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ORIGINAL ARTICLE

MUCORMYCOSIS IN PATIENTS ADMITTED TO A UNIVERSITY HOSPITAL: A CASE SERIES

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ABSTRACT

Mucormycosis is an aggressive disease with high morbidity and mortality caused by fungi from the Mucorales order. They are fungi widely present in nature but may also be related to nosocomial infections. We present four cases of mucormycosis identified through histopathological analysis and involving the rhino-sinus region. All the cases were related to decompensated diabetes mellitus. Among these patients, two of them had lesions that affected their eyes and central nervous system (CNS). Although there were no fatalities, the two patients with ocular and CNS lesions experienced severe complications, including loss of vision and definitive chronic renal failure.

KEY WORDS: Mucormycosis; Covid-19; Sars-cov-2; diabetes mellitus; rhino-orbital.

INTRODUCTION

Mucormycosis is an angioinvasive disease, with hematogenous dissemination and high lethality, caused by fungi from the Mucorales order. Eleven genera and around 27 species under Mucorales are associated with human infections. *Rhizopus arrhizus* is the most common agent causing mucormycosis across the globe, followed by *Lichtheimia, Apophysomyces, Rhizomucor, Mucor* and *Cunninghamella* species (Prakash & Chakrabarti, 2019). The main risk factors involved in the infection are diabetes mellitus (DM), malnutrition, neoplasms (mainly hematological, due to neutropenia), kidney failure, organ transplants, burns, immunosuppressive therapies, cirrhosis, liver diseases, chemotherapy,

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use of intravenous drugs, acquired immunodeficiency virus infection and use of calcineurin inhibitors. Furthermore, patients with diabetic ketoacidosis, dialysis and those using the iron chelator deferoxamine are more susceptible (Sharma et al., 2023). On the Asian continent, the main factor is DM, while in Europe and in the United States, mucormycosis is mainly associated with hematological malignancies and transplants (Prakash & Chakrabarti, 2019).

The incidence is growing globally, notably in India and China, due to the significant high number of decompensated diabetics. According to estimates, the annual prevalence could be approximately 910,000 cases globally. Despite being community-acquired fungi, nosocomial mucormycosis associated with contaminated devices has recently increased (Prakash & Chakrabarti, 2019).

In Brazil, there has been a significant increase of cases since 2018. Throughout this year, 27 cases were reported to the Ministry of Health, and 31 in 2019 (Ministry of Health, 2022). The rise in cases during and after the COVID-19 pandemic is unquestionable, adding up to 85 hospitalizations due to mucormycosis in Brazil in 2020 and 2021. This fact may be related to the greater need for intensive care, long periods of hospitalization and the use of corticosteroids, which increase the risk of invasive fungal diseases (Santos et al., 2023).

Diagnosis requires professionals with the expertise to evaluate imaging tests and mycological and histological investigations. Generally, mucormycosis is inferred by direct microscopy results with specific stains, such as hematoxylin-eosin (HE), periodic acid-Schiff (PAS), or silver methenamine (Grocott-Gomori's). The hyphae are broad, with non-to-rare septation, with branches at a 90-degree angle. Culture is essential since it allows species identification and susceptibility testing; unfortunately, culture is falsely negative in more than 50% of the cases of mucormycosis. The organisms grow well *in vitro*, but homogenization of the tissue may cause viability loss of the fragile hyphal forms of these fungi (Cornely et al., 2019).

The polymerase chain reaction (PCR) is essential for diagnosing species not identified in culture. It is positive, with an average of up to four days before histological exams/ culture and up to one day before positive imaging. Furthermore, evaluating therapeutic response may be favorable, as it can become negative in up to seven days (Garnes & Kontoyiannis, 2023).

In treatment, Amphotericin B (AMB) is the first FDA-approved drug for treating mucormycosis infections. It has been noted that *in vitro* AMB activity against Mucorales varies greatly. Based on recent *in vivo* and *in vitro* studies, it is proposed that to treat mucormycosis effectively, one must consider the availability of surgical debridement and antifungal treatments. For step-down therapy, we may use triazoles. Both posaconazole and isavuconazole are members of the triazole drug class; these drugs exhibit higher activity against Mucorales *in vitro* than other triazoles (Smith & Lee, 2022).

This study aims to describe a series of cases of mucormycosis, whose main risk factor was the presence of DM.

