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# Rhino-orbito-cerebral mucormycosis in an acute lymphoblastic leukemia pediatric patient. Case report and review of literature

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## SUMMARY

Mucormycosis is a disease caused by opportunistic fungi of the order Mucorales that generally affects immunocompromised patients or those with underlying disease. It has a high mortality rate and is the third most common invasive fungal infection. The following is a case report of a 12-year-old pediatric patient diagnosed with B-cell acute lymphoblastic leukemia, who presented an aggressive infectious disease two months after beginning chemotherapy, which began in the right frontal and maxillary sinuses, with subsequent progression and extension, progressively deteriorating the patient's clinical status. Culture and biopsy of the affected areas were performed, confirming by histopathology and isolation a rhino-orbito-cerebral mucormycosis due to *Actinomucor elegans*. The patient was treated with specific antifungal therapy as an inpatient and left the service after obtaining negative cultures, continuing with outpatient antifungal treatment.

*Keywords*: mucormycosis, pediatrics, leukemia, amphotericin B, posaconazole.

## INTRODUCTION

Mucormycosis is an acute or subacute, rapidly progressive and highly fatal opportunistic infection, caused by fungi of the order Mucorales, being *Rhizopus* spp. and *Mucor* spp. the most frequent etiologies [1].
According to the TRANSNET (Transplant-Associated Infection Surveillance Network) study, mucormycosis represents the third most common invasive fungal infection after aspergillosis and candidiasis, accounting for the 8% of cases [2]; and according to the SEIFEM (Sorveglianza Epidemiologica Infezioni Fungine nelle Emopatie Maligne - Epidemiological Surveillance in Fungal Infections in Malignant Hemopathies) study, the incidence of mucormycosis is 0.1% in patients with hematological malignancies [3]. Mucormycosis has acquired more importance during the COVID-19 pandemic and it has been reported a significant increase in the number of mucormycosis cases around the world associated with COVID-19, particularly in India [4].
Mucormycosis mainly affects immunosuppressed patients, patients with hematological malignancies, transplant recipients, uncontrolled diabetic patients, among others [5]. It is classified into six clinical forms: rhino-orbito-cerebral, pulmonary,

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cutaneous, gastrointestinal, disseminated and infrequent rare forms (e.g. endocarditis, osteomyelitis, among others) [6].
Rhino-orbito-cerebral mucormycosis is the most common form in diabetic patients and the second most common form in oncologic and transplant patients. It occurs after inhalation of sporangiospores that reach the paranasal sinuses, spread and invade the palate, sphenoid sinus, cavernous sinus, orbits and reach into the skull and brain. Symptoms of sinusitis and periorbital cellulitis are the initial clinical manifestations. It can also include ocular pain, facial numbness, blurred vision, blepharopsis, among others [6]. Confirmatory diagnosis is done by histopathology and fungi isolation, but estimation of damage caused by infection is done by imaging studies [6].
Here we report a rhino-orbito-cerebral mucormycosis in a pediatric patient diagnosed with an oncologic disease.

## CASE REPORT

A 12-year-old male patient from the department of Huila, originally from San Vicente del Caguán municipality, department of Caquetá, Colombia, diagnosed with high-risk B-cell acute lymphoblastic leukemia due to the presence of the Philadelphia chromosome, who started chemotherapy with the "total therapy" protocol in the department of Huila, which had to be suspended on multiple occasions due to complications that occurred during therapy, attended to the Pediatric Oncology and Pediatric Infectology Services of the "Instituto Nacional de Cancerología", Bogotá D.C., Colombia [7].
Two months after receiving chemotherapy, the patient attended to the chemotherapy emergency department presenting a clinical picture characterized by fever up to 39°C associated with severe right hemicranial headache, purulent rhinorrhea and foreign body sensation in the ipsilateral nostril. The following day, erythema and right eyelid edema were observed, with ocular opening limitation and the presence of necrotic crusts in both nostrils. For that reason, a simple skull tomography was requested (Figure 1).
The patient was evaluated by the ophthalmology and otorhinolaryngology services, who considered a possible diagnosis of bacterial or fungal

**Table 1** - Review of literature of mucormycosis in pediatric patients diagnosed with leukemia.

| *Case* | *Author* | *Year* | *Age/Sex* | *Species* | *Type of leukemia* | *Need of surgery* | *Antifungal treatment* | *Sequelae* |
|---|---|---|---|---|---|---|---|---|
| 1 | Almannai et al. [12] | 2013 | 3/F | *Rhizopus* spp. | B-cell precursor acute lymphoblastic leukemia | Yes | amphotericin B, caspofungin, posaconazole | Left lower eyelid ectropion |
| 2 | Cofré et al. [13] | 2015 | 2/F | *Rhizopus arrhizus* | Acute lymphoblastic leukemia-L1 | Yes | amphotericin B, caspofungin, posaconazole | None |
| 3 | De Leonardis et al. [14] | 2015 | 12/F | None* | High-risk T-cell acute lymphoblastic leukemia | Yes | amphotericin B, caspofungin, posaconazole | Mild cosmetic impairment |
| 4 | Mutchnick et al. [15] | 2015 | 2/M | *Mucor* spp. | B-cell precursor acute lymphocytic leukemia | Yes | amphotericin B, posaconazole, micafungin | Binocular vision |
| 5 | Jensen et al. [16] | 2017 | 3/F | *Lichteimia corymbifera* | Moderate-risk Pre-B acute lymphoblastic leukemia | Yes | amphotericin B, posaconazole, terbinafine | Loss of vision on the right side |
| 6 | Ojeda-Diezbarroso et al. [17] | 2019 | 12/F | *Rhizopus oryzae* | Acute lymphoblastic leukemia-L2 | Yes | amphotericin B, posaconazole | None |

