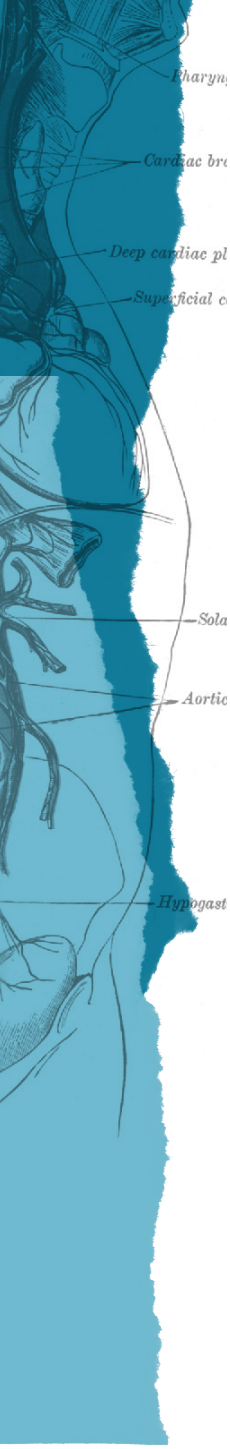

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CASO CLÍNICO

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Rhino-Orbito-Cerebral Mucormycosis as a Cause of Orbital Apex Syndrome in an Immunocompetent Patient: A Case Report

Mucormicosis rino-órbito-cerebral como causa del síndrome del ápice orbitario en un paciente inmunocompetente: un caso clínico

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ABSTRACT

Background: Rhino-orbito-cerebral mucormycosis (ROCM) is a rare, an-gio-invasive fungal infection associated with high morbidity and mortality, even with early therapeutic intervention. Although it typically occurs in immunocompromised individuals, its presentation in immunocompetent hosts is exceedingly rare and presents a significant diagnostic challenge.

Objective: To present an unusual case of ROCM manifesting as orbital apex syn-drome (OAS) in an immunocompetent patient, noting a partial treatment response and a favorable quality-of-life outcome, while highlighting the importance of early recognition and multidisciplinary management.

Case report: A 57-year-old male with an unremarkable past medical history pre-sented to the emergency department with a 30-day history of moderate, pulsatile, right-sided hemicranial headache, exacerbated by positional changes. The pain progressed and was accompanied by ipsilateral ocular pain, diplopia, ptosis, and decreased visual acuity, prompting multiple emergency department visits. Neuro-logical examination revealed a non-reactive right pupil, ptosis, and complete palsy of the right third (III), fourth (IV), and sixth (VI) cranial nerves. Neuroimaging showed inflammation and mass effect at the right orbital apex.

Treatment and outcome: Based on high clinical and radiological suspicion, em-pirical systemic antifungal therapy was initiated prior to histopathological confirma-tion. Subsequent surgical exploration and biopsy definitively confirmed mu-cormycosis. This aggressive management led to partial resolution of symptoms and improved quality of life, although residual ophthalmoplegia and vision loss persisted as sequelae.

Conclusions: This case demonstrates that ROCM can manifest as orbital apex syndrome even in immunocompetent hosts. The favorable outcome, despite a sig-nificant delay in definitive diagnosis, underscores the fact a high index of clinical suspicion and the prompt initiation of empirical, multidisciplinary therapy are critical for survival in this life-threatening infection.

Keywords: mucormycosis, rhino-orbito-cerebral, orbital apex syndrome, ophthal-moplegia, fungal infection, immunocompetent host

RESUMEN

Antecedentes: La mucormicosis rino-órbito-cerebral (ROCM, por sus siglas en inglés) es una infección fúngica angioinvasiva poco común, asociada con una alta morbilidad y mortalidad, incluso con intervención terapéutica. Aunque típicamente ocurre en individuos inmunocomprometidos, su presentación en personas inmunocompetentes es rara y representa un desafío diagnóstico.

Objetivo: Presentar un caso inusual de ROCM que se manifiesta como síndrome del vértice orbitario (OAS) en un paciente inmunocompetente, con respuesta parcial al tratamiento y un desenlace favorable en calidad de vida, destacando la importancia del reconocimiento temprano y el manejo multidisciplinario.

Reporte de caso: Paciente masculino de 57 años, sin antecedentes médicos relevantes, acudió al servicio de urgencias con un cuadro de 30 días de cefalea hemicraneal derecha, de intensidad moderada, pulsátil y exacerbada por cambios posturales. El dolor progresó y se acompañó de dolor ocular ipsilateral, diplopía, ptosis y disminución de la agudeza visual, lo que motivó múltiples consultas en urgencias. El examen neurológico reveló pupila derecha no reactiva, ptosis y parálisis completa de los nervios craneales tercero (III), cuarto (IV) y sexto (VI) derechos. La neuroimagen mostró inflamación y efecto de masa en el vértice orbitario derecho.