MATERIAL AND METHODS

A case series of patients (Table) admitted with mucormycosis to a teaching hospital in the city of Goiânia, the State capital in the central-west region of Brazil, with approximately 1,437,366 inhabitants (IBGE, 2022) were included. This hospital has 260 beds, divided into 116 surgical and 144 clinical beds (Rodrigues et al., 2021). All cases received care from a multidisciplinary team covering infectious disease, ophthalmology, otorhinolaryngology, neurology, neurosurgery, endocrinology, nutrition, phono-audiology, physiotherapy and pharmacy teams. The institution's Ethics Committee approved the study under the number 6,317,632.

CASE 1

A sixty-one-year-old man with hypertensive disease, diabetes and suffering from coronary disease with irregular treatments started experiencing pain in the jaw region, associated with nasal discharge and moderate amounts of bleeding. He used several oral antibiotics without improvement. After two months, he sought an otorhinolaryngology (ear-nose-throat/ ENT) team, who decided on surgical debridement, and mucormycosis was diagnosed in histopathological analysis. Figure 1 shows the radiological findings.

He was referred to the Clinical Hospital from the Federal University of Goiás (HC-UFG) for a specific treatment and he started on liposomal amphotericin B (L-AMB, 5 mg/kg/day). Two days after admission, he was diagnosed with COVID-19 without the need for oxygen therapy. He underwent fourteen days of antibiotic therapy to treat a secondary bacterial infection, with good clinical evolution. After ten days of intravenous antifungal medication, he presented changes in renal function, and posaconazole (POSA) oral suspension (40mg/mL) was prescribed for continued treatment with 400mg (10 mL) twice a day. However, due to the unavailability of the oral antifungal, he completed treatment with L-AMB in outpatient parenteral antimicrobial therapy (OPAT) for 60 days. Four months after the end of treatment, the patient temporarily underwent renal replacement therapy for six months. He is now experiencing recovered kidney function without requiring any hemodialysis and there are no signs of fungal recurrence.

Table. Summary of patients hospitalized with mucormycosis at HC-UFG in 2021, 2022 and 2023.

Patient	Gender	Year of Occurrence	Age (years)	Comorbidities	Evolution time before treatment (days)	Clinical Form	Treatment (surgical debridement and antifungals)	Outcome
1	Male	2021	61	DM/ SAH/ CAD	60	Rhino-sinusal	Amphotericin B: 60 days Posaconazole: did not use	Cure
2	Female	2022	54	DM	30	Rhino-orbital-cerebral	Amphotericin B: 176 days Posaconazole: 12 months Dual therapy for 35 days Posaconazole: continuous use	Active disease
3	Male	2022	41	DM	90	Rhino-orbital-cerebral	Amphotericin B: 152 days Posaconazole: 360 days	Cure
4	Female	2023	66	DM/SAH	90	Rhino-sinusal	Amphotericin B: 47 days Posaconazole: 170 days	Cure

DM: Diabetes Mellitus; SAH: Systemic Arterial Hypertension; CAD: Coronary Artery Disease.
*All patients received concomitant surgical treatment and extensive debridement.

