Contents available at **PubMed**
www.anmm.org.mx

PERMANYER

Gac Med Mex. 2016;152:688-98

Rhino-Orbital Mucormycosis. Cohort study of its treatment according to disease extent and reversion of its pathophysiology

Héctor Manuel Prado-Calleros[1], Germán Fajardo-Dolci[2], Olga Plowes-Hernández[1] and Carlos Jiménez-Gutiérrez[3]*

[1]Otorhinolaryngology Division, Hospital General Dr. Manuel Gea González; [2]Education, Research and Health Policies Unit, IMSS; [3]Research Division, Hospital General Dr. Manuel Gea González, Mexico City, Mexico

Abstract

Mucormycosis is a lethal opportunistic fungal infection, described mostly in immunocompromised patients. A comparative cohort study was conducted to compare the evolution of the study group patients with rhino-orbital mucormycosis, in which a therapeutic protocol was instituted, in which the pterygomaxillary fossa is systematically surgically approached and orbital exenteration is performed or not based on the spreading of the infection to the orbital apex or the orbital fissure, with a historical group where these criteria were not applied. Fifteen cases were included, eight in historic group A and seven in the study group B. Medical treatment was provided with control of the underlying disease (amphotericin B and low molecular weight heparin) as well as surgical treatment with extensive debridement including endoscopic ethmoidectomy and exploration of the pterygomaxillary fossa, also performing orbital exenteration only in patients who presented orbital apex syndrome in group B. In group A, there was a mortality rate of 50%, in group B all patients were clinical cured; however, the two patients with hematologic diseases died of complications not related to the fungal infection. With the standardization of a diagnostic and therapeutic protocol, good results in healing and survival of patients can be obtained. (Gac Med Mex. 2016;152:688-98)

Corresponding author: *Héctor Manuel Prado-Calleros, hmpradoc@hotmail.com*

KEY WORDS: *Diagnosis. Mucormycosis. Surgery.*

Introduction

Rhino-orbital-cerebral mucormycosis is an opportunistic and highly lethal infection; it is the most common clinical form of the disease. Although it is relatively rare, its incidence has increased[1,2].

It is an acute infection caused by saprophyte fungi of the Zygomycetes class, Mucorales order, which includes Rhizopus as the most common cause, followed by Rhizomucor (Mucor) and other species[1,3].

It typically affects immunocompromised patients in 90% of cases, being particularly found in patients with ketoacidosis-decompensated diabetes mellitus, in hematologic malignancies such as leukemia, in post-transplanted subjects and in other cases with neutropenia. Generally, it affects adult patients, with slight predisposition for the male gender[1-3].

Its pathophysiology is associated with microorganism virulence factors and host immunity factors in a determinate microenvironment. Mucorales are prone to spread through tissues, with high affinity to arteries,

Correspondence:
*Héctor Manuel Prado-Calleros
Durango, 49-801
Col. Roma, Del. Cuauhtémoc
C.P. 06700, Ciudad de México, México
E-mail: hmpradoc@hotmail.com

Date of reception: 19-09-2015
Date of acceptance: 20-02-2016

causing extensive endothelial harm, which results in arterial thrombosis with ischemia and necrosis of surrounding tissues; acidotic status of the host favors their growth[3-5].

The disease starts in the nasal cavity and rapidly spreads to paranasal sinuses, with its progression continuing by direct or hematogenous spread to other structures through several routes, particularly by invasion via the pterygomaxillary fissure, where nerves and blood vessels that are important to sinonasal irrigation are located, towards the palate and orbit through the orbital fissure; extension to the cavernous sinus and brain occurs via the orbital apex[4,5].

After pterygopalatine fossa and inferior orbital fissure invasion, regional vascular thrombosis occurs, which results in edema of the eyelids, chemosis and proptosis; ophthalmoplegia can occur secondarily to orbital infiltration through the superior orbital fissure, and infection at this moment rapidly spreads to the retrobulbar space and orbital apex; optic nerve invasion and/or retinal artery thrombosis result in irreversible loss of visual acuity, with potential thrombosis of the cavernous sinus, which warrants early treatment in order to limit intracranial extension[4].

Clinical presentation includes unilateral nasal and orbital progressive signs and symptoms, facial pain and fever; rhinorrhea may be observed, with subsequent appearance of necrotic areas in the nasal mucosa and adjacent tissues. Sinonasal and facial necrosis is caused by sphenopalatine artery branches thrombosis in the pterygopalatine fossa[4,5].

Orbital involvement is found in 66-100% of cases; the degree of ophthalmoplegia is generally correlated with the severity of orbital inflammation[4].

The diagnosis is confirmed with non-septate thick hyphae with right angle branching found on histopathology analysis; culture is useful to determine the type of mycotic or over-aggregated infection and to guide the employed therapeutics[4].

The diagnostic protocol should include imaging studies to characterize the lesion and to establish the disease extension. Computed tomography is unspecific, but it can demonstrate sinus involvement; magnetic resonance has more diagnostic sensitivity, since mycotic infections characteristically appear hypointense both in T1 and T2 sequences[5].

The treatment of rhino-orbital-cerebral mucormycosis requires the combination of surgical treatment, medical therapy with amphotericin B, and reversion of the ketoacidotic or immunosuppressed state[2].

Aggressive surgical debridement is a fundamental element of treatment that considerably increases survival, and it is essential for the removal of necrotic tissue, for the reduction of fungal spore concentration and to facilitate antifungal agents' action[5].

