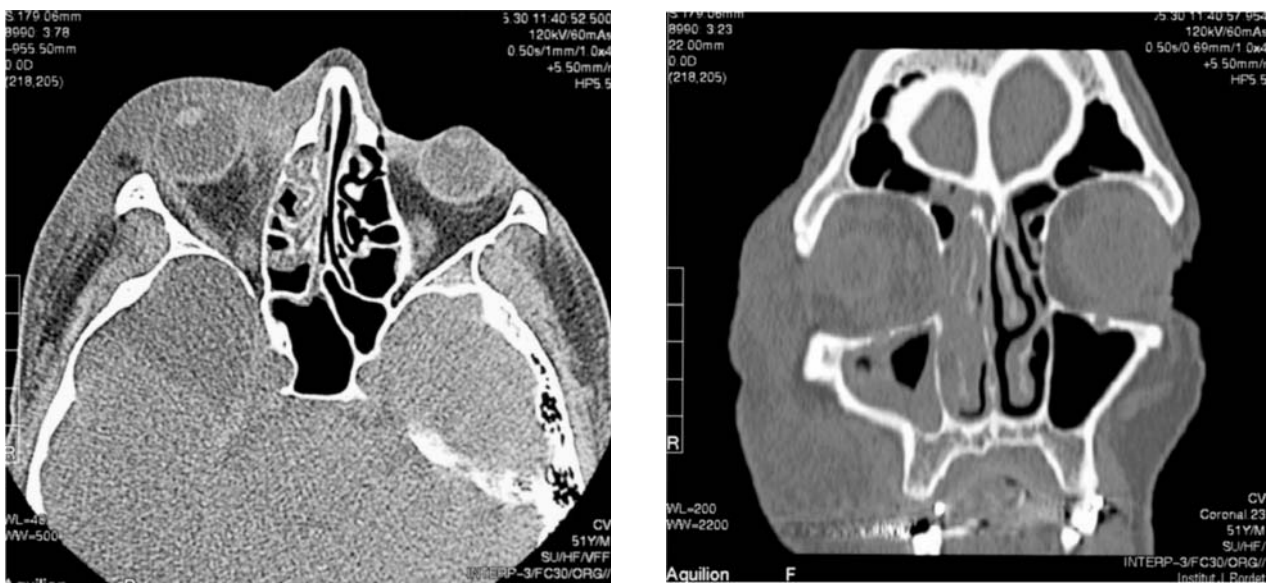


Figure 2. Sinus CT-Scan demonstrating an important right sinusitis with a discrete effraction of the bone(1st day of presentation)

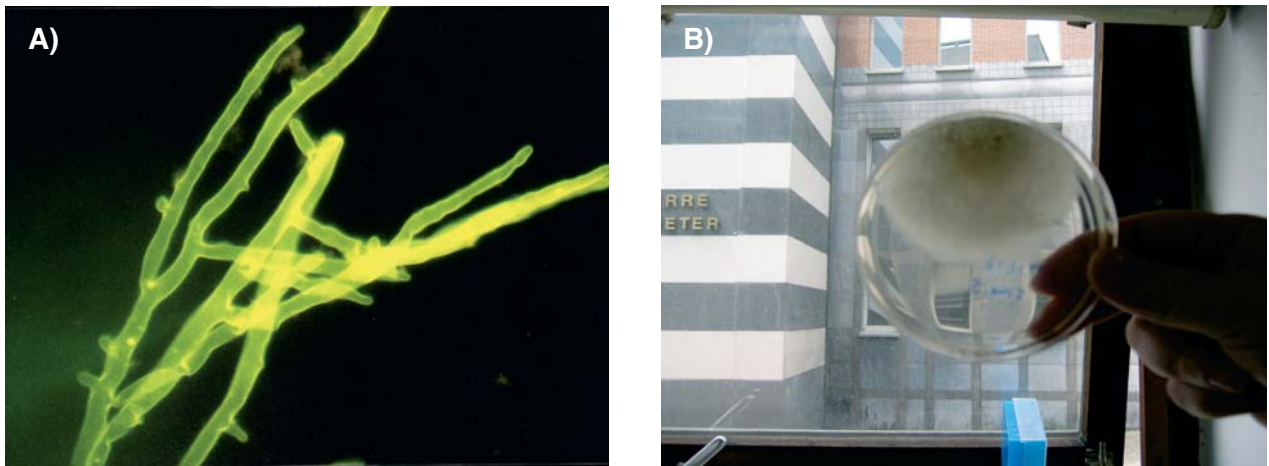


Figure 3. Sinus aspiration. A) Direct exam of calcofluor staining showing filamentous mycelium; B) Culture on Sabouraud, dextrose agar

re 3). The patient was treated with 3 mg/kg/ day of liposomal Amphotericin B (AmBisome®) according to the Ambiload protocol (1). The mould was identified as *Absidia corymbifera*. The fever decreased rapidly and after surgical debridement, the patient's condition improved significantly. Unfortunately there was no response to his chemotherapy; blasts persisted in peripheral blood and in marrow and a new induction chemotherapy with cytosine-arabioside and amsacrine was started. The patient was maintained on AmBisome® till sinusitis was clinically resolved; he totally received 7800 mg of AmBisome® during 40 days, with an excellent tolerability (Figure 4).