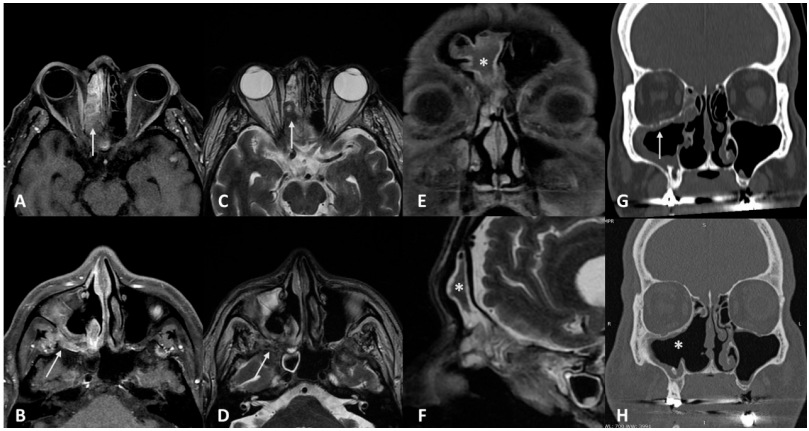

Figure 1. Rhinosinusitis necrotizing erosive fungal disease (mucormycosis) A and B. Ax T1FS ct +: White arrow - Regions of lack of enhancement, related to necrosis in the walls of the ethmoidal cells and in the right maxillary sinus, insinuating into the pterygopalatine fossa. C and D. Ax T2: White arrow - The regions of necrosis have marked T2 hyposignal. E and F. * Color T1FS ct + and Sag T2: * Thick secretion due to a fungal component inside the right frontal sinus. G. Bone CT Color: White arrow - Bone erosion with a "moth-eaten" appearance. H. Post-treatment. Bone CT Color: * Wide sinusectomy maxilloethmoid and total turbinectomy.
Ax: Axial. Sag: Sagittal. Color: Coronal. Ct +: Post-contrast sequences. FS: Fat saturation.

CASE 2

A fifty-four-year-old woman presented with altered mental status, confusion and significant glycemic changes requiring the Intensive Care Unit (ICU). She was diagnosed with hyperosmolar hyperglycemic state and decompensated DM, with glycosylated hemoglobin of 9%. During hospitalization, she presented edema in the left eye, associated with phlogistic signs and limited eye-opening. She remained in the ICU for eleven days and she was transferred to the ward for continued antibiotic therapy, using several empiric antimicrobial regimens (ceftriaxone 1g 12/12h; oxacillin 2g 4/4h; piperacillin-tazobactam 4.5g 6/6h; vancomycin 1g 12/12h). As nasofibroscopy revealed extensive necrosis with perforation of the nasal septum, she started on amphotericin B deoxycholate 50mg/day. After one month, she was forwarded to a reference hospital (HC-UFG), where she started on L-AMB 10 mg/kg/day. She underwent a surgical approach by the ENT team, and a frozen section biopsy revealed structures suggestive of mucormycosis, further confirmed by histopathological analysis.

After two months, due to disease progression, debridement of necrotic tissue and exenteration of the left eyeball was performed. However, diffuse bone fungal involvement was still in the frontal bone, skull base, mastoid, hard palate, jaw, sphenoidal processes, alveolar processes and mastoid (Figure 2). After a comprehensive evaluation by ENT, neurosurgery, and head and neck surgery teams, they determined that surgery was unfeasible due to extensiveness, aggressiveness and mutilating process, in addition to the risk of the skull base collapsing.

She was discharged for L-AMB 10 mg/kg/day OPAT due to the initial unavailability of oral therapy, after almost six months of L-AMB treatment, she was treated by oral POSA 400mg (10 mL) twice a day for another 12 months. After this period, she presented with a new episode of epistaxis, periorbital pain associated with phlogistic signs, rhinorrhea with a foul odor and myiasis in the left orbital cavity, requiring local hygiene and antimicrobials for secondary bacterial infection. By evaluating imaging tests (magnetic resonance imaging of the skull), the worsening of rhino-orbital-cerebral mucormycosis was confirmed, with the reintroduction of L-AMB 10 mg/kg/day in association with POSA 400mg 12/12h. She received dual therapy for 35 days, with improvement in the symptoms presented upon admission.

After discharge, she maintained oral POSA in the same dose and periodic reevaluations. Due to the persistence of areas of necrosis at the skull basis, without debridement feasibility, indefinite POSA maintenance therapy was recommended. Due to the risk of skull base collapse and herniation, the extensive lesion still showing signs of activity could not be removed, leading to the risk of frequent recurrences and progression of the lesions, with or without withdrawal of the medication. This had occurred previously, requiring a new induction of treatment with L-AMB combined with POSA. Continuous medication was ensured by the State after medical reports justifying the condition and legal proceedings with the Public Prosecutor's Office.

CASE 3

A forty-one-year-old previously healthy man had a history of upper left dental pain that started three months before the onset of the condition. Within the last two weeks, the patient progressed to periorbital and ipsilateral maxillary edema. He underwent tooth extraction and multiple oral antimicrobial treatments, with partial improvement. He was diagnosed with type 2 DM, and he started insulin therapy. An imaging examination (magnetic resonance imaging of the skull) demonstrated the presence of hypoattenuating material in ethmoid cells, mucous thickening of the left maxillary sinus and sphenoid sinuses, densification of the salpingopharyngeal fold and left pharyngeal tonsil, extending to the chewing space and pterygopalatine fossa, in addition to pachymeningeal infiltration in the left middle cranial fossa and vasogenic edema (Figure 3).