Orbital exenteration appears to improve survival in patients with progressive orbital involvement; however, there is controversy on the indications for practicing this procedure and its influence on disease progression[4].

The mortality rate currently ranges from 35 to 40% in spite of opportune treatment, depending on the underlying disease and other variables. In patients with hematological disease or post-transplanted subjects, mortality increases by up to 65-90%; other indicators of poor prognosis include cutaneous or palatal necrosis, bilateral disease, intracranial extension and treatment initiation delay[1,3].

Material and methods

The objective was to assess the evolution of the study group of patients with rhino-orbital mucormycosis, in which a therapeutic protocol was implemented where the pterygomaxillary fossa is systematically exposed and orbital exenteration is performed if there is infection extension to the orbital apex, or exenteration is not performed if extension is limited to the orbital fissure, versus a historical group where these criteria did not apply.

A comparative cohort study was carried out between the study group and a historical group. The cases of patients with confirmed histological diagnosis of invasive rhino-orbital mucormycosis attended at the Dr. Manuel Gea González General Hospital in the Division of Otorhinolaryngology and Head and Neck Surgery were assessed: group A, from a first historical period (treated within the period encompassed from January 2008 to December 2012), and study group B (treated within the period encompassed from January 2013 to December 2014).

At inclusion, all patients underwent otorhinolaryngological assessment as the diagnostic protocol, which included nasal endoscopy, ophthalmological evaluation, contrasted tomography, magnetic resonance, as well as imprint of direct mucosal smear, sinonasal mucosa biopsy and culture to corroborate the diagnosis.

In both groups, based on clinical and imaging findings, patients were staged in the following groups: a) those with orbital involvement limited to the orbital fissure (orbital fissure syndrome) and those with orbital involvement extended to the orbital apex (orbital apex syndrome) with or without cavernous sinus thrombosis (intracranial extension).

All patients were provided the same medical management, which included metabolic/hematologic control, systemic antifungal treatment (amphotericin B at 1-1.5 mg/kg/day doses), nasal irrigations every 8 h with amphotericin B 50 mg/500 ml physiological saline and enoxaparin 1 mg/kg/day (except in patients with hematological conditions and those in the historical group).

All patients underwent surgical debridement by means of nose and paranasal sinuses endoscopic surgery or combined endoscopic and external surgery, prior to 24 h of admission. Patients in the historical group (group A) underwent necrotic tissue debridement, with orbital exenteration if they had any kind of orbital involvement, and radical maxillectomy in the cases of extensive maxillary or palatal involvement. Patients of study group B underwent pterygomaxillary fossa debridement by means of endoscopic removal of the maxillary sinus posterior wall; those without ophthalmologic involvement or extension limited to the superior orbital fissure (group B1) had no orbital exenteration practiced, whereas patients with ophthalmologic involvement extended to the orbital apex (group B2) had orbital exenteration practiced in collaboration with the Oculoplasty Department.

All patients granted informed consent for treatment. The results are presented with descriptive statistics.

Results

Demographic data

Historical group A was comprised by 8 patients (4 males and 4 females), with ages ranging from 18 to 78 years (mean age of 48 years).

Study group B was comprised by 7 adult patients (4 males and 3 females [1.5:1 ratio]) with ages ranging from 23 to 74 years (mean age of 52 years).

Clinical presentation

In historical group A, all patients had some immunosuppression-determining comorbidity at the moment of diagnosis: diabetes mellitus (newly onset or poorly controlled) in 7/8 patients (87.5%) or hematological disease in 1/8 patients (12.5%).

In study group B, all patients had some immunosuppression-determining comorbidity at the moment of diagnosis: diabetes mellitus (newly onset or poorly controlled) in 5/7 patients (71.4%) or hematological disease in 2/7 patients (28.6%).

The time elapsed since symptom onset until the patients sought medical attention or diagnosis was established was 4-30 days, with a mean of 22.8 days, which was similar in both groups.

All historical-group A patients had unilateral rhino-orbital involvement; 50% occurred clinically with ophthalmologic symptoms (proptosis, ophthalmoplegia), 37.5% with sinonasal symptoms and 12.5% with fever.

In study group B, all patients had rhino-orbital involvement at presentation, all of them unilaterally: 4 left cases (57%) and 3 right cases (43%). Five patients (71.4%) had ophthalmic symptoms as initial manifestation (proptosis, ophthalmoplegia, blindness); in 2 patients (29%), the initial manifestation was persistent fever. Only one patient had sinonasal symptoms (14%). Three patients experienced disorientation/alterations of the state of alertness. Two patients also displayed peripheral facial paralysis (29%).

In group A, mucosal or facial skin necrosis was found in 100% of cases; in group B, nasal endoscopy showed overt mucosal necrosis, characterized by blackish scabs in 4/7 (57%) and mucosal pallor/discoloration in 3/7 patients (43%), with clinical suspicion being determinant for them.

In all sinonasal mucosa cytology imprints or biopsies that were taken, the test for fungi reported broad hyphae consistent with Mucor. In the culture for fungi, Rhizomucor grew in 13/15 (86.6%), Rhizopus in 1/15 (6.6%) of group B and invasive aspergillosis in 1/15 (6.6%) of group A patients.