Discussion

Zygomycosis is a rare, infection due to fungi belonging to the class of Zygomycetes; clinical manifestations may vary but the most fulminant one is the rhinocerebral form usually occurring in diabetic and immunocompromised patients (2, 3). The most common species implicated in human disease are members of the order of Mucorales and of the order of Entomophthorales. They are ubiquitous in nature and can be found on decaying plants and in the soil. Within the order Mucorales, *Rhizopus spp*, *Mucor*, *Rhizomucor*, *Absidia*, *Apophysomyces*, *Saksenaea*, *Cunninghamella*, *Cokeromyces* and *Syncephalastrum spp* are the organisms

that are most often encountered in zygomycosis; spores can be inhaled, ingested or transmitted via the skin in large amounts since they are produced and released in the air in enormous quantities (4).

The underlying conditions that predispose to zygomycosis include diabetes, metabolic acidosis, corticosteroid therapy, prolonged neutropenia, organ or bone marrow transplantation, treatment with desferroxamine, AIDS, IV injection drug use and burn or trauma patients (4, 5). However, in the recent years some cases of zygomycosis are reported without any identifiable underlying condition (5).

The clinical picture includes rhinocerebral, sinusitis, pulmonary, gastrointestinal, cutaneous, renal, isolated CNS focal presentation and disseminated forms (3, 6-8). Moulds of the order Mucorales are angiotropic: small blood vessels are invaded and infarction with local necrosis is observed in human tissues (Figure 5). The evolution of the disease is rapidly fatal, since no adequate treatment is established.

Rhinocerebral zygomycosis is the most common presentation and almost always associated with hyperglycemia and metabolic acidosis (5). The onset of the disease is acute: fever, stuffed nose, purulent nasal droppings, headache and tender sinuses. Ethmoidal, maxillary, frontal and sphenoidal sinuses may be involved; the infection progresses by local infarction and they can spread to brain, orbits, skin and big blood vessels.



Figure 4. Regression of the periorbital and facial cellulitis on day 13 of antifungal treatment and after surgical debridement

Sinusitis with or without pulmonary lesions is frequently described in immunocompromised patients such as haematological patients, solid organ transplant recipients and patients receiving immunosuppressive



Figure 5. Tissue infarction and necrotizing lesion

therapy or deferoxamine (4, 5, 9, 10). Zygomycosis mimics *Aspergillus* infection (11): fever, signs and symptoms of sinusitis, cough, haemoptysis, dyspnoea, pleuritic chest pain are present in both entities, while microbiological documentation may be lacking. Inadequate choice of treatment may jeopardise the prognosis of the disease (12, 13).

Gastrointestinal zygomycosis is rarely observed and almost always in malnourished or immunocompromised patients; the stomach is the most involved organ followed by the colon. The mortality rates are extremely high when there is a bowel perforation (14). *Renal, cutaneous and isolated lesions of the central nervous system* have also been described; they result from direct trauma and inoculation or from haematogenous dissemination (5, 15).

The diagnosis of zygomycosis is particularly pertinent to establish since the clinical presentation may mimic other filamentous fungi infection or severe bacterial infection. Clinical suspicion should be raised when a patient, especially an immunocompromised one, presents signs and symptoms of sinusitis or pneumonia. Microbiological documentation is of major interest; sinus aspirates, bronchoalveolar lavage, cerebrospinal fluid and biopsy material must be examined carefully. Despite extensive microbiological documentation, the cultures may remain negative and a lot of cases are diagnosed at autopsy (3, 5).

The successful management of zygomycosis is based on three major elements: early surgical treat-

ment, appropriate antifungal therapy and resolution of the underlying condition (3, 5). Amphotericin B remains the gold standard in the treatment of zygomycosis; the introduction of Amphotericin B in the 60's revolutionised the outcome of zygomycosis (5). Lipid formulations of Amphotericin B allow a longer duration of treatment with a good tolerability and less side effects (11, 16, 17). Among new antifungal drugs posaconazole offers a good alternative for salvage treatment and for oral maintenance therapy (18, 19). Unfortunately, a lot of cases of zygomycosis still have a fatal outcome even when diagnosed early and adequately treated (20).

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Correspondence: Aspasia Georgala
Infectious Disease Department
of the Jules Bordet Institute
Brussels, Belgium
E-mail: nathalie.cardinal@bordet.be