* Fungal hyphae were seen in the histopathology but isolation in cultures were negative.

infection, so antimicrobial treatment with fluconazole and cefepime at therapeutic doses was started, showing unsuccessful response with sudden deterioration of the clinical picture, requiring transfer and management in the pediatric intensive care unit, and initiation of inotropic and vasopressor support measures.

Once stable, a biopsy of the nasal septum, right maxilla, sphenoid sinus, periorbita and orbit of the same side was taken.

A histopathological examination was performed with hematoxylin and eosin staining, in which the presence of non-septate broad filamentous fungi with right-angled branches along with areas of necrosis were identified. Due to the unavailability of liposomal amphotericin B, antimicrobial treatment with posaconazole (dose of 17 mg/kg/day) and oxacillin (dose of 300 mg/kg/day) was started.

Microbiological studies were performed on tissue biopsies, which were inoculated on Sabouraud's agar. Fungal growth was studied macroscopically and by microscopy after Lactophenol Cotton Blue staining. Culture isolation results were reported ten days after the biopsy was taken, in which growth of colonies compatible with *Actinomucor elegans* were observed. The patient's symptomatology persisted and progressed despite antimicrobial treatment was started, so he was referred to the "Instituto Nacional de Cancerología" where he was admitted two months after the initial diagnosis, in poor general condition, multi-supported, and with septic shock of tegumentary origin.

Management with liposomal amphotericin B was immediately started, in addition to meropenem, oxacillin, vancomycin and metronidazole to improve antibiotic coverage due to septic shock and also to avoid possible co-infections with nosocomial microorganisms. Additionally, a nuclear magnetic resonance of the cerebral and facial massif was performed, in which involvement of the ocular orbit and right skull base due to the fungal rhinosinusitis was evidenced. For this reason, an assessment was requested to the otorhinolaryngology and ophthalmology services, which performed a transnasal functional endoscopy surgery procedure with local debridement and excision of the right orbit for biopsy.

During surgery, a wide nasal perforation was observed with involvement of the right maxilla and sphenoid sinus together with the formation of fibrotic tissue in the right orbit and periorbita. Antibiotic and antifungal management was continued with the addition of nasal washes with saline solution, observing improvement and adequate clinical evolution of the patient. As a sequel, the patient developed amaurosis of the right eye, requiring enucleation of the right eye.

Negative cultures were obtained after two months of antibiotic and surgical management. The patient was discharged after this time and continued outpatient treatment with liposomal amphotericin B and posaconazole until further evaluation pediatric infectious diseases service.

## LITERATURE SEARCH

A literature search was performed in PubMed/MEDLINE database using the terms "rhinocerebral mucormycosis" and "lymphoblastic leukemia". A total of 32 research papers have been retrieved. Only case reports in which cases were similar to the one presented in this manuscript were considered. A total of seven case reports were included in the review, whose main characteristics have been summarized in Table 1.

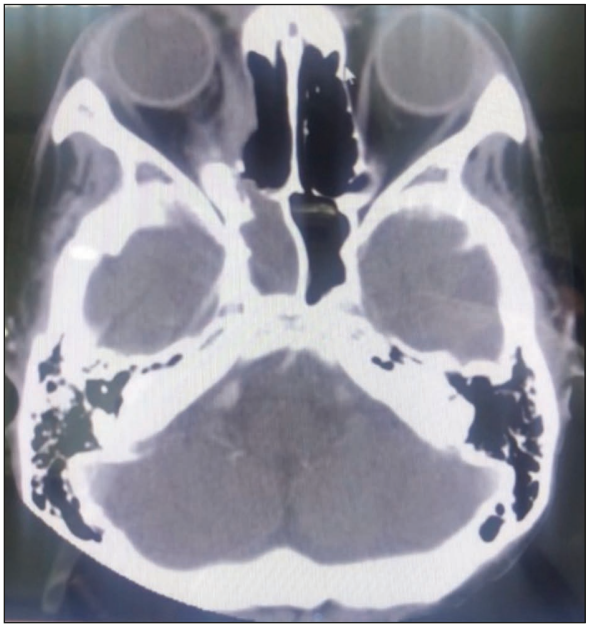

**Figure 1** - Simple skull tomography image. Right sinus/sphenoidal occupation by material with soft tissue density, widening the sinus without cortical disruption.