He developed facial hemiparesis and left palate necrosis, purulent rhinorrhea and fever. He was then forwarded to HC-UFG. A direct mycological examination of the nasal region showed the presence of large, coenocytic, hyaline hyphae, suggesting mucormycosis, which was confirmed by histopathology. Due to the difficulty in eating due to a palatal fistula, with the return of the ingested diet, he underwent gastrostomy and subsequent treatment of the palate injury. During a long period of hospitalization, he developed renal injury due to the prolonged use of intravenous L-AMB (10 mg/kg/day), in addition to hydroelectrolyte disorders and peripheral neuropathy. After four months of admission, in joint follow-up with the ophthalmology team, he presented worsening ocular hyperemia and decreased visual acuity, progressing to enucleation of the left eyeball without complications. One month after this surgery, he received L-AMB OPAT for another two weeks, followed by oral POSA 400mg 12/12h as maintenance of antifungal treatment.

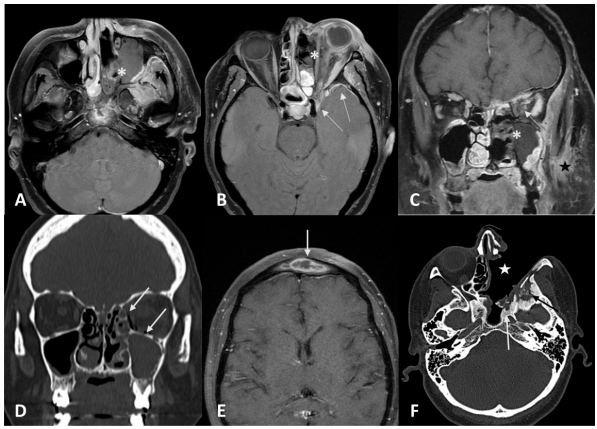

Figure 2. Rhinosinusitis necrotizing erosive fungal disease (mucormycosis) A. Ax T1FS ct +: * Regions of necrosis in the left maxillary sinus, insinuating itself into the respective nasal cavity, characterized by lack of enhancement. B. Ax T1FS ct +: * Regions of ethmoid necrosis, with erosion and invasion of the lamina papyracea, extending to the orbit, affecting the conal muscles, optic nerve, and intra and extraconal fat, causing ocular proptosis. White arrow - Intracranial pachymeningeal enhancement. C. * Color T1FS ct +: * Ethmoidomaxillarynecrosis. White arrow - Optic nerve necrosis. Star - secondary inflammatory/infectious process of the musculoadipose planes of the left hemiface. D. Bone CT Color: White arrow - Bone erosion with a "moth-eaten" appearance. E and F. Post-treatment. AND. Ax T1FS ct +: White arrow - Area of recurrence with bilateral frontal necrosis. F. Post surgical Ax Bone CT: Star - Wide sinusectomy, orbitectomy and total turbinectomy. White arrow refers to bone hyperostosis related to chronicity. Black arrow - necrotic remains in the greater wing of the sphenoid.

Ax: Axial. Color: Coronal. Ct +: Post-contrast sequences. FS: Fat saturation.

Eight months after hospital discharge, he sought emergency care due to bilateral purulent nasal discharge and the presence of myiasis. After removing the larvae, he underwent antibiotic therapy for acute rhinosinusitis associated with an abscess in the orbital cavity. POSA was suspended after one year, and he had a total of 18 months of antifungal treatment. The patient had disfiguring facial sequelae due to the loss of the eyeball, in addition to intense dysesthesia, requiring chronic use of opioids for pain control.

