

CASE REPORTS

RHINO-ORBITAL-CEREBRAL MUCORMYCOSIS IN A PEDIATRIC CANCER PATIENT

MUCORMICOSE RINO-ORBITO-CEREBRAL NUM DOENTE ONCOLÓGICO PEDIÁTRICO

Maria Eduarda Couto¹ , Tereza Oliva², Pedro Alberto³ , Ana Lebre⁴ , Armando Pinto² , Ana Maia Ferreira²

ABSTRACT

Aim: Mucormycosis infections are highly lethal in immunosuppressed patients. The authors present a rare case of successful treatment of the condition.

Case description: A 14-year-old male with acute lymphoblastic lymphoma in remission was diagnosed with pansinusitis, cerebral osteomyelitis, and encephalitis with an abscess caused by *Rhizopus* sp. Neurosurgical drainage, endoscopic sinus surgery, and left eye enucleation were performed, and the patient was simultaneously treated with liposomal-amphotericin B and posaconazol (later replaced by isavuconazol). However, complications (left frontal lobe herniation and cerebrospinal fluid fistula) ensued, requiring surgical reoperation. Chemotherapy was restarted four months later.

Comments: This is a rare case report, in which early and aggressive surgery, antifungal treatment, and multidisciplinary team work were crucial for the successful outcome.

Keywords: antifungal; encephalitis; mucormycosis; osteomyelitis; *Rhizopus* sp

RESUMO

Objetivo: As infeções por mucormicose associam-se a elevada mortalidade em doentes imunocomprometidos. Os autores descrevem um raro caso clínico de tratamento com sucesso da condição.

Descrição do caso: Um rapaz de 14 anos de idade com linfoma linfoblástico agudo em remissão foi diagnosticado com pansinusite, osteomielite cerebral e encefalite com abscesso causada por *Rhizopus* sp. Foi realizada drenagem neurocirúrgica, cirurgia endoscópica naso-sinusal e enucleação do olho esquerdo. O doente iniciou tratamento com anfotericina B lipossómica e posaconazol (posteriormente substituído por isavuconazol). No entanto, o desenvolvimento de complicações (herniação do lobo frontal esquerdo e fístula de líquido cefalorraquídeo) exigiu reintervenção cirúrgica. Quatro meses depois, foi reiniciada quimioterapia.

Comentários: Este é um caso clínico raro, no qual cirurgia precoce e agressiva, antifúngicos adequados e abordagem por uma equipa multidisciplinar foram determinantes para o sucesso alcançado.

Palavras-chave: antifúngico; encefalite; mucormicose; osteomielite; *Rhizopus* sp

1. Department of Onco-Hematology, Instituto Português de Oncologia do Porto Francisco Gentil. 4200-072 Porto, Portugal. eduarda.scouto@gmail.com
2. Department of Pediatrics, Instituto Português de Oncologia do Porto Francisco Gentil. 4200-072 Porto, Portugal. tereza.oliva@sapo.pt; armando.pinto.pediatria@gmail.com; maiaferreira.ana@gmail.com
3. Department of Neurosurgery, Centro Hospitalar e Universitário São João. 4200-319 Porto, Portugal. pedroalbertosilva.neurocirurgia@gmail.com
4. Department of Infectious Disease, Instituto Português de Oncologia do Porto. 4200-072 Porto, Portugal. anaflebre@gmail.com

INTRODUCTION

Acute invasive fungal infection (AIFI) is a life-threatening condition with an annual incidence of 1.7/1 million inhabitants in the United States of America.¹⁻⁴ The most common etiological agents are *Aspergillus*, *Rhizopus*, and *Mucor* species, which are often present in the natural environment and transmitted through inhalation or ingestion of spores, causing illness in immunosuppressed patients.⁴ Their fungal hyphae are highly destructive for the mucosae, invade blood vessels and bones, and cause neutrophilic infiltration and tissue necrosis.¹⁻⁴

Mucormycosis is a rare AIFI infection caused by a group of fungi called Mucormycotina. Nineteen mucormycosis cases were identified in Portugal between 2001 and 2015, both in adults and children. Relevant risk factors associated with the disease include hematological disorders, HIV infection, transplant history, chemotherapy or corticosteroids exposure, prolonged antibiotic therapy, diabetic ketoacidosis, renal failure, and intravenous drug use.³⁻⁷

