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Mucormycosis in a child with acute lymphoblastic leukemia: Case report

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ABSTRACT

Mucormycosis is an opportunistic fungal infection with high mortality, especially in immunocompromised patients. This article emphasizes the importance of early diagnosis and aggressive treatment. We describe the case of a child with leukemia treated with corticosteroids, vincristine, and daunorubicin, who developed rhino-orbital mucormycosis. Treatment included extensive surgical debridement until the right orbital contents emptied and prolonged antifungal therapy with liposomal amphotericin and anidulafungin. The article highlights the need for an early multidisciplinary approach to improve prognosis.

Keywords: *mucormycosis; zygomycosis; immunosuppression; leukemia.*

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INTRODUCTION

Mucormycosis comprises a heterogeneous group of opportunistic, emerging, high-mortality fungal infections.[1] Risk factors for its development include prolonged use of systemic steroids, primary or secondary immunodeficiencies, treatment with deferoxamine, use of intravenous drugs, malnutrition, burns, accidental trauma, natural disasters, and diabetic ketoacidosis.[2-4]

Treatment consists of aggressive surgical debridement combined with high doses of amphotericin and control of predisposing factors such as neutropenia or hyperglycemia whenever possible.[2,3,5,6]

The main objective of this publication is to highlight clinical aspects that facilitate timely diagnosis and the importance of the interdisciplinary approach. It emphasizes the need for early, broad, aggressive, and repeated surgical debridement to remove necrotic tissue and allow the antifungal agent to reach the site of infection.[5]

CLINICAL CASE

We present the case of a 3-year-old boy diagnosed with acute lymphoblastic leukemia, who presented with fever and follicular conjunctivitis, accompanied by pain in the inner corner of the right eye, 11 days after starting treatment, according to the GATLA 2010 protocol with high doses of corticosteroids, daunorubicin, and vincristine. The clinical picture was interpreted as high-risk febrile neutropenia with mucocutaneous focus, which led to empirical treatment with piperacillin-tazobactam and vancomycin.

The following day, a progression of the lesion with preseptal cellulitis was observed, which motivated the extension of the empirical antibiotic coverage with meropenem and vancomycin. Five days after the onset of ocular involvement, an ecchymotic lesion was evidenced in the inner corner of the right eye (*Figure 1*). Given the suspicion of invasive fungal infection, magnetic resonance imaging of the brain and paranasal sinuses was performed (*Figure 2*). Maxillary sinus aspiration was performed; samples were sent for mycological culture, common germs, and mycobacteria. On direct observation, coenocytic hyphae without septum were identified, later typed as *Rhizopus* spp.

The patient started antifungal treatment with liposomal amphotericin at 10 mg/kg/day and anidulafungin at 1.5 mg/kg/day. At 24 hours, progression of the infection was observed, with the appearance of a necrotic lesion on the palate (*Figure 3*). The serum galactomannan detection test was negative. Due to the development of volume-refratory septic shock without isolation of germs, the patient required admission to the intensive care unit. He received granulocyte infusions. Multiple surgical debridements of the affected areas were performed, culminating