## DISCUSSION

Mucormycosis is rapidly progressing, highly aggressive and highly fatal opportunistic infection that usually leads to devastating outcomes, thus it is important to suspect it promptly and treat it as quickly as possible [1]. The risk of developing mucormycosis depends on many factors related to the patient's immune status and underlying diseases that may favor the progression and severity of the infection [1, 6].

Therefore, the approach of mucormycosis is based on four important aspects: first, suspicion and early diagnosis to promptly initiate therapeutic interventions to prevent progressive tissue invasion and devastating sequelae; second, interruption of the underlying predisposing factors and management of the patient's comorbidities; third, the early administration of active antifungal agents and other types of therapeutic methods; and finally, performing a complete surgical debridement to remove all compromised and infected tissues [5, 6, 8].

Mucorales are highly resistant to most antifungals *in vitro*, with amphotericin B being the most effective and active antifungal against mucormycosis; however, other antifungals like posaconazole and isavuconazole are also active [8]. According to the ESCMID (European Society of Clinical Microbiology and Infectious Diseases), ECMM (European Confederation of Medical Mycology) and ECIL-6 (European Conference on Infections in Leukemia), the lipid formulation of amphotericin B should be used as first-line therapy for mucormycosis at a dose of 5 mg/kg/day with a maximum of 10 mg/kg/day in cases of central nervous system involvement [9, 10]. However, the use of triazoles such as posaconazole is controversial. The ECIL-6 recommends posaconazole as maintenance therapy after initial treatment with amphotericin B, and ESCMID and ECMM propose that posaconazole be used as first-line treatment [10, 9].

Surgery is particularly useful in rhino-orbito-cerebral cases and should be performed when necessary. Necrotic and surroundings tissues should be removed as they may also be infected due to the speed of spread of mucormycosis. Tissue debridement combined with medical therapy is associated with a better outcome than medical treatment alone. Those patients with extensive tissue debridement are often left with disfigured areas, thus, plastic surgery can be performed to correct them [8, 11].

Other therapies such as the use of hyperbaric oxygen have been shown to have some antimicrobial activity and can also generate synergy with antimicrobial agents; hyperbaric oxygen can also enhance and improve the cellular immune system, as well as promote tissue repair [11]. However, there are not enough studies that can support whether hyperbaric oxygen is effective in the treatment of mucormycosis.

Although an early diagnosis of the disease was made in the reported case, the initial antimicrobial treatment was not adequate, causing the progression of the infection and therefore the clinical deterioration of the patient, which prolonged his hospitalization and exposed him to complications that could be avoidable. Initial empiric therapy with fluconazole, which should not be used in suspected cases of mucormycosis, as it is an anti-candidal agent with no activity against filamentous fungi, which are by far the main etiologies of severe rhinosinusitis in patients with hematologic malignancies, could have favored the progression of the disease. Delayed surgery time and low serum concentrations of posaconazole may be other reasons for fungal disease progression and poor response to treatment occurred in the present case. Therapeutic drug monitoring may be of great importance in severe and potentially fulminant infections as rhino-orbito-cerebral mucormycosis.

Even with all the delays presented in the management, the patient's evolution was favorable once the appropriate treatment was administered. Although some guidelines suggest that posaconazole can be used as first-line antifungal treatment, in the reported case posaconazole alone did not work, making necessary to begin treatment with amphotericin B before treatment with posaconazole as maintenance therapy. Seven other cases of rhino-orbito-cerebral mucormycosis in pediatric patients with leukemia are reported in the literature [9, 12-18]. Table 1 shows a summary of six of them. One was not included as some information about diagnosis and treatment performed was missing [18]. In the six reported cases, the good performance of sequential therapy with high doses of liposomal amphotericin B and posaconazole was evidenced. Liposomal amphotericin B was

used as first-line antifungal, and posaconazole alone as maintenance therapy or combined with amphotericin B as first-line treatment. Surgery was necessary in all cases [19].

This is the first reported case of rhino-orbito-cerebral mucormycosis due to *Actinomucor elegans* in a pediatric patient with leukemia. It was previously reported in a 5-year-old patient with acute lymphoblastic leukemia, however, in this case an invasive pulmonary mucormycosis was developed [20].

In conclusion, the diagnosis and treatment of mucormycosis remain a challenge. The clinical presentation is nonspecific, and when it becomes apparent, the infection usually has a significant extension and tissue involvement, being too late to manage it only with antifungal treatment. Treatment of mucormycosis includes management of underlying factors, administration of antifungal active agents, surgical intervention and various complementary therapies that contribute to improvement. Although amphotericin B and posaconazole are effective antifungal therapies, they must be administered with care considering disease progression in mind to hasten patient improvement.

**Declaration of competing interest**

The authors have no conflicts of interest to disclose in relation to this work.

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**Ethical statement**

No individually identifiable patient information has been revealed in this article. The study procedure was done according with the Helsinki Declaration. The patient's consent was obtained through the Free and Informed Consent Form.

**Authors contribution**

CC Abril Rincón and J Amuruz Arancibia wrote the draft manuscript; MC Prada-Avella and A Suárez attended the patient; CR Silva-Ramos wrote the original manuscript. All authors read, revised critically and approved the final manuscript. All authors meet the ICMJE authorship criteria.

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