The most common mucormycosis locations are rhino-orbital-cerebral sites (33-44%), skin (10-16%), and lung (10-11%). The most common agent is *Rhizopus* sp (37% of cases), followed by *Mucor* sp. and *Rhizopus* spp. Fungi are ubiquitous in the environment and a rare but substantial cause of infection in immunosuppressed persons and surgery patients. Frequent clinical signs of rhino-orbital-cerebral mucormycosis include fever, face swelling, diplopia, decreased vision, nasal discharge, facial pain, headache, decreased mental function, black nasal discharge crusts, turbinate necrosis, ulceration, and palatal perforation. Cerebral infarction with neutrophilic infiltration and angioinvasion can also occur.¹⁻⁴

The diagnosis is established based on clinical symptoms combined with risk factors and imaging assessment, as well as tissue biopsy for culture (positive in 33-61%) and histopathology.^{1-4,8,9}

Regarding treatment options, liposomal amphotericin B (L-Amb B) and posaconazol/isavuconazol are first- and second-line antifungal options that should be used in addition to aggressive surgical treatment. The choice of the agent for central nervous system (CNS) infection depends on CSF penetration and activity spectrum. L-Amb B has relatively limited distribution in CSF but achieves detectable therapeutic levels in CNS. Posaconazol achieves negligible concentrations in CSF, but isavuconazol has considerable efficacy in CNS infections.³ Successful use of isavuconazol has been mostly reported in adults, but also in children.³

Despite aggressive surgical debridement, immune restoration therapy, and long-term high-dose antifungal treatment, the risk of recurrence is high.^{1-4,8,9} In the course of rhino-orbital-cerebral mucormycosis, morbidity varies between 30-97%, and mortality between 70-80%.^{3,9-12}

CASE REPORT

A 14-year-old male was diagnosed with acute T-lymphoblastic lymphoma (mediastinal mass, testicular and cutaneous disease at presentation; no CNS involvement). Chemotherapy was prescribed according to CLG-EORTC arm AR2 protocol (high average risk), with complete response after one month.

While in the seventh month of reinduction chemotherapy, the patient was admitted to the Emergency Department with discrete left facial paresthesia. No neurologic deficits were found, as well as no neutropenia in blood work. Cerebral computerized tomography (CT) scan disclosed no abnormalities, and the boy was discharged home with a reevaluation appointment scheduled for less than one week.

On the following day, the boy returned to the hospital with left peripheral facial paresis and neutropenia. Cerebral CT scan was repeated, showing rapidly progressive pansinusitis, and the patient was admitted for intravenous therapy with meropenem, vancomycin, and L-Amb B 3 mg/kg. On the next day, he developed diplopia, ophthalmoplegia, and left ptosis, requiring neurological evaluation. CT scan showed a completely different image from the previous day, suggestive of mucormycosis with extension to the left orbit and nasal region. On day four, the patient developed fever, together with right deviation of the labial commissure and amaurosis. On day five, magnetic resonance imaging (MRI) of the brain confirmed pansinusitis with extension to pterygoids muscles and posterior part of the nasopharynx and orbit, facial cellulitis, thrombosis of the left cavernous sinus, venous congestion of the left orbit and proptosis, left carotid artery stenosis, and encephalitis of the left temporal lobe and orbital portion of the left frontal lobe. L-Amb B was increased to 5 mg/kg and prophylactic enoxaparin was started. On day six, microbiological analysis of a sample aspirate confirmed *Rhizopus* sp infection. Sequential blood cultures collected since admission were all negative, and CSF cytological and microbiological analysis was negative for other infections and malignant disease.

On day 12, control MRI (**Figures 1 and 2**) showed pansinusitis worsening and extension of the infection through muscular and adipose tissues, optic nerve, and optical chiasma; invasion of the II, III, IV, V, and VI nerves; and irregular fronto-temporo-insular cerebral abscess, with 51 x 42 x 46 mm, causing a mass effect. At this time, L-Amb B was increased to 10 mg/kg and posaconazol was added.

On day 13, successful multidisciplinary surgery involving Neurosurgery, Ophthalmology, and Otorhinolaryngology was conducted. The procedure included removal of the affected area of the brain and surroundings, lateral and upper orbitotomy, optical nerve section, enucleation of the left orbit, and endoscopic sinus surgery.

