



## BRIEF COMMUNICATION

# Rhino-Orbito-Cerebral Mucormycosis. Management Strategies to Avoid or Limit Intracranial Affection and Improve Survival<sup>☆</sup>



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### KEYWORDS

Rhino-orbito-cerebral mucormycosis;  
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**Abstract** Mucormycosis is a rare opportunistic infection. The aim of the study was to review the management in our department with rhino-orbital mucormycosis as well as to describe the clinical protocol, diagnosis and therapy used in these patients.

We conducted a retrospective, longitudinal, descriptive study, in which we evaluated the records of patients with rhino-orbital mucormycosis in the period from January to October 2013.

We found 5 cases. Pterigomaxillary fossa disease was found in 100% of our patients. Medical and surgical treatment performed early by extensive endoscopic debridement (including debridement and resection of pterygomaxillary fossa) and orbital exenteration in patients presenting with orbital apex syndrome in conjunction with the ophthalmology department of our hospital, with excellent results in the survival of our patients (all patients survived).

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### PALABRAS CLAVE

Mucormicosis rino-orbito-cerebral;  
Rinosinusitis micótica invasiva

**Manejo de la mucormicosis rino-orbito-cerebral. Estrategias para evitar o limitar afección intracraneal y mejorar la supervivencia**

**Resumen** La mucormicosis es una infección rara y oportunista. El objetivo del estudio fue revisar los casos presentados en nuestro servicio con mucormicosis rino-orbitaria y describir el protocolo clínico, diagnóstico y terapéutico empleado en estos pacientes.

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Se realizó un estudio retrospectivo, longitudinal, descriptivo, en el que se evaluaron expedientes de pacientes con mucormycosis rino-orbitaria del periodo de enero a octubre de 2013. Se encontraron 5 casos, con afección de fosa pterigomaxilar en el 100% de nuestros pacientes. Se realizó tratamiento médico y quirúrgico temprano mediante desbridamiento extenso endoscópico (incluyendo desbridamiento y resección de fosa pterigomaxilar) y exenteración orbitaria a los pacientes que se presentaron con síndrome de ápex orbitario en conjunto con el servicio de oftalmología de nuestro hospital, obteniendo excelentes resultados en la supervivencia (100% de supervivencia).

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## Introduction

Rhino-orbito-cerebral mucormycosis is a rare, opportunistic, potentially deadly infection that occurs mainly in immunocompromised patients,<sup>1</sup> principally through haematological diseases, caused by saprophytic and opportunistic aerobic fungi of the Zygomycetes class. Mucorales have a great affinity for the arteries: they grow throughout the internal plate, dissecting it and causing extensive endothelial damage. This in turn results in thrombosis and ischaemia of the surrounding tissues. Acidotic condition of the host favours *Mucor* growth, as well as vascular invasion, leading to ischaemia.

The disease begins in the nasal cavity and paranasal sinuses. It develops through direct extension or haematogenous dissemination towards the palate, pharynx and orbit, with later intracranial dissemination by invasion through the superior orbital fissure, ophthalmic veins, cribriform plate or carotid.

The characteristic findings are nasal and orbital signs and symptom. The degree of ophthalmoplegia correlates to the severity of orbital inflammation.<sup>2</sup>

Survival depends on host factors, early diagnosis and rapid commencement of treatment. Mortality rate ranges between 40% and 50%, in spite of early treatment.

The backbone of treatment of rhino-orbital-cerebral mucormycosis consists of surgical debridement, early medical therapy with amphotericin B and reversing the ketoacidotic or immunocompromised state of the host.<sup>3</sup> The extension and time required for the surgical debridement to maximise the results have never been defined.<sup>4</sup>

Orbital exenteration seems to improve survival in patients with ophthalmoplegia. However, there are contradictions in the literature as to the indications for performing this procedure and its influence in the progression of the disease.

The objective of this study was to describe the clinical presentation, treatment and disease progression in patients with rhino-orbital-cerebral mucormycosis, as well as to establish the extension of the infection, especially towards the pterygomaxillary, infratemporal, superior orbital, orbital apex and intracranial fissures.

## Materials and Methods

This was a longitudinal, retrospective descriptive study. We reviewed the clinical case histories of patients diagnosed

**Table 1** Clinical Presentation of Patients With Rhino-Orbital Mucormycosis.

Signs and symptoms	Patients (n=5)
Alteration of ocular movements	5
Proptosis	4
Compromise of visual sharpness	3
Chemosis	2
Facial hypoesthesia	3
Facial paralysis	2
Headache	2
Alteration in alertness	1
Rhinorrhoea	1
Nasal crusting	4
Necrosis of the palate	1
Fever	1

with rhino-orbital mucormycosis seen in our hospital by the otorhinolaryngology and head and neck surgery division in 2013 to describe the clinical presentation, treatment and evolution of the infection, as well as to establish its extension.