Extension of disease

All historical group A patients had unilateral rhino-orbital involvement: 4/8 had orbital fissure syndrome (50%) and 4/8 had orbital apex syndrome (50%).

In group B, disease orbital extension involved orbital fissure syndrome in 4 patients (57%, group B1) and orbital apex syndrome in 3 patients (43%, group B2) (Fig. 1).

All patients displayed sinus involvement on imaging studies. The most commonly reported findings in the skull tomography were mucosal thickening and partial unilateral occupation by paranasal sinuses soft tissue density. Most affected paranasal sinuses were, in decreasing order: maxillary sinus (100%), anterior ethmoidal sinus (87%), posterior ethmoidal sinus (53%), sphenoidal sinus (26.5%) and frontal sinus (13%).

Tomography axial slices showed that in 100% of cases there was pterygomaxillary fossa involvement, whereas in 3/15 cases (20%) there was also dissemination to the infratemporal fossa (Fig. 2).

In 14/15 patients, facial or orbital soft tissue thickening was also revealed by tomography.

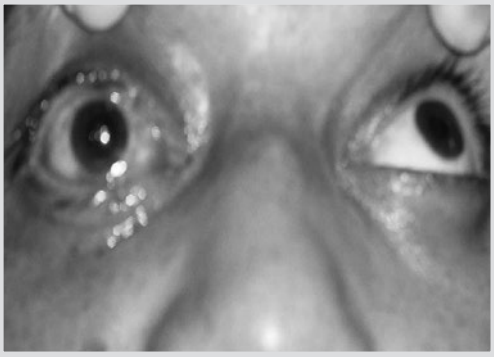

Figure 1. *Orbital apex syndrome, with chemosis, mydriasis, ophthalmoplegia and blindness.*

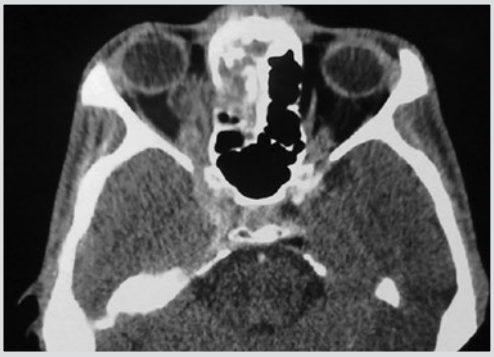

Figure 2. *Computed axial tomography, where etmoidal sinus and orbital apex occupation with extension to the right cavernous sinus by mucormycosis is observed.*

Paranasal sinuses and affected tissue hypointensities were observed in magnetic resonance T2 sequences in all patients; cavernous sinus thrombosis was identified in 7 patients (46.6%) who were experiencing alertness state alterations and orbital apex syndrome.

Surgical treatment and type of practiced surgery

Group A patients had necrotic tissue surgical debridement practiced, with endoscopic ethmoidectomy and/or sphenoidotomy, external radical maxillectomy to 3/8, endoscopic medial maxillectomy to 1/8 and orbital exenteration to 4/8 (50%): to 2 patients with orbital apex syndrome and to other 2 patients with orbital fissure syndrome.

In group B, all patients underwent necrotic tissue surgical debridement by means of endoscopic ethmoidectomy and/or sphenoidotomy, with endoscopic medial maxillectomy and maxillary sinus posterior wall removal for pterygomaxillary fossa exploration; 5/7 patients also underwent sublabial approach for maxillary sinus debridement (Fig. 3).

One patient in group B with wide extension to the infratemporal fossa required a combined external approach with lateral rhinotomy plus endoscopic surgery of the nose and paranasal sinuses. One patient in group B underwent debridement and hard and soft palate partial surgical resection due to infection extension to this area.

In group B, three patients with cavernous sinus thrombosis and who were diagnosed with orbital apex syndrome (group B2) also had orbital exenteration practiced in collaboration with the Oculoplasty Department of the Ophthalmology Division from our hospital.

Four patients (57%) of group B required a second surgical intervention in the operating room, with necrotic tissue debridement margins being broadened by the endoscopic route. All patients had postoperative debridements practiced at the office.

In patients who underwent exenteration, once the tissues were healed, had an ocular prosthesis adapted (Fig. 4).

Surgical specimens obtained during the procedures were sent to the Pathology Department; in 100% of patients was the invasive mycosis diagnosis confirmed.

Medical treatment

In group A, all patients were treated with amphotericin B at a 1 mg/kg dose, with the treatment being discontinued when 2 g were accumulated.

In group B, all patients were treated with amphotericin B at 1-1.5 mg/kg doses. Amphotericin B cumulative dose ranged from 2.165 to 4.540 g, with an average of 2.972 g. Antifungal treatment duration was determined based on the presence or absence of necrosis and on the results of biopsies taken at the office, with treatment being discontinued when no necrosis or hyphae were found in tissue.