One week later, posaconazol was replaced by intravenous isavuconazol 200 mg twice daily, and fever decreased. Hyperbaric

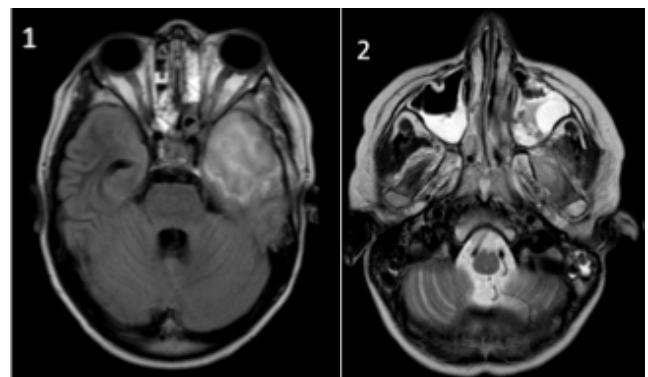
chamber treatment was also attempted to improve local tissue vascularization but was poorly tolerated, with nausea and vomiting, and suspended after four sessions. The patient developed severe hypokalemia, decreased renal clearance, nausea, vomiting (assumed as an adverse event of the antifungal agents), and stable thrombocytopenia ($\approx 90.000 \times 10^9/L$ platelets; no bleeding).

The need to remove the invaded orbital walls, together with orbital enucleation, left the patient with no anatomical support for the surrounding structures. Progressive left frontal herniation through the bony defect occurred, leading to a CSF fistula. Brain MRI performed two weeks later (**Figures 3 and 4**) confirmed cerebral herniation of the frontal lobe, with no ischemic tissue and slight improvement of fungal encephalitis. Persistence of osteomyelitis and infection of muscles and cerebral parenchyma were evident, besides multiple newly diagnosed mycotic aneurysms in the left internal carotid and middle cerebral arteries, and severe reduction of the left internal carotid artery flow.

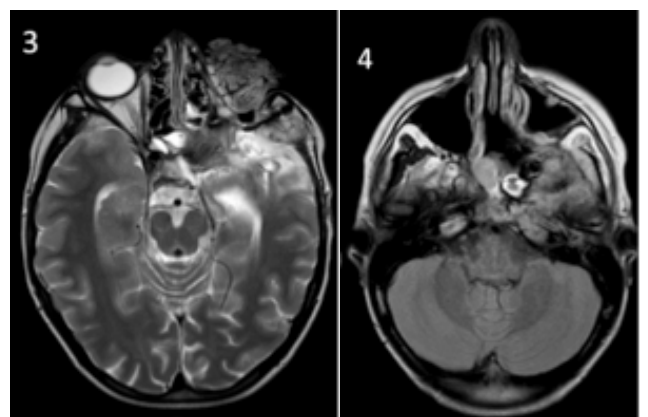
The day before scheduled angiography, the patient had a spontaneous severe mouth and nose bleeding that coursed with self-limited hypovolemic shock. He was transfused, intubated, and admitted to the Intensive Care Unit (ICU) for surveillance. Brain CT and angiography suggested post-hemorrhage spontaneous thrombosis of mycotic aneurysms, subsequently confirmed by MRI. This warranted neurosurgical reintervention through orbital reconstruction (with a titanium plate and patient's abdominal fat) and correction of the CSF fistula and frontal lobe herniation, with extraction of devitalized tissues (**Figures 5 and 6**). After this surgery, the patient developed acute pancreatitis with small-volume bilateral pleural effusions, small-volume ascites, and decreased renal clearance with metabolic acidosis. He was discharged from the ICU one week later.

Overall, the boy remained in the hospital for four months since diagnosis, under L-Amb B and isavuconazol treatment, ionic supplementation, and physical rehabilitation. Subsequently, the same dosage of intravenous antifungal therapy was administered in outpatient setting. He is currently completely autonomous and cognitively able to have a normal social life, with initial concerns about cognitive frontal lobe impairment shown to be unfounded.

Chemotherapy was restarted four months after infection diagnosis, and the patient is currently in the maintenance phase (oral 6-mercaptopurine and methotrexate). L-Amb B was deescalated to 5 mg/kg six months after the infection (MRI showed a more limited infectious region), being stopped after 15 months. Intravenous isavuconazol was replaced by an oral formulation after 15 months, being still in use. The patient was reoperated two more times due to relapse of the frontal hernia and CSF fistula, with progressive fistula resolution.



Figures 1 and 2 - Different sections of the first brain MRI at diagnosis



Figures 3 and 4 - Brain MRI after the first surgery



Figure 5 - Frontal lobe herniation



Figure 6 - Empty left orbit after correction of frontal lobe herniation

DISCUSSION

Case reports of mucormycosis infections in immunosuppressed patients are scarce, challenging the definition of the best approach.¹³⁻²¹ This case highlights that immunosuppressive treatment is a relevant risk factor for fungal infection. With the availability of new and more potent drugs, the ideal prophylactic antifungal agent is yet to be defined.

