CASE REPORT

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Rhino-cerebral zygomycosis after allogeneic transplant: case report and literature review

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Abstract

The proportion of patients with hematological malignancies (HM) who develop rare invasive fungal infections (IFI) has increased worldwide over the past few decades. Zygomycosis is an opportunistic fungal infection, which begins in the nose and paranasal sinuses due to inhalation of fungal spores. Rhino-cerebral zygomycosis is the most common form of the disease, it typically develops in diabetic or immunocompromised patients and presents as an acute fulminate infection, which is often lethal. We report a case of rhino-cerebral zygomycosis in an allotransplanted patient to emphasize early diagnosis and treatment of this potentially fatal fungal infection. We discuss different risk factors, specific diagnosis procedures and review the current concepts in management of zygomycosis.

Keywords: mucormycosis, zygomycosis, rhino-cerebral, allogeneic transplant.

Introduction

Zygomycosis also called as mucormycosis was first described by Paltauf A in 1885 [1] is an opportunistic frequently fulminating fungal infection that is caused by *Mucorales*. These causative fungi are saprophytic fungi frequently found in the upper respiratory tract and are nonpathogenic in normal hosts. Numerous spores may be inhaled by human hosts and when spores are converted into hyphae, they become invasive and may spread through the paranasal sinuses into the brain and orbits, either by direct invasion or through the blood vessels [2]. The fungus invades the arteries leading to thrombosis that subsequently causes necrosis of hard and soft tissues [3]. We herein describe the clinical and MR imaging findings of a patient with rhino-cerebral zygomycosis developed after allogeneic transplant for acute myeloblastic leukemia.

Patient, Methods and Results

An 18-year-old male patient with acute myeloblastic leukemia associated with myelodysplastic features was allotransplanted from sibling donor in first complete remission. He developed acute gastrointestinal graft *vs.* host disease (GVHD) and he was treated with methyl-prednisolone 2 mg/kg body weight, as first line therapy of GVHD. The patient received antifungal prophylaxis with posaconazole, but due to the gut disturbance, the prophylaxis was changed with voriconazole. The GVHD responded very well, but the patient developed diabetes due to the corticotherapy.

He presented to Bone Marrow Transplantation Unit from Fundeni Clinical Institute, Bucharest, in day + 84 after allotransplant with right facial pain, anesthesia of the affected side and periorbital edema appeared during the last 12 hours. The lab tests: Hb 9.9 g/dL; WBC 7300/cmm; neutrophils 55%; PLT 34 000/cmm; CRP 202 mg/L; glucose blood count 503 mg/dL; normal liver and renal tests. Bone marrow aspirate normal; 100% donor chimerism. The neurological exam diagnosed cranial nerves syndrome involving nerves I, III, V.

Urgency MRI revealed: inflammation involving right orbit and the entire maxillo-ethmoidal region, with extension on soft tissues, in association with meningeal involvement and right ophthalmic vein thrombosis (Figure 1).

During the following 24 hours, he developed dyplopia, ptosis of the eyelid, decreased visual acuity progressing to blindness, necrotic lesion on right palate, dark blood nasal discharge.

Two swabs from sinusal secretion were performed and cultured on SDA (Sabouraud dextrose agar), SBA (Sheep blood agar) and CLED agar. After 24 hours, many colonies of filamentous fungi were observed (Figure 2). The fungi grew rapidly and after 48 hours, the whole surface of the agar plate was covered

(Figure 3). The colonies present a wooly aerial mycelium. The color was initially white and became grayish in time. This rapidly growing strongly suggests one of *Zygomycetes* fungi.

Microscopic examination performed by culture, with adhesive type (lacto phenol smear), revealed aseptate hyphae (without transverse septation), which are broad and branch from the main hyphae trunk, most of them angled 90^0 (Figure 4). We note the lack of apophysis and rhizoids. The conidiophores are terminated in a globe-like columella. Sporangiospores are freely spread (Figure 5).

The treatment with posaconazole (400 mg ×3/day) was started after 24 hours from first clinical signs. Amphotericin B is not registered in Romania, but the patients received as donation Fungysone (amphotericin B deoxycholate) maximum tolerated dose (1 mg/kg body weight/day, seven weeks).