## Results

The study group consisted of 5 patients (3 men and 2 women; ratio 1.5:1) with a mean age of 57 years. All patients had poorly controlled diabetes mellitus type 2 (Table 1).

The time between symptom onset until the patients sought medical attention was from 4 to 30 days; 100% of the patients began with ophthalmological symptomatology, with orbital apex syndrome being found in 60%. The most frequent otorhinolaryngological signs and symptoms were nasal obstruction, pale turbinates and nasal crusting (80%), facial hypoesthesia (60%) and facial paralysis (40%), while 1 patient (20%) had necrotic eschar in the palate (Fig. 1).

Upon admission, patients were given complete otorhinolaryngological and ophthalmological assessments, nasal contrast culture, direct smear test for fungi, simple and contrast tomography of the skull and cranial magnetic resonance.

The imaging studies revealed intracranial involvement (thrombosis of the cavernous sinus) in 3 patients (60%), 2 of which showed facial paralysis, disorientation, fluctuating

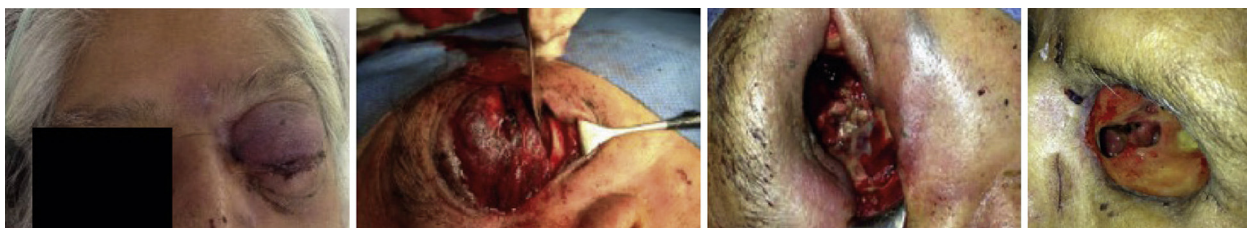


Figure 1 Favourable evolution of a patient with orbital apex syndrome.