Mucormycosis diagnosis demands a high index of suspicion and involvement of a multidisciplinary team to manage the accelerated destruction of infected structures, organ dysfunction, and mortality. Chemotherapy must be immediately stopped after diagnosis. Early and aggressive surgery seems to be the most relevant indicator of success, by controlling the infectious focus. Additionally, medical treatment must be optimized by selecting the most suitable agents against Mucorales – in the present case, L-Amb B in high dose (10 mg/kg/daily) and isavuconazol. The use of adjuvant therapies (such as hyperbaric chamber treatment) should be considered, if appropriate.

To the authors' knowledge, this is the first report of (off-label) use of isavuconazol in the pediatric setting in Portugal. The drug is associated with less resistance compared to posaconazol and better CNS penetration.²²⁻²⁵ Side effects likely attributed to this agent have been reported, and include nausea, vomiting, hypokalemia, and renal impairment. In the present case, fever subsided as soon as the drug was started. A double antifungal strategy, previously described in similar case reports, was justified given the high disease severity in an immunosuppressed patient.²⁶⁻²⁷ The combination of a new and highly effective option with limited use in pediatric patients (isavuconazol) and an old and well-known drug (L-Amb B) provided the rationale for improved CNS penetration and patient outcomes, by using the most suitable antifungals available for this

type of infection with no known interactions. The patient currently remains on oral isavuconazol and maintenance chemotherapy. L-Amb B proved to be a suitable first-line option for mucormycosis and an adequate agent to combine with isavuconazol. Although there are no guidelines stating for how long antifungal treatments should be maintained, waiting for chemotherapy completion and imaging resolution seems advisable.

After a long inpatient period, the boy's functional status started improving with daily physical rehabilitation. He is currently accompanied by a multidisciplinary team including Pediatric Oncology, Neurosurgery, Otorhinolaryngology, and Ophthalmology. Chemotherapy was continued, with no other relevant adverse events. Psychological, psychiatric, social, and nutritional support were also provided. Close communication with the patient and family facilitated understanding and acceptance of medical team decisions, an important step to achieve success.

ABBREVIATIONS

<i>AIFI</i>	<i>acute invasive fungal infection</i>
<i>L-Amb B</i>	<i>liposomal amphotericin B</i>
<i>CNS</i>	<i>central nervous system</i>
<i>CT</i>	<i>computerized tomography</i>
<i>MRI</i>	<i>Magnetic resonance imaging</i>
<i>CSF</i>	<i>cerebrospinal fluid</i>
<i>ICU</i>	<i>intensive care unit</i>

REFERENCES

1. Paknezhad H, Borchard NA, Charville GW, Ayoub NF, Choby GW, Thamboo A, *et al.* Evidence for a 'preinvasive' variant of fungal sinusitis: Tissue invasion without angioinvasion. *World Journal of Otorhinolaryngology - Head and Neck Surgery.* 2017;3:37-43.
2. Deshazo RD. Syndromes of invasive fungal sinusitis. *Medical Mycology.* 2009;47:S309-14.
3. Góral ska K, Blaszkowska J, Dzikowiec M. Neuroinfections caused by fungi. *Infection.* 2018;46:443-59.
4. Skiada A, Lanternier F, Groll AH, Pagano L, Zimmerli S, Herbrecht R, *et al.* Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3). *Haematologica.* 2013;98:492-504.
5. Sabino R, Veríssimo C, Brandão J, Martins C, Alves D, Pais C, *et al.* Serious fungal infections in Portugal. *European Journal of Clinical Microbiology and Infectious Diseases.* 2017;36:1345-52.