Figure 1. Ecchymotic lesion in the internal corner of the eye

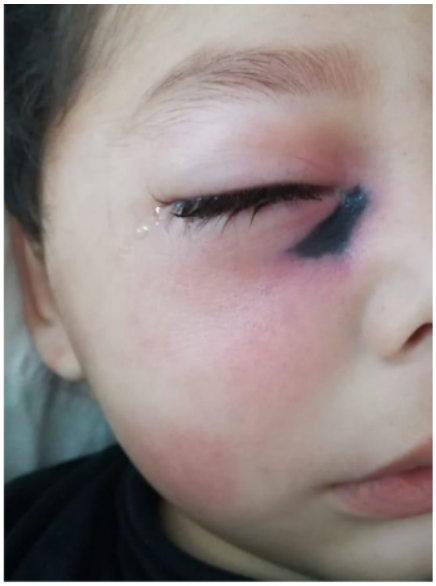
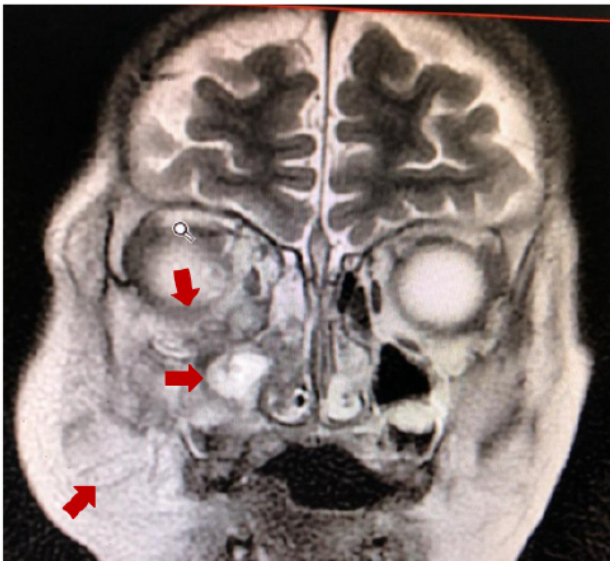
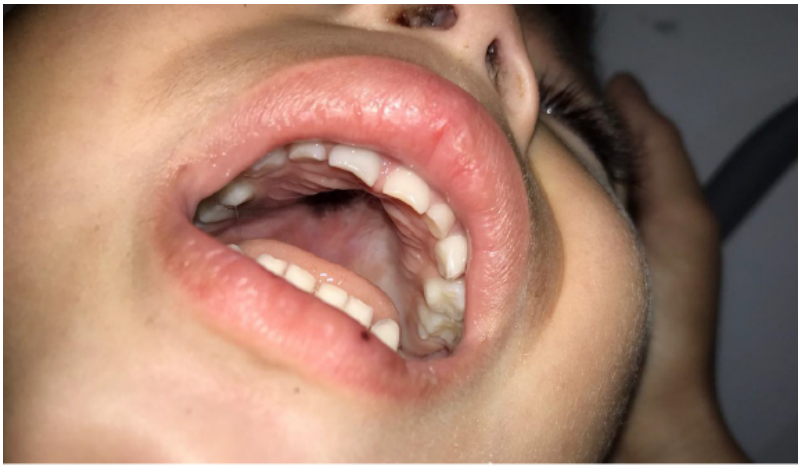


Figure 2. Magnetic resonance imaging of the paranasal sinuses and brain



Right periorbital soft tissue enlargement, thickening of the right lacrimal sac, discrete increase in the diameter of the proximal third of the homolateral nasolacrimal duct, and occupation of the maxillary sinus with obliteration of the ostium and right ethmoidal cells by soft tissue density material (ethmoiditis) were revealed—no involvement of the central nervous system.

Figure 3. Necrotic lesion on the palate



in the emptying of the right orbital contents due to worsening of the lesion with soft tissue involvement.

Computed axial tomography of the brain, thorax, abdomen, and pelvis was performed to detect disease dissemination; a pulmonary lesion was evidenced in the right upper lobe. Although the lavage bronchoalveolar examination revealed no mycotic elements, due to the progression of the pulmonary lesion in the tomography and no galactomannan detection, it was decided to perform an upper lobectomy. The anatomopathological analysis of the specimen did not reveal any mycotic elements in the lung tissue.

The patient required mechanical ventilation for 23 days. Mycological cultures were negative after 63 days of antifungal and surgical treatments. From a hematological point of view, the treatment was adjusted by suspending the anthracyclines and continuing with the rest of the drugs. On the 33rd day of chemotherapy treatment, the

leukemia was in remission.

He received combined treatment: liposomal amphotericin B at 10 mg/kg/day for 150 days and anidulafungin for 54 days. Subsequently, he continued therapy with liposomal amphotericin 10 mg/kg/dose three times a week; then started posaconazole at 18 mg/kg/day orally. At 24 months of antifungal treatment, positron emission computed tomography (PET-CT) of the orbit was performed, and treatment was discontinued, continuing with secondary prophylaxis during periods of neutropenia.

He presented good clinical evolution without relapses of the infection.