In addition, the patient received Desferasirox (Exjade) 1000 mg/day for iron chelation and Insulin therapy for correction of hyperglycemia. Surgical treatment was performed several times during the first two months and consisted in: inferior and right median cornectomy, mucosal excision of right maxillar sinus, right ethmoidectomy, right sphenoidectomy, excision of necrotic palate lesion.

After stopping amphotericin B deoxycholate (total dose 3250 g), at seven days, the radiological status was stable but the clinical status indicates progression: reappearance of fever, pain and worsening ocular protrusion. He was referred to Infectious Diseases Unit, San Martino Hospital, University of Genoa, for continue the treatment. He received high dose of liposomal amphotericin B (Ambisome) 10 mg/kg body weight for three months. MRI evaluation exam revealed improving of initial sites lesions, but in addition carotidal involvement (Figure 6).

He returns in BMT Unit, Fundeni Hospital, at nine months after allogeneic transplant with stable clinical status, without any immunosuppressive therapy, without any signs of leukemia and full donor chimerism.

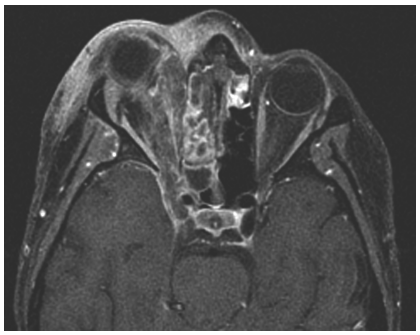

Figure 1 – ***Important inflammatory lesions of the right orbit, right ethmoidal region and meninges (anterior part of temporal lobe). Superior ophthalmic vein appears partial thrombosis (Fundeni Clinical Institute, Bucharest).***

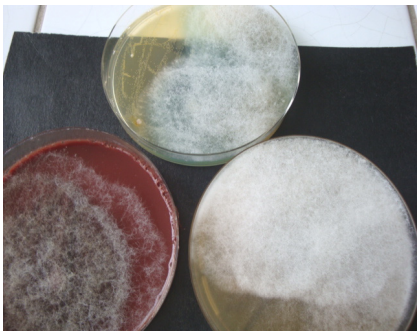

Figure 2 – ***Sinusal secretion cultured on SDA, SBA and CLED agar. After 24 hours, many colonies of filamentous fungi were observed.***

Figure 3 – ***Sinusal secretion cultured on SDA. After 48 hours, the whole surface of the agar plate was covered.***

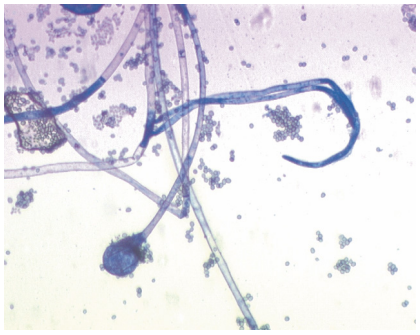

Figure 4 – ***Microscopic examination performed by culture, with adhesive type (lacto phenol smear), revealed aseptate hyphae (without transverse septation), which are broad and branch from the main hyphae trunk, most of them angled 90^0.***

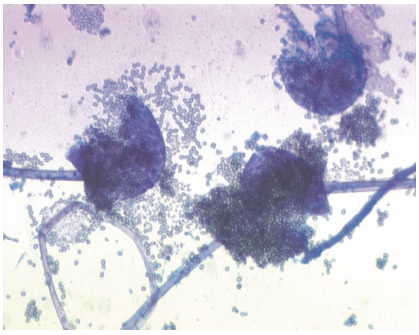

Figure 5 – ***Microscopic examination. We note the lack of apophysis and rhizoids. The conidiophores are terminated in a globe-like columella. Sporangiospores are freely spread.***

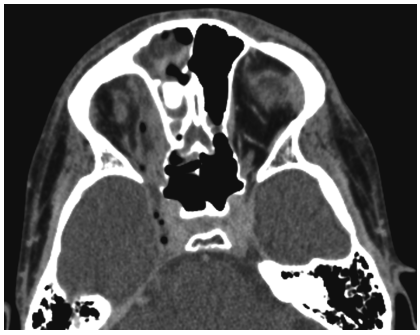

Figure 6 – ***Air bubbles at the level of cavernous sinus, bordering the right internal carotid artery (San Martino Hospital, Genoa).***

Discussion

Zygomycosis is an increasingly emerging life-threatening infection. The prevalence and overall mortality of zygomycosis in hematological diseases were 17% and 66%, respectively [4]. It was suggested that two major factors predispose patients to zygomycosis: defect in neutrophil and monocytic count and function and metabolic acidosis [5].