6. Ferguson B. Mucormycosis of the nose and paranasal sinuses. *Otolaryngol Clin North Am.* 2000;33:349-65.
7. Cornely OA, Arikian-Akdagli S, Dannaoui E, Groll AH, Lagrou K, Chakrabarti A, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. *Clinical Microbiology and Infection.* 2014;20:5–26.
8. Tissot F, Agrawal S, Pagano L, Petrikos G, Groll AH, Skiada A, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. *Haematologica.* 2017;102:433-44.
9. Avet J, Kline LB, Sillers MJ. Endoscopic sinus surgery in the management of mucormycosis. *Neuropathology.* 1999;19:56-61.
10. Santos Gorjón P, Blanco Pérez P, Batuecas Caletrío A, Muñoz Herrera AM, Sánchez González F, de la Fuente Cañibano R. Rhino-orbito-cerebral mucormycosis, a retrospective study of 7 cases. *Acta Otorrinolaringologica Española.* 2010;61:48-53.
11. Chen CY, Sheng WH, Cheng A, Chen YC, Tsay W, Tang JL, et al. Invasive fungal sinusitis in patients with hematological malignancy: 15 years experience in a single university hospital in Taiwan. *BMC Infectious Diseases.* 2011;11:250.
12. Garlapati K, Chavva S, Vaddeswarupu RM, Surampudi J. Fulminant Mucormycosis Involving Paranasal Sinuses: A Rare Case Report. *Case Reports in Dentistry.* 2014:465919.
13. Steve AK, Hurdle VA, Brown JY. Orbitomaxillofacial Mucormycosis Requiring Complex Multifactorial Management. *Orbitomaxillofacial Mucormycosis.* 2018;6:e1927.
14. Haliloglu NU, Yesilirmak Z, Erden A, Erden I. Rhino-orbito-cerebral mucormycosis: report of two cases and review of the literature. *Dentomaxillofacial Radiology.* 2008;37:161–6.
15. Kerezoudis P, Watts CR, Bydon M, Dababneh AS, Deyo CN, Frye JM, et al. Diagnosis and Treatment of Isolated Cerebral Mucormycosis: Patient-Level Data Meta-Analysis and Mayo Clinic Experience. *World Neurosurgery.* 2019;123:425-34.
16. Bae MS, Kim EJ, Lee KM, Choi WS. Rapidly Progressive Rhino-orbito-cerebral Mucormycosis Complicated with Unilateral Internal Carotid Artery Occlusion: A Case Report. *Neurointervention.* 2012;7:45-9.
17. Prabhu S, Alqahtani M, Al Shehabi M. A fatal case of rhinocerebral mucormycosis of the jaw after dental extractions and review of literature. *Journal of Infection and Public Health.* 2018;11:301-3
18. Sharma RR, Pawar SJ, Delmendo A, Lad SD, Athale SD. Fatal rhino-orbito-cerebral mucormycosis in an apparently normal host: case report and literature review. *Journal of Clinical Neuroscience.* 2001;8:583-6.
19. Jeevanan J, Gendeh BS, Faridah HA, Vikneswaran T. Rhino-orbito-cerebral mucormycosis: a treatment dilemma. *Medical Journal of Malaysia.* 2006; 61:6.
20. Simmons JH, Zeitler PS, Fenton LZ, Abzug MJ, Fiallo-Scharer RV, Klingensmith GJ. Rhinocerebral mucormycosis complicated by internal carotid artery thrombosis in a pediatric patient with type 1 diabetes mellitus: a case report and review of the literature. *Pediatric Diabetes.* 2005;6:234–8.
21. Zafar S, Prabhu A. Rhino-orbito-cerebral mucormycosis: recovery against the odds. *Practical Neurology.* 2017;17:485–8.
22. Barg AA, Malkiel S, Bartuv M, Greenberg G, Toren A, Keller N. Successful treatment of invasive mucormycosis with isavuconazole in pediatric patients. *Pediatric Blood Cancer.* 2018;65:e27281.
23. Miceli MH, Kauffman CA. Isavuconazole: A New Broad-Spectrum Triazole Antifungal Agent. *Clinical Infectious Diseases.* 2015; 15;61:1558-65.
24. Marty FM, Ostrosky-Zeichner L, Cornely OA, Mullane KM, Perfect JR, Thompson GR, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. *Lancet Infectious Diseases.* 2016;16:828-37.
25. Shirley M, Scott LJ. Isavuconazole: A Review in Invasive Aspergillosis and Mucormycosis. *Drugs.* 2016;76:1647-57.
26. Ferreira IS, Teixeira G, Abecasis M. *Alternaria alternata* Invasive Fungal Infection in a Patient with Fanconi's Anemia after an Unrelated Bone Marrow Transplant. *Clinical Drug Investigation.* 2013;33:S33–6.
27. Athanasiadou KI, Athanasiadis DI, Constantinidis J, Anastasiou A, Roilides E, Papakonstantinou E. Successful treatment of rhinoorbital mucormycosis due to *Rhizopus arrhizus* with liposomal amphotericin B, posaconazole and surgical debridement in a child with neuroblastoma. *Medical Mycology Case Reports.* 2019;25:10-4.

CORRESPONDENCE TO

Maria Eduarda Couto
 Department of Onco-Hematology
 Instituto Português de Oncologia do Porto Francisco Gentil
 Rua Dr. António Bernardino de Almeida 62
 4200-072 Porto
 Email: eduarda.scouto@gmail.com

Received for publication: 27.03.2020
 Accepted in revised form: 16.02.2021