DISCUSSION

Mucormycosis is a heterogeneous group of opportunistic, emerging, and high mortality fungal infections caused by hyaline filamentous fungi belonging to the class Zygomycetes, of the order Mucorales and Entomophthorales and genus *Rhizopus*.[2,5,7]

Mucorales are ubiquitous saprophytic microorganisms commonly found in decaying organic matter such as vegetables, seeds, fruits, wood, and aged bread, as well as in soil, animal excreta, and even in hospital environments.[4,8] These fungi are fast-growing and release a large number of spores that are dispersed in the air.[5-7] Their colonies are visible to the naked eye and have a cottony appearance. Direct observation of clinical specimens with 10% KOH or calcofluor white allows the identification of irregular filamentous elements characterized by long, broad, non-septate hyphae, often branching at right angles.[8] These criteria help identify infection by fungi of the family *Mucoraceae* and differentiate them from other septate filamentous fungi, such as *Aspergillus* sp. and *Fusarium* sp.

It is transmitted by inhaling spores from the environment or percutaneously by traumatic spore implantation in areas of injured skin, such as catheter insertion, burns, drug injections or tattoos, and insect bites since the causative agents of mucormycosis cannot penetrate intact skin.[8]

The pathophysiological characteristics relevant to this infection are vasotropism and angioinvasion.[5] After the spores penetrate the organism, they develop in deep tissues, invade blood vessels, perforate their walls, and cause thrombosis with subsequent necrosis, facilitating hematogenous dissemination.[4,8]

In immunocompetent individuals, macrophages prevent the development of fungal infection by phagocytosis and oxidative death of spores. However, once infection is established, neutrophils die due to their oxidative cytotoxic system. Given the large size of the hyphae, they cannot be phagocytosed by inflammatory cells; therefore, immunocompromised hosts with granulocyte deficiency are at an increased risk of developing this infection.[4]

The absence of blood flow in the affected tissues explains the difficulty of antifungals reaching the site of infection and eliminating the fungus. In this context, surgical debridement is essential to eradicate necrosis and reduce the infection load.[5]

The onset of symptoms is usually acute. Depending on the clinical presentation and the specific anatomical site affected, the following clinical categories have been identified:

- Rhino-orbital-cerebral (sinus 39%; cerebral 9%): Starts with inhalation of spores into the sinuses and may spread to the brain. Initial symptoms mimic acute sinusitis with facial pain, nasal congestion, fever, soft-tissue edema, and headache. It may be associated with nasal ulceration and progress rapidly, with extension to adjacent tissues; thrombosis and necrosis produce a painful black eschar on the palate or nasal mucosa. Orbital involvement manifests with periorbital edema, proptosis, and blindness. The intracranial invasion can cause encephalopathy, cerebritis, cavernous sinus thrombosis, and stroke.[4-9]
- Pulmonary (24%).
- Cutaneous (19%).
- Gastrointestinal (7%).
- Disseminated (6%).
- Other manifestations: peritonitis, renal abscess, mediastinitis, tracheitis, osteomyelitis, endocarditis, myocarditis, otitis externa and keratitis.[4,6-8]

Clinical suspicion is crucial for diagnosis. The characteristic lesion is a necrotic ulcer with blackish eschar. Computed tomography and nuclear magnetic resonance imaging help evaluate the extent of the lesion to adjacent tissues and identify intravascular thrombosis and lesions in deep structures, including the central nervous system (CNS).

Early antifungal treatment improves prognosis; late initiation (6 days after diagnosis) doubles mortality after 12 weeks.[4] Deoxycholate amphotericin B is a drug, but lipid formulations of amphotericin are less nephrotoxic. They can

be administered at higher doses and for longer periods.[3,8] Liposomal amphotericin is used at a dose of 5 to 10 mg/kg/day,[4] increasing to 10 mg/kg/day in cases with CNS involvement.[5] Posaconazole and isavuconazole are treatment alternatives when the evolution is favorable,[4] and salvage treatment when the response is not as expected. There are anecdotal case reports of combined salvage treatments of amphotericin and echinocandins without demonstrated benefit in oncohematological patients.[10] The duration of treatment varies according to clinical resolution, stabilization, and/or normalization of radiographic signs, and recovery of the underlying immunosuppression.[8]

Mucormycosis is an extremely aggressive opportunistic fungal infection with high mortality. Despite a better understanding of the disease and the availability of more therapeutic options, survival rates in mucormycosis remain low. ■

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