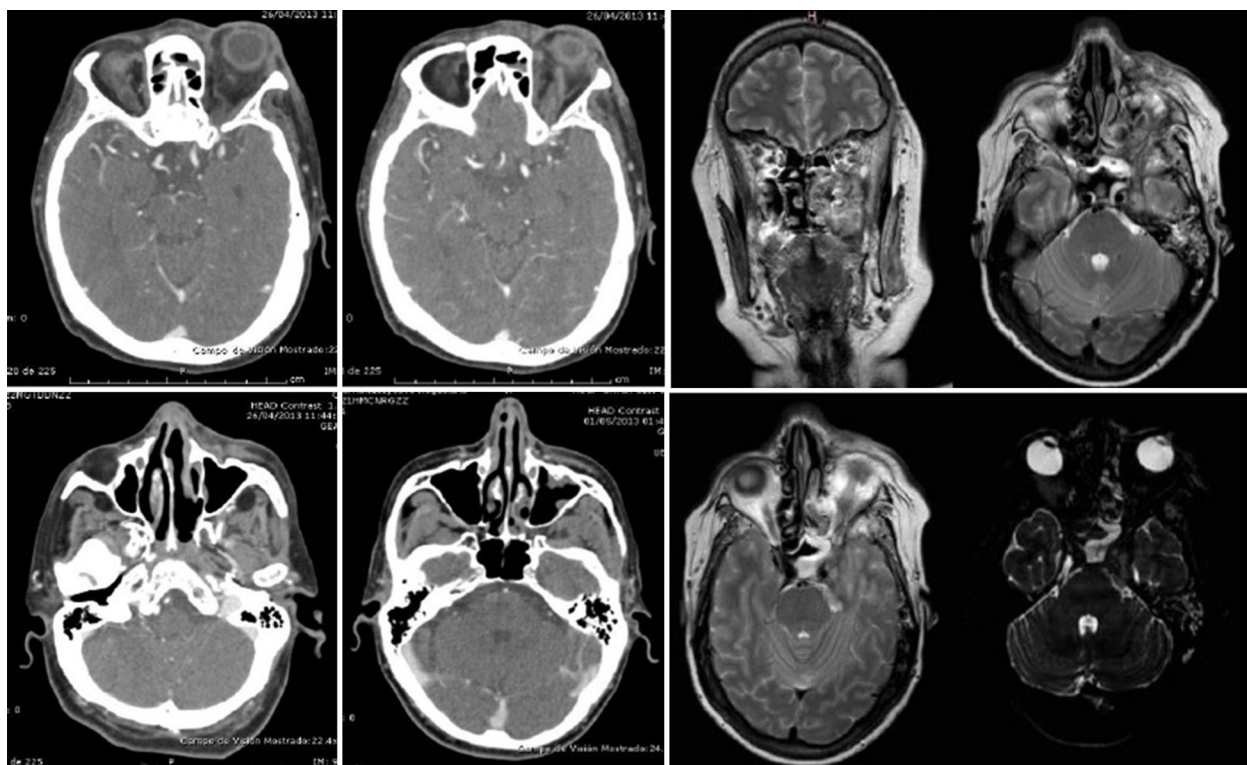


Figure 2 Computed axial tomography scan and magnetic resonance imaging of the skull.

alertness and somnolence. The most frequent finding reported in the tomography was mucosal thickening and unilateral thickening of orbital tissue, including extra-ocular muscles (5/5). Pterygomaxillary fissure involvement was seen in 100% of the patients, while only 60% presented dissemination towards the infratemporal fossa. The patients who evolved with orbital apex syndrome presented with an aggressive infection (Fig. 2).

The patients were managed with strict metabolic control, systemic antimycotic (amphotericin B at 1–1.5 mg/kg/day), reaching an accumulated dosage of 3112 g on average, nasal washes every 8 h with amphotericin B 50 mg/500 ml saline solution, anticoagulant prophylaxis (subcutaneous enoxaparin at 1 mg/kg/day).

Surgical debridement was performed on all patients, using sinonasal endoscopy, in the first 24 h of their admission. Three patients who presented with thrombosis of the cavernous sinus and orbital apex syndrome received orbital exenteration. Two patients (40%) required a second surgical

intervention, extending the margins of debridement of necrotic tissue through endoscopy.

Postoperative debridement was performed on all patients in the doctor's surgery. In 100% of our patients, the histopathological diagnosis of rhino-orbital mucormycosis was confirmed.

All the patients progressed favourably; our mortality rate was 0%.

## Discussion

Rhino-orbital mucormycosis is the most frequent form of presentation of this entity. In earlier publications, the pulmonary form was reported to have the greatest incidence.

There are multiple reports in the literature about the predominance of mucormycosis in patients with haematological malignancies such as leukaemia.<sup>5</sup> In addition, neutropenia is reported to be one of the main factors of risk for the development of this infection.<sup>6</sup> Despite these facts,

all the patients in our series had diabetes mellitus type 2 as the immunocompromise factor, 3 of them with a recent episode of ketoacidosis. In 1 of the largest literature reviews performed (from 1985 through 2004), it was found that 36% (n=337) of the 929 cases of confirmed mucormycosis involved diabetes mellitus, 34% of which had documented ketoacidosis.<sup>7</sup>

Paranasal sinus involvement seems to be the location most greatly affected in diabetic patients.<sup>8</sup> Of the 929 cases described by Roden et al.,<sup>5</sup> compromise of the paranasal sinuses was the most common form of infection, representing 39% of the cases. These cases presented with lesions in the nose, paranasal sinuses (maxillary sinus being the most frequently affected), orbit and cavernous sinus, coinciding with the findings in our cohort.

Orbital compromise is seen in 66%–100% of cases,<sup>9</sup> and 100% of our patients had ophthalmological involvement.

Thrombosis of the sphenopalatine branches in the pterygopalatine fissure and/or anterior ethmoidal branches in the orbit can explain nasal necrosis; consequently, blackish crusting should be considered indicative of vascular necrosis, rather than the site of *Mucor* inoculation.<sup>10</sup>

In agreement with Seiff et al.,<sup>11</sup> the pterygopalatine fissure, through the sphenopalatine foramen, is the main reservoir for *Mucor* and acts as a conduit for disseminating the infection to other locations. That is why we always remove the posterior wall of the maxillary sinus, exposing this fissure, regardless of the approach used in or the extension of the surgery.

After the invasion of the pterygopalatine and superior orbital fissures, regional vascular thrombosis occurs, with rapid progression towards orbital tissues, causing orbital apex syndrome.<sup>12</sup> Orbital exenteration, together with debridement of the pterygopalatine and superior orbital fissures, should be performed in patients with progressive ocular involvement, to eliminate the fungal reservoir and prevent intracranial invasion. Hargrove et al.<sup>13</sup> reported that patients with the same symptomatology and factors of risk, when exenterated, have a higher survival rate. The indication to exenterate these patients is controversial<sup>14</sup>; our criterion for exenteration was only patients with orbital apex syndrome with thrombosis of the cavernous sinus, given that this implies a greater risk of intracranial extension.<sup>15</sup>