Neutropenia represent the most common risk factors for opportunistic infections in hematological patients,

because the neutrophils represent the cells responsible for the defense against fungus. There are reports who suggested that the ability of serum of immunocompromised patients to inhibit *Rhizopus in vitro* is reduced, which makes them suitable hosts to opportunistic fungal infections [6].

In diabetic patients, metabolic acidosis interferes with the ability of transferring to bind iron, thereby leading to high iron levels in tissue that enhance the growth of fungal organism. Moreover, reduced neutrophil chemotaxis and adhesions to hyphae have been demonstrated in diabetic patients [5]. Thus, a patient with hematological disease (with neutrophil defect) and diabetes has probably a higher risk to develop a zygomycosis.

Another risk factor for zygomycosis, in hematological patients it has been suggested to be prophylaxis with voriconazole. Antifungal prophylaxis with azoles is a routine practice in high-risk hematology patients. There are reports [7, 8] suggesting that breakthrough zygomycosis could occur after voriconazole prophylaxis. On the other hand, there are data that suggest that breakthrough zygomycosis could occur with any prophylactic azoles that do not have activity against *Zygomycetes* [9, 10]. An exception among azoles is represented by posaconazole, a new extended-spectrum azoles antifungal with a demonstrated *in vitro* and *in vivo* activity against *Zygomycetes*.

The diagnosis is establish either histological or by culture. A positive culture for a *Zygomycetes* organism can be obtained between 50–70% of cases; the capacity to recover these organisms by cultures has significantly improved over time. *Rhizopus* species were the most commonly recovered organisms [4].

Radiological procedures (standard X-ray and computed tomography (CT) scans) are frequently nonspecific at initial diagnosis for rhino-cerebral zygomycosis: dense opacification of paranasal sinuses with variable mucosal thickening and usual absence of fluid levels [11, 12]. Magnetic resonance (MRI) is more sensitive to evidence the infection of soft tissues of the orbit [13]. Sequential MRI can determine the extension and monitor the response of disease.

During last years, a new diagnostic quantitative polymerase chain reaction (PCR) assay system has been developed for the detection of the most common medically important genera of *Zygomycetes* giving support to the histopathological diagnosis [14]. This assay could be very important because of the accurate and rapid diagnosis, which can be the main prognostic factor for survival.

The successful management of zygomycosis is based on four major elements: early diagnosis, appropriate, aggressive antifungal therapy, surgical debridement and resolution of the underlying condition [4, 15, 20].

The majority of zygomycetes have been shown to demonstrate resistance to fluconazole, itraconazole and 5-fluorocytosine. As for new antifungal agents, many studies have demonstrated a lack of efficacy by echinocandins and voriconazole in inhibiting fungal growth.

Amphotericin B remains the gold standard in the treatment of zygomycosis; the introduction of amphotericin B in the 60's revolutionized the outcome of zygomycosis [4]. Lipid formulations of amphotericin B allow a longer duration of treatment with a good tolerability and less side effects [16]. Lipid formulations of AmB enable the drug to deposit into the reticuloendothelial system, including local sites of infection, which is the reason for their therapeutic advantage [5]. Liposomal amphotericin B has become the therapeutic agent of choice, with a response rate ranging from 67% to 71% [17–21]. Among new antifungal drugs, posaconazole offers a good alternative for salvage treatment and for oral maintenance therapy [22, 23].

Available data suggest that newer iron chelators, particularly, deferasirox, should be used as an adjuvant therapy, due to the fact that iron is essential for the growth and virulence of zygomycetes [4]. Also, the hyperbaric oxygen therapy has been reported to be useful in treating zygomycosis, due to reducing the tissue hypoxia and acidosis that accompany vascular invasion by the fungus [24].

Conclusions

A rhino-sinusal simptomatology in a hematology patient with/without diabetes may alert the clinician of possible zygomycotic infection**.** Early diagnosis and prompt administration of antifungal therapy has been increasingly recognized as predictive factors of the outcome in patients with invasive mould infection.

Acknowledgments

This paper is partially supported by the Sectoral Operational Programme Human Resources Development, financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/89/1.5/S/64109.

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Received: January 15th, 2011

Accepted: May 23rd, 2011