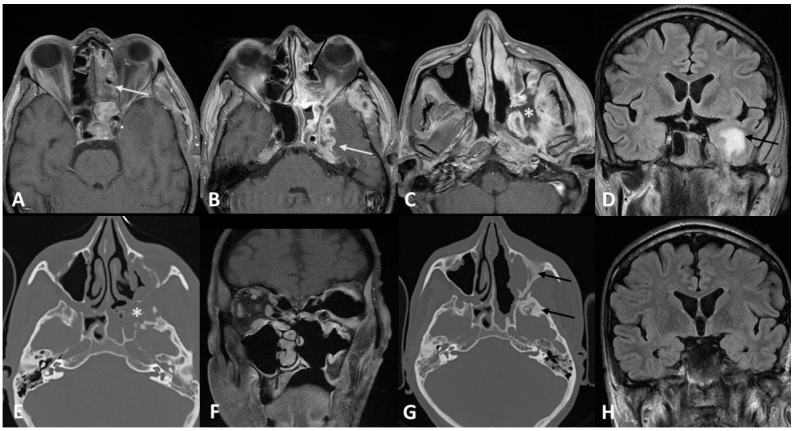

Figure 3. Rhinosinusitis necrotizing erosive fungal disease (mucormycosis) A. Ax T1FS ct +: White arrow - Regions of lack of enhancement related to necrosis in the walls of the left ethmoidal cells and lamina papyracea. B. Ax T1FS ct +: White arrow - Pachymeningeal intracranial necrosis, extending to the temporal brain parenchyma. C. Ax T1FS ct +: * Region of retromaxillary necrosis and left pterygopalatine cistern. A large secondary inflammatory component is also noted in the chewing space on that side. D. FLAIR color: Black arrow - Edema of the temporal brain parenchyma on the left. E. Ax Bone CT: * Bone erosion with a "moth-eaten" appearance. F, G and H. Post-treatment. F. Color T1FS ct +: Wide maxilloethmoid sinusectomy, total turbinectomy and orbitectomy. G. Ax Bone CT: Black Arrows - Regions of hyperostosis, indicating chronification and reduction of the erosive aspect. A small region of necrosis persists inside the greater wing of the sphenoid. H. Color FLAIR: Note the resolution of edema in the left temporal brain parenchyma.
Ax: Axial. Color: Coronal. Ct +: Post-contrast sequences. FS: Fat saturation.

CASE 4

A sixty-six-year-old woman, previously hypertensive and diabetic under regular treatment, reported COVID-19, requiring hospitalization due to dysglycemia, but without supplemental oxygen therapy or corticosteroids. Since that time, she began pain in the right hemiface, predominantly in the malar and periorbital regions, which progressed with worsening pain and

significant paresthesia. After the ENT team evaluation, she underwent a sinusectomy with tissue collection. Anatomopathological results revealed non-septate micellar hyphae suggestive of mucormycosis. Two months after the onset of the condition, she was referred to HC-UFG due to continued holocranial headache associated with retro-orbital and right maxillary pain and mandibular claudication. Figure 4 demonstrate MRI findings. At this time, she underwent a new sinusectomy and debridement of residual necrotic tissues. She received L-AMB (5 mg/kg/day) for a total of 47 days and, after clinical stabilization, continued antifungal treatment on an outpatient basis with oral POSA for another seven months. To date, there is no evidence of fungal activity.

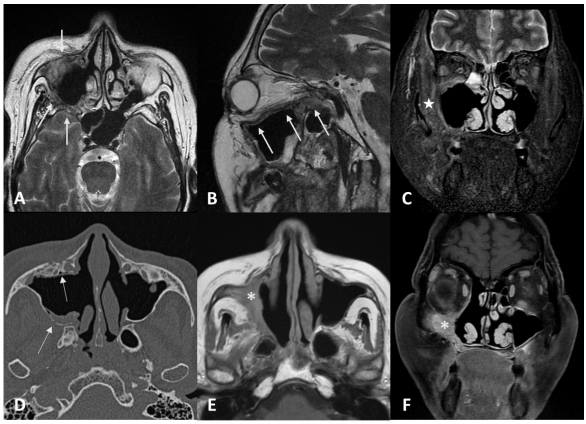

Figure 4. Rhinosinusitis erosive necrotizing fungal disease (mucormycosis) A and B. Ax and Color T2, respectively: White arrows - Regions of marked hyposignal, related to necrosis. C. STIR Color: Star - Edema of the adipose muscle planes of the right hemiface. D. Ax Bone CT: White arrows - Bone erosion with a "moth-eaten" appearance. E and F. Post-treatment. AND. Ax T1 ct +: * Atelectasis of the right maxillary sinus with residual fibrocicatricial inflammatory mucous thickening. F. Color T1FS ct +: Star - Maxilloethmoid sinusectomy and middle and superior turbinectomy, noticing residual fibrocicatricial inflammatory mucous thickening.
Ax: Axial. Sag: Sagittal. Color: Coronal. Ct +: Post-contrast sequences. FS: Fat saturation.