Three diabetic patients had nasal and soft tissue bacterial overcolonization, with gram-negative bacteria such as multiresistant *Acinetobacter baumanii* complex being cultured, which drove the Infectology Department to add antibiotic management (cephalosporins and

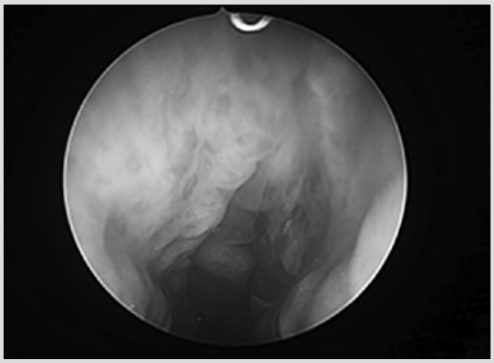

Figure 3. *Endoscopic surgery, where nasal lateral wall necrosis is observed.*

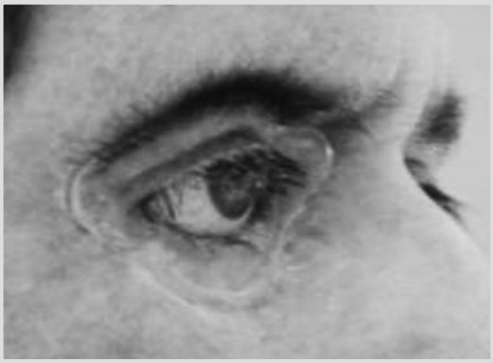

Figure 4. *Ocular prosthesis.*

carbapenems). In both groups, diabetic patients received insulin for metabolic control, while patients with hematological conditions received chemotherapeutic treatment.

Patient's hospital length of stay, including their stay at the Intensive Therapy Unit, ranged from 32 to 54 days, with a mean of 40 days, which was similar in both groups.

Treatment complications

The incidence and severity of the adverse effects reported in our patients was: fever in 4 patients (26%) after amphotericin B administration, which could be controlled with antipyretics (2 patients in group A and 2 patients in group B); transient elevation of nitrogen compounds was also observed.

Evolution

In group A there was a disease-related mortality of 50%; it should be highlighted that patients with apex syndrome who did not undergo exenteration did not survive, whereas among those who had the procedure practiced, 50% did survive (Table 1).

Among the patients who underwent maxillectomy there was a trend towards cure (Table 2).

In all treated patients of study group B (group B1 100% and group B2 100%) was mucormycosis clinical and bacteriological cure achieved. In this group there was no mortality directly associated with mucormycosis. Orbital differentiated surgical management should be highlighted. All 5 patients with diabetes mellitus survived free of disease. The two patients with hematological conditions died a few weeks after treatment completion for other causes unrelated to mycosis (Tables 3 and 4).

Exenterated patients were rehabilitated with ocular prostheses.

Discussion

Over the past few years, we have observed an increased incidence of mucormycosis cases, which has been acknowledged by other authors and creates the necessity to establish a standardized diagnostic-therapeutic protocol. Our group implemented the currently used protocol since two years ago, after analyzing our own previous experiences and those published by other authors, in an attempt to revert the pathophysiological aspects of this lethal disease. The most important changes to the protocol were the selection of patients in whom exenteration is performed and the performance of endoscopic maxillectomy with maxillary sinus posterior wall resection instead of external radical maxillectomy, which we had observed to be a favorable prognostic factor and that allowed to continue removing a main infection reservoir, but reducing surgical treatment-associated mortality and increasing patient survival[1-3].

In our series, 87.5% of patients in group A and 71% in group B had decompensated type 2 diabetes mellitus with ketoacidosis as immunocompromise factor, and neutropenia due to some hematological condition in 12.5% of group A and 29% of group B. Similar to our case series, Zygomycosis in its rhino-orbital-cerebral form is more commonly observed in patients with diabetes, while the pulmonary form is more frequently observed in patients with hematological neoplasms[1,6].

Table 1. Evolution according to disease extension and treatment (group A)

n	Comorbidity	Disease extension	Surgical treatment	Orbital exenteration	Mucormycosis cure	Disease-related death	Non disease-related intra-hospital death
1	Type 1 diabetes mellitus	Orbital fissure syndrome	Maxillectomy	Yes	Yes	No	No
2	Type 2 diabetes mellitus	Orbital apex syndrome	Ethmoidectomy and nasal tissue extensive resection	No	No	Yes	–
3	Type 2 diabetes mellitus	Orbital fissure syndrome	Maxillectomy	No	Yes	No	No
4	Type 2 diabetes mellitus	Orbital fissure syndrome	Endoscopic ethmoidectomy	Yes	No	Yes	–
5	Type 2 diabetes mellitus	Orbital apex syndrome	Ethmoidectomy	Yes	No	Yes	–
6	Type 2 diabetes mellitus	Orbital apex syndrome	Maxillectomy	Yes	Yes	No	No
7	Acute leukemia	Orbital fissure syndrome	Endoscopic ethmoidectomy, endoscopic medial maxillectomy	No	Yes	No	No
8	Type 2 diabetes mellitus	Orbital apex syndrome	Endoscopic ethmoidectomy, sphenoidotomy	No	No	Yes	–

Table 2. Cure with or without maxillectomy

Group	Surgical treatment	Mucormycosis cure	Disease-related death	Overall mortality
A	External or endoscopic maxillectomy with or without orbital exenteration	4/4 (100%)	0%	4/8 (50%)
	External or endoscopic ethmoidectomy with or without orbital exenteration	0/4 (0%)	4/4 (100%)	

In patients with hematological conditions, mucormycosis constitutes the third cause of invasive mycosis, after candidiasis and aspergillosis; among our cases, only in one patient of group A was invasive aspergillosis identified. This knowledge is useful for antimycotic medication selection.

In patients with hematological conditions and mucormycosis, acute myeloid leukemia cases are predominant, with neutropenia being one of the main risk factors for the development of this infection, and being difficult to revert. In the studied period, among our cases, one patient had acute leukemia in group A, whereas in group B, one patient had acute leukemia and another had aplastic anemia[6,7].