Two of our patients had peripheral facial paralysis; this represents 40% of our population, a much higher figure than that reported in the literature. This could be explained by the extratemporal irrigation of the facial nerve, through infratemporal fissure involvement, as has been described by Meas et al.<sup>16</sup>

Diagnosis should begin with early clinical picture suspicion to improve patient survival; computed axial tomography should be included to describe the lesion and establish the extension of the disease. Magnetic resonance imaging is much more sensitive and specific, given that mycotic infections are characteristically seen as hypointense in both weighted T1 and T2 images, and should be confirmed with cultures or biopsies of the areas involved that demonstrate tissue invasion by the characteristic hyphae.<sup>14</sup>

Ischaemic tissue creates a favourable environment that promotes fungal proliferation, while the scant blood supply

due to the thrombosis involved in the disease itself prevents the antifungal therapy from reaching the tissues and eradicating the infection. Seiff et al.<sup>15</sup> considered that local irrigations with amphotericin B are useful as adjuvant therapy in the control of rhino-orbital fungal infections, especially in patients with a reversible immunocompromised state.

In the immediate postoperative period, our patients received nasal washes with saline solution (500 ml) with a 50 mg vial of amphotericin B every 8 h, administered by the otorhinolaryngology service at our hospital.

Successful treatment of mucormycosis requires 4 factors: (1) early diagnosis, (2) reversal of the predisposing risk factors, (3) appropriate early surgical debridement, and (4) rapid antifungal therapy. The extension and time of surgical debridement needed to maximise results is not clearly defined, although the disease is known to be rapidly progressive. In our cases, debridement was performed within the first 24 h after the confirmation of the diagnosis by imprint smear in all our patients; second interventions were performed on patients requiring them based on clinical and endoscopic findings that suggested persistence of necrotic tissue in the nasal cavity and in the paranasal sinuses.

The vascular thrombosis that leads to tissue necrosis in mucormycosis justifies the use of the anticoagulants we employed, although a controlled study to establish their usefulness is needed.<sup>16</sup>

Early medical management based on antifungal therapy (amphotericin B) is one of the key pillars in patient survival. In our centre, liposomal amphotericin is unavailable, despite it being the antifungal of choice because of its greater efficacy and lower toxicity than traditional amphotericin.<sup>17</sup> Once treatment with 2 g was completed, the length of therapy was based on clinical improvement and on tissue biopsies that established the necrotic infection no longer remained. Therapy using azole antifungal agents has not established better results in comparison with amphotericin B; however, it is considered a therapeutic option for patients with intolerant mucormycosis or polyols.<sup>4</sup> Some authors use hyperbaric oxygen as a complementary treatment, to reduce tissue hypoxia and acidosis,<sup>18</sup> increasing cure rates. However, this equipment is unavailable in our hospital, which is why it was not used.

## Conclusions

Mucormycosis, in spite of being a rare entity, should be considered as a diagnosis for every diabetic patient with rapid introduction of ophthalmological involvement. These patients should receive complete microbiological, radiological, endoscopic and clinical evaluation to corroborate or rule out mycotic infection and establish its extension, if applicable.

In our experience, good results have been achieved through appropriate early, multidisciplinary medical and surgical treatment, in which the necrotic tissue is extensively debrided, the pterygomaxillary fissure is examined in all cases and exenteration is chosen based on whether orbital apex syndrome exists or not. For that reason, we propose a diagnostic and therapeutic flow chart (Fig. 3).

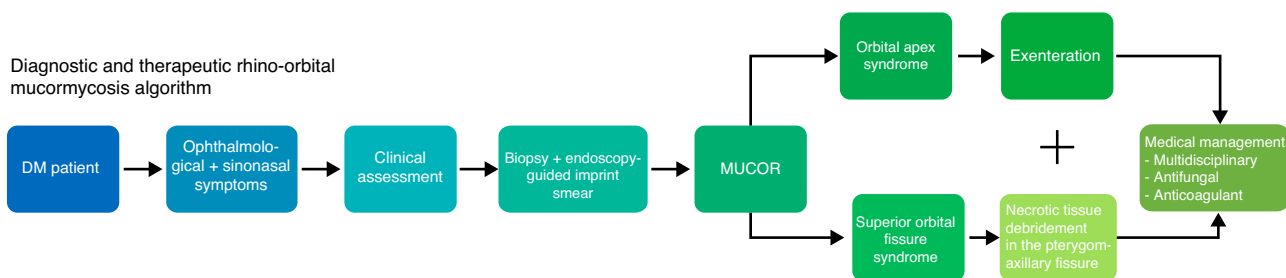


Figure 3 Proposal of diagnostic and treatment flow chart.

## Conflict of Interests

The authors have no conflicts of interest to declare.

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