DISCUSSION

Mucormycosis is a disease with high morbidity and rapid evolution and relies on high clinical suspicion for an early diagnosis. It is more common in immunocompromised patients, and its main risk factor is decompensated DM (Prakash & Chakrabarti, 2019). With the advent of the SARS-CoV-2 pandemic, cases were significantly increased, primarily related to corticosteroid use in high doses (Nayak et al., 2022).

The four cases described demonstrated that the common risk factor for all was the presence of decompensated DM. A single patient had reasonable glycemic control but had dysglycemia during the COVID-19 onset. Only this patient had SARS-Cov-2 disease preceding the fungal infection, which differs from the literature within most reports demonstrating mucormycosis during COVID-19.

The most common form is rhino-orbital-cerebral, which is more frequent in patients with decompensated DM and diabetic ketoacidosis. Some common symptoms are fever, headache, facial pain, nasal discharge, epistaxis, sinusitis, nasal ulcer, palatal fistula, cranial nerve involvement and bone destruction (Sharma et al., 2023). As it can be seen, the most common symptoms found in our patients were headache, facial pain, nasal discharge and bone destruction. Only one patient had a palatal fistula.

We have reported two women and two men (Table), aged 40-66 years, diagnosed during the COVID-19 pandemic. Among them, two patients presented the rhino-orbital-cerebral form, with a severe condition and the need for extensive debridement, including ocular enucleation. Intra-orbital and central nervous system involvements are associated with poor outcomes, reaching a fatality rate of approximately 80% (Cornely et al., 2019; Nielsen et al., 2023). Although there were no fatalities, these two patients with ocular and CNS lesions experienced severe complications, including loss of vision and definitive chronic renal failure. Liposomal amphotericin B is the cornerstone of treatment; however, the ideal dose depends on the disease and patient's condition, with the central guidelines recommending 10mg/kg/day if the CNS is involved and in patients with solid organ transplants. In progressive disease, using L-AMB associated with POSA may be recommended (Garnes & Kontoyiannis, 2023; Nielsen et al., 2023). Maintenance therapy with triazoles is recommended after therapy with L-AMB, and those with demonstrated efficacy are POSA and isavuconazole (Garnes & Kontoyiannis, 2023). Some treatment perspectives are based on the use of adjuvant immune therapies, such as granulocyte transfusion (Garnes & Kontoyiannis, 2023), and some authors have described associated therapies of L-AMB and echinocandins, notably in refractory cases (Smith & Lee, 2022).

Only through histopathology in all four cases it was possible to confirm the diagnosis. Since surgical debridement was performed mainly after starting antifungal treatment, the accuracy of the cultures may have decreased. Additionally, our hospital does not have the capability for molecular diagnosis of invasive fungal infections. All patients used the recommended antifungal treatment doses and presented changes in renal function, in addition to hydro electrolyte disorders, such as hypokalemia, hyponatremia, hypomagnesemia and metabolic acidosis, with residual renal impairment. The patient 1 temporarily required hemodialysis. After using L-AMB, almost all patients used POSA, except the patient 1, who was treated and cured with the isolated

use of amphotericin B formulations. Most authors reported similar adverse effects and some advocate indefinite maintenance therapy with oral triazoles (Smith & Lee, 2022).

Surgery, in combination with systemic antifungal therapies, plays a vital role in the treatment, removing necrotic and devitalized tissues, which happened in all reported patients (Garnes & Kontoyiannis, 2023). In those with no feasibility for a surgical procedure, topical or intravitreal use of L-AMB has been studied (Garnes & Kontoyiannis, 2023). In patient 2, it was not possible to perform debridement of the entire involved bone due to its large extension, including skull base bones, with a high possibility of cranial collapse and death.

To this date, three patients have been cured, with no evidence of reactivation of the disease. Patient 2 presented symptoms of a worsening condition and she was re-hospitalized with the administration of L-AMB associated with POSA, with stabilization of the condition and continuation of oral outpatient therapy. In our case, the unfavorable outcome was probably due to the impossibility of complete debridement.

Mucormycosis is an aggressive and mutilating disease. It is necessary to improve the accessibility of diagnostic tools and studies with antifungals with lower toxicity for induction treatment. Financing in public health programs that focus on the prevention, control and proper treatment of diabetes is crucial in managing the burden of the disease (Jian et al., 2022). This may help prevent complications, deaths and reduce the treatment costs for the public health system.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest to disclose.

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