Invasive fungal acute rhinosinusitis clinical presentation is unspecific, with frequent diagnostic delay. In our cases, ocular signs and symptoms were predominant both in group A and group B patients with diabetes, while fever was predominant in cases with underlying hematological conditions, which is why we consider that mucormycosis should be suspected and ruled out in every immunosuppressed patient with rapidly establishing ocular symptoms or persistent fever. Clinical suspicion, diagnosis and early treatment can improve patient survival[2,4,7].

Table 3. Evolution according to disease extension and treatment (group B)

n	Comorbidity	Disease extension	Surgical treatment	Orbital exenteration	Mucormycosis cure	Disease-related death	Non disease-related intra-hospital death
1	Type 2 diabetes mellitus Ketoacidosis	Superior orbital fissure syndrome	Endoscopic + sublabial* + pterygomaxillary exploration	No	Yes	No	No
2	Type 2 diabetes mellitus	Orbital apex syndrome	Endoscopic + sublabial + pterygomaxillary exploration	Yes	Yes	No	No
3	Type 2 diabetes mellitus	Orbital apex syndrome	Endoscopic + sublabial* + pterygomaxillary exploration	Yes	Yes	No	No
4	Type 2 diabetes mellitus Ketoacidosis	Orbital apex syndrome	Endoscopic + sublabial* + pterygomaxillary exploration	Yes	Yes	No	No
5	Type 2 diabetes mellitus	Superior orbital fissure syndrome	Endoscopic + lateral rhinotomy + pterygomaxillary exploration	No	Yes	No	No
6	Hematological disorder (acute leukemia)	Orbital cellulitis	Endoscopic + sublabial + pterygomaxillary exploration	No	Yes	No	Yes
7	Hematological disorder (aplastic anemia)	Superior orbital fissure syndrome	Endoscopic + sublabial* + pterygomaxillary exploration	No	Yes	No	Yes

*Required surgical intervention.

Table 4. Cure in exenterated and non-exenterated groups (group B)

Group	Disease extension	Surgical treatment	Orbital exenteration	Mucormycosis cure	Disease-related death	Overall mortality (non disease-related)
B1	Superior orbital fissure syndrome or without orbital involvement	Endoscopic + sublabial ethmoidomaxillectomy or lateral rhinotomy + pterygomaxillary exploration	No	4/4 (100%)	0%	2/7 (28.5%)
B2	Orbital apex syndrome	Endoscopic + sublabial ethmoidomaxillectomy or lateral rhinotomy + pterygomaxillary exploration	Yes	3/3 (100%)	0%	

In half of group B cases where the disease was diagnosed at early stages, only mucosal pallor or violet areas, without necrosis, were observed by endoscopy; these findings, in the appropriate clinical scenario should suffice to raise clinical suspicion and to obtain cytology imprints or biopsies for mucormycosis early diagnosis and treatment[4,6-9].

Orbital involvement is observed in 66-100% of reported cases, which is consistent with 100% of our patients having ophthalmologic involvement and requiring multidisciplinary protocol-based management[4].

Although this is a rapidly progressive condition, the timing for surgical debridement to limit its extension and to maximize the results is not clearly defined. Survival has been reported to increase by up to 35% if treatment is started within the first week of clinical presentation. In all our cases, surgery was performed within the first 24 h after the diagnosis was confirmed. In those patients who required a second intervention, it was carried out based on endoscopic clinical findings, as well as on histopathological results obtained from repeated biopsies suggesting and confirming the persistence of infected necrotic tissue on sinonasal cavities[6].

Endoscopic surgery or external approaches combined with endoscopic surgery enable accessing ethmoidal cavities and the base of the skull to remove affected tissues, have less morbidity and comparable results to standard techniques; their diagnostic and therapeutic usefulness has been demonstrated in several sinonasal ailments, including fungal infection. All patients in historical group A underwent external or combined approaches with endoscopic surgery and maxillectomy, while in group B radical maxillectomy was not required in any case. Anyway, regardless of the approach, repeated debridement may be required[6,10].

The pterygopalatine fossa is one of the most important routes for infection dissemination to the orbital, facial and intracranial regions, and can be a mucormycosis infection reservoir site. In historical group A, greater survival was observed in patients who underwent radical maxillectomy, which effectively exposes this fossa, and for this reason, systematically removing the maxillary sinus posterior wall by the endoscopic route was considered in group B in order to expose the pterygomaxillary fossa to remove the infected tissue without a radical maxillectomy being performed, which yielded similar results with less morbidity[4].

The indication for orbital exenteration in patients with mucormycosis and orbital involvement is controversial. In some reports of patients with the same risk factors, when being exenterated, they have shown higher survival; however, this has not universally been observed. The decision for exenteration should depend on the immunocompromise state of the patient, on infection extension, and on patients' informed decision. Unlike group A, where patients could undergo exenteration with any kind of orbital involvement, for study group B, our exenteration criteria were mainly based on the type of orbital involvement extension. Orbital exenteration was performed only in patients with orbital apex syndrome and cavernous sinus thrombosis, which represents a more advanced stage of the disease and implies higher risk of intracranial extension and, in addition, patients already have irreversible loss of the visual function; in the cases where there was only orbit fissure syndrome, fungal reservoir could be removed and disease progression stopped with pterygopalatine fossa and orbital fissure debridement, without exenteration, with cure being achieved with this protocol in both B1 and B2 groups[5,11,12].

In comparison with patients with orbital fissure, patients with orbital apex syndrome had more aggressive and extended infection compared with the rest of the cohort, and this is why their hospital stay was more prolonged, amphotericine B cumulative dose was also higher and more surgical procedures were required for necrotic tissue debridement[5].

The use of antifungals is also fundamental for treatment. Amphotericin B at 0.5-1.5 mg/kg doses with a cumulative dose of 2 g on average has been the basis of antimycotic treatment, and this was the range that was observed in study group A while in group B it was higher; however, we consider that the cumulative dose should not be established based on a fixed scheme, but should be objectively individualized based on repeated endoscopic assessments where tissue necrosis is no longer observed and based on fungus histological eradication demonstrated by repeated postoperative biopsies, as it was done in group B. On the other hand, less toxic formulations such as liposomal amphotericin can deliver higher doses (5 mg/kg/day) in less time, and the use of antifungal combinations (amphotericin + posaconazole or echinocandins) can be useful in severe or refractory cases; the use of other antifungals (voriconazole) is recommended in cases caused by infections other than mucormycosis, such as invasive aspergillosis, which occurs frequently in patients with hematological disorders[6,7,13].

Ischemic tissue creates a favorable environment that promotes fungal proliferation, and the poor blood supply by the thrombosis inherent to the disease prevents

Table 5. Published series of five or more cases with rhino-orbital mucormycosis with medical and surgical treatment that report the outcome (survival or cure)

Authors (period of study)	Cases	Underlying disease	Treatment	Survival/mucormycosis cure
Reed et al.	41	Diabetes mellitus (83%), cancer (34%), corticosteroids (46%), neutropenia (12%) and transplantation (10%)	Amphotericin B or amphotericin with caspofungin + surgical debridement	14/34 (41%) with amphotericin monotherapy and 6/7 (86%) with combination therapy with caspofungin
Bhansali	35	Diabetes mellitus	Amphotericin B + surgical debridement in 26/35 (74%)	21/35 (60%)
Rangel	22	Diabetes mellitus (20/22)	Amphotericin B + debridement	15/22 (68%)
Süslü et al. (2000-2006)	19	Hematological neoplasm, 13/19; the rest, other factors	Amphotericin B + debridement (13/19) or amphotericin B without surgery (6/19)	Medical treatment + surgery in 6/13 (46%) No surgery in 0/6 (0%)
Bala et al. (2010-2011)	17	Diabetes mellitus (74%)	Liposomal amphotericin B 5 mg/kg/day + debridement	15/17 (88%)
Nithyanandam et al. (1992-2000)	16	Diabetes mellitus	Amphotericin B 0.7 mg/kg/day + intraorbital amphotericin B + group A nasal-sinus debridement and group B nasal-sinus debridement + orbital exenteration	Group A 7/7 **(100%)** Group B 1/9 (11%) Total 50%
Prado et al. (present study) (2008-2012 and 2013-2014)	15	Diabetes mellitus, 12/15 Hematological condition, 3/15	Amphotericin B + amphotericin B irrigation surgical debridement according to extension, with or without exenteration, with maxillectomy or pterygomaxillary exploration	Historical group A 4/8 (50%) Study group B 7/7 **(100%)**
Abedi et al. (1957-1982)	14	Diabetes mellitus (9/14), leukemia (2/14), transplantation (2/14) and disseminated cancer (1/14)	Amphotericin B + surgical debridement	10/14 (71%)
Sun et al. (2003-2007)	11	Solid organ transplantation	Amphotericin B (LAmB or AmBd) + debridement)	7/11 (63.6%)
Pagano et al.	10	Hematological malignancies	Amphotericin B + surgical debridement (4/6)	6/10 (60%)
Shpitzer et al.	10	Diabetes mellitus	Amphotericin B + debridement	2/10 (20%)
Guevara et al. (1973-2001)	9	Diabetes mellitus	Amphotericin B + external or endoscopic debridement	5/9 (55.5%)
Ghafur et al. (2000-2010)	9	Diabetes mellitus	Amphotericin B + surgical debridement	7/9 (77.7%)
Kohn and Hepler	8	Diabetes mellitus	Amphotericin B + surgical debridement (without orbital exenteration) and irrigations with amphotericin B	8/8 (100%)
Talmi et al.	8	Hematological and other malignant neoplasms	Amphotericin B 0.5-1.5 mg/kg + debridement	5/8 (62.5%)

(Continued)

Table 5. Published series of five or more cases with rhino-orbital mucormycosis with medical and surgical treatment that report the outcome (survival or cure) (Continued)

Authors (period of study)	Cases	Underlying disease	Treatment	Survival/mucormycosis cure
Gorjón et al. (1998-2006)	7	Hematological disease (7/7) and diabetes mellitus (3/7)	Amphotericin B + debridement	2/7 (28.5%)
Charfi et al.	7	Diabetes mellitus (6/7)	Amphotericin B + debridement	5/7 (71.4%)
Bhadada et al. (2001- 2004)	6	Type 1 diabetes mellitus (6/6	Amphotericin B + debridement (5/6)	4/6 (66.6%)
Sachdeva	6	Diabetes mellitus (6/6)	Amphotericin B + debridement (4/6)	4/6 (66.6%)
Arda et al. (2007-2010)	6	Hematological disease (aplastic anemia and others)	Amphotericin B + surgical debridement	4/6 (66.6%)
Alobid et al. (1995-2001)	5	Diabetes mellitus (5/5)	Amphotericin B + debridement with exenteration (2/5) or endoscopic surgery (3/5)	5/5 **(100%)**
Toumi et al. (1995-2007)	5	Diabetes mellitus (5/5)	Amphotericin B (5/5) + debridement (4/5)	2/5 (40%)
Total	**286**			172 (60.1%)

LAmB: Liposomal Amphotericin B; AmBd: Amphotericin B deoxycholate

antifungal therapy from reaching the tissues and fighting the infection. This situation can warrant the use of anticoagulants such as enoxaparine as ancillary therapy to revert this aspect of its pathophysiology, although performing a controlled study would be required to establish its usefulness. In addition, Seiffetal et al. considered that local irrigations with amphotericin B, by directly delivering an elevated concentration to involved tissues, are useful as coadjuvant therapy in the control of rhino-orbital fungal infections, particularly in patients with reversible immunosuppression, as used in our patients of both groups[10,14,15].

We agree with reports stating that successful treatment of mucormycosis requires a multidisciplinary strategy where at least the following factors are covered to revert its pathophysiology: a) early diagnosis, b) reversion of predisposing systemic factors with control of the underlying condition (blood glucose control with acid-base status restoration in diabetic patients and immunosuppression status reversal in hematologic patients), c) early and adequate surgical debridement and d) prompt, adequate and sufficient antifungal therapy[6].

Clinical and bacteriological cure of 100% of patients in group B contrasts with historical group A 50% mortality, and is better than that reported in the literature, currently of 60-70%. We consider that this is largely due to the employed strategy, where treatment was standardized to revert the patophysiology of disease and to prevent and/or limit its natural progression to intracranial structures, thus individualizing medical treatment duration and surgical treatment extent based on disease extension, but reducing surgical treatment-associated morbidity; however, 2 patients with hematological disease in group B died during hospitalization for causes related to their underlying condition, which highlights the importance of underlying conditions control for these patients' survival[6,10].

When in February 2015 a search was carried out in PubMed looking for published articles with the term Rhino-Orbital Mucormycositis and no limitations, it yielded 118 results, among which no controlled clinical trials were found, with the majority referring to isolated cases or series of 2-4 cases, and only 21 publications involving 5 or more cases being found. This study represents one of the investigations with the largest number of cases reporting patient evolution with medical and surgical combined treatment, and is one of the few cohort studies ever conducted[16-36] (Table 5).

This patient cohort (study group B), together with the cohort published by Khon[28] of 8 patients surgically

treated without orbital exenteration, together with one of the 7-patient groups reported by Nithyanandam[21], the cohort reported by Alobid[35] with 5 patients treated with endoscopic surgery and the cohort reported by González[37] with 4 patients, represents the only published series with a successful treatment strategy in 100% of cases with mucormycosis in its rhino-orbital form. These strategies, although with certain differences, have medical and surgical treatment focused on removing only irreversibly affected tissues with repeated resections or by means of endoscopy and amphotericin B local (even intraconal) application as a common denominator[21.28.35.37].

This work shows the differences between both therapeutic protocols employed; it offers useful criteria for rhino-orbital mucormycosis surgical management depending on its extension in order decrease its mortality and limit the morbidity associated with surgical treatment.

Controlled clinical trials assessing different therapeutic variables are required to determine the optimal management protocol and to consistently improve survival in this condition[13].

References

1. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005;41:634-53.
2. Saegeman V, Maertens J, Ectors N, et al. Epidemiology of mucormycosis: review of 18 cases in a tertiary care hospital. Med Mycol. 2010;48: 245-54.
3. Ibrahima A, Kontoyiannis D. Update on mucormycosis pathogenesis. Curr Opin Infect Dis. 2013;26:508-15.
4. Mousa S, Peyman B. Rhinocerebral mucormycosis: pathways of spread. Eur Arch Otorhinolaryngol. 2005;262:932-8.
5. Talmi YP, Goldschmied-Reouven A, Bakon M, et al. Rhino-orbital and rhino-orbito-cerebral mucormycosis. Otolaryngol Head Neck Surg. 2002; 127:22-31.
6. Skiada A, Lanternier F, Groll A, et al. Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia. Haematologica. 2013;98(4):492-504.
7. Muszewska A, Pawlowska J, Krzyściak P. Biology, systematics, and clinical manifestations of Zygomycota infections. Eur J ClinMicrobiol Infect Dis. 2014;33:1273-87.
8. Piromchai P, Thanaviratananich S. Acute versus chronic invasive fungal rhinosinusitis: a case control study. Infect Dis: Research and Treatment. 2012;5:43-8.
9. Meas T, Mouly S, Kania R, et al. Zygomycosis: an uncommon cause for peripheral facial palsy in diabetes. Diabetes Metab. 2007;33:227-9.
10. Saedi B, Sadeghi M, Seilani P. Endoscopic management of rhinocerebral mucormycosis with topical and intravenous amphotericin B. J Laryngol Otol. 2011;125:807-10.
11. Hargrove R, Wesley R, Klippenstein K, Fleming JC, Haik BG. Indications for orbital exenteration in mucormycosis. Opthal Plast Reconstr Surg. 2006;22:286-91.
12. Songu M, Unlu HH, Gunhan K, Iker SS, Nese N. Orbital exenteration: A dilemma in mucormycosis presented with orbital apex syndrome. Am J Rhinol. 2008;22:98-103.
13. Spellberg B, Walsh TJ, Kontoyiannis DP, Edwards J Jr, Ibrahim AS. Recent advances in the management of mucormycosis: from bench to bedside. Clin Infect Dis. 2009;15:48(12):1743-51.
14. Chamilos G, Lewis RE, Konoyiannis DP. Delaying amphotericin B- based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomicosis. Clin Infet Dis. 2008; 47:503-9.
15. Seiff SR, Choo PH, Carter SR. Role of local amphotericin B therapy for sino-orbital fungal infections. Opthal Plast Reconstr Surg. 1999;15:28-31.
16. Reed C, Bryant R, Ibrahim AS, et al. Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. Clin Infect Dis. 2008;47(3):364-71.
17. Bhansali A , Bhadada S, Sharma A, et al. Presentation and outcome of rhino-orbital-cerebral mucormycosis in patients with diabetes. Postgrad Med J. 2004;80(949):670-4.
18. Rangel R, Martínez H, Sáenz C, Bosques F, Estrada I. Rhinocerebral and systemic mucormycosis. Clinical experience with 36 cases. J Neurol Sci. 1996;143(1-2):19-30.
19. Süslü A, Öfretmenoflu O, Süslü N, Yücel O, ÖnerciT. Acute invasive fungal rhinosinusitis: our experience with 19 patients. Eur Arch Otorhinolaryngol. 2009;266:77-82.
20. Bala K, Chander J, Handa U, Punia R, Attri A. A prospective study of mucormycosis in north India: Experience from a tertiary care hospital. Med Mycol. 2015;53:248-57.
21. Nithyanandam S, Jacob M, Battu R, et al. Rhino-orbito-cerebral mucormycosis. A retrospective analysis of clinical features and treatment outcomes. Indian J Ophthalmol. 2003;51(3):231-6.
22. Abedi E, Sismanis A, Choi K, Pastore P. Twenty-five years' experience treating cerebro-rhino-orbital mucormycosis. Laryngoscope. 1984;94(8): 1060-2.
23. Sun H, Forrest G, Gupta K, et al. Rhino-orbital-cerebral zygomycosis in solid organ transplant recipients. Transplantation. 2010;90:85-92.
24. Pagano L, Ricci P, Tonso A, et al. Mucormycosis in patientes with haematological malignancies: a retrospective clinical study of 37 cases. GIMEMA Infection Program (Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto). Br J Haematol. 1997;99:331-6.
25. Shpitzer T, Stern Y, Anavi Y, et al. Mucormycosis: experience with 10 patients. Clin Otolaryngol. 1995;20:374-9.
26. Guevara N, Roy D, Dutruc-Rosset C, et al. Mucormycosis -early diagnosis and treatment. Rev Laryngol Otol Rhinol (Bord). 2004;125(2):127-31.
27. Ghafur A, Shareek P, Senthur N, et al. Mucormycosis in Patients without Cancer: A Case Series from A Tertiary Care Hospital in South India. J Assoc Physicians India. 2013;61:305-8.
28. Kohn R, Hepler R. Management of limited rhino-orbital mucormycosis without exenteration. Ophthalmology. 1985;92(10):1440-4.
29. Talmi Y, Goldschmied-Reouven A, Bakon M, et al. Rhino-orbital and rhino-orbito-cerebral mucormycosis. Otolaryngol Head Neck Surg. 2002; 127:22-31.
30. Santos Gorjón P, Blanco Pérez P, Batuecas Caletrío Á, et al. Rhino-orbito-cerebral mucormycosis, a retrospective study of 7 cases. Acta Otorrinolaringol Esp. 2010;61(1):48-53.
31. Charfi S, Ayadi L, Makni S, et al. Rhinocerebral mucormycosis: Anatomoclinical study of seventh cases. Journal de Mycologie Médicale. 2008;18:46-52.
32. Bhadada S, Bhansali A, Reddy K, Bhat R, Khandelwal N, Gupta A. Rhino-orbital-cerebral mucormycosis in type 1 diabetes mellitus. Indian J Pediatr. 2005;72(8):671-4.
33. Sachdeva K. Rhino-oculo Cerebral Mucormycosis with Multiple Cranial Nerve Palsy in Diabetic Patient: Review of Six Cases. Indian J Otolaryngol Head Neck Surg. 2013;65(4):375-9.
34. Arda B, Erdem A, Sipahi O, et al. Mucormycosis: retrospective evaluation of 12 cases. Mikrobiyol Bul. 2011;45(3):504-11.
35. Alobid I, Bernal M, Menéndez L, et al. Cirugía Endoscópica Nasosinusal en la Sinusitis Fúngica. Nuestra Experiencia. Acta Otorrinolaringol Esp. 2002;53:393-7.
36. Toumi A, Larbi Ammari F, Loussaief C, et al. Rhino-orbito-cerebral mucormycosis: five cases. Med Mal Infect. 2012;42(12):591-8.
37. González-Ramos M, Bertrán-Pasarell J, Guiot H, et al. Clinical experience with posaconazole in patients with invasive mucormycosis: a case series. P R Health Sci J. 2008;27:328-32.