Tratamiento y desenlace: Ante la alta sospecha clínica y radiológica, se inició tratamiento antifúngico sistémico empírico antes de la confirmación histopatológica. La posterior exploración quirúrgica y biopsia confirmaron definitivamente mucormicosis. Este manejo agresivo condujo a una resolución parcial de los síntomas y una mejora en la calidad de vida, aunque persistieron secuelas como oftalmoplejía y pérdida visual.

Conclusiones: Este caso demuestra que la ROCM puede manifestarse como síndrome del vértice orbitario incluso en personas inmunocompetentes. El desenlace favorable, a pesar de un retraso considerable en el diagnóstico definitivo, resalta que un alto índice de sospecha clínica y la pronta instauración de una terapia empírica y multidisciplinaria son fundamentales para la supervivencia ante esta infección potencialmente mortal.

Palabras clave: mucormicosis, rino-órbito-cerebral, síndrome del vértice orbitario, oftalmoplejía, infección fúngica, huésped inmunocompetente.

INTRODUCTION

Mucormycosis is a rare yet emerging, fulminant, and life-threatening opportunistic fungal infection characterized by a high mortality rate (1). It is caused by fungi of the order Mucorales, which are ubiquitous saprophytes commonly found in soil, decaying organic matter, and contaminated food. This order is distinguished by broad, pauciseptate or aseptate, ribbon-like hyphae (5). Globally, *Rhizopus arrhizus* is the most common causative agent of mucormycosis, followed by species within the genera Lichtheimia, Apophysomyces, Rhizomucor, Mucor, and Cunninghamella. In total, 11 genera and 27 species of Mucorales have been implicated in human disease.

Human infection predominantly occurs predominantly through the inhalation of sporangiospores, and less commonly via ingestion or traumatic inoculation (1), (2). In this regard, mucormycosis has a significant global health impact, with mortality rates reaching 40%-80% depending on anatomical site and host factors (3), (4). The clinical manifestations of mucormycosis vary depending on the host's immune status and the site of infection. The most common and distinctive presentation is rhino-orbito-cerebral mucormycosis (ROCM), which typically begins with the inhalation of fungal spores into the paranasal sinuses. Initially, the infection may remain localized, presenting as acute sinusitis characterized by fever, headache, and nasal congestion (2). In susceptible hosts, however, the infection can rapidly progress, invading the palate and orbit, with subsequent extension into the cerebrum [7]. Consequently, angioinvasion remains the pathological hallmark, leading to thrombosis, ischemia, and tissue necrosis [6].

While ROCM predominantly affects immunocompromised individuals, rare cases in immunocompetent hosts highlight the local mucosal breaches as potential entry points [8], [9]. Vision loss, a devastating complication of ROCM, can result from optic nerve infarction due to occlusion of the ophthalmic or central retinal artery, or from direct involvement of the orbital apex [1], [3]. Intracranial progression, typically occurring within days, can proceed via direct extension or angioinvasion [10]. Notably, by the time intracranial disease is diagnosed, orbital involvement is nearly universal [11].

A key clinical presentation of ROCM is the orbital apex syndrome (OAS), a constellation of signs and symptoms resulting from a pathological process affecting structures within the orbital apex [12]. The syndrome is defined by dysfunction of the optic (II), oculomotor (III), trochlear (IV), and

abducens (VI) cranial nerves, as well as the ophthalmic division (V1) of the trigeminal nerve. Key clinical features include vision loss, pain, and ophthalmoplegia. The etiologies of OAS are diverse, encompassing inflammatory, neoplastic, and infectious processes [13]. Among infectious causes, fungal infections—most commonly due to Aspergillus and Mucor species—are a critical consideration. Furthermore, neuroimaging plays a pivotal role, with MRI demonstrating infiltrative processes and CT guiding surgical planning [13]. The diagnostic cornerstones for mucormycosis remain direct microscopy, histopathology, and fungal culture of surgical specimens, though the prognosis can be guarded even with timely treatment [1]. Liposomal amphotericin B constitutes first-line therapy, with surgical debridement essential for source control [14].

Given the rarity of this condition in immunocompetent hosts and the frequent delays in diagnosis, reporting such cases is essential to improve our collective understanding of its pathology, clinical features, and management. Herein, we present the case of an otherwise healthy, immunocompetent patient who presented with ophthalmoplegia and diplopia that rapidly progressed to ipsilateral blindness, in whom a timely diagnosis and multidisciplinary treatment plan were achieved.

CASE DESCRIPTION

A 57-year-old man with no relevant past medical history presented in October 2022 with a 20-day history of an insidious onset, right-sided, pulsatile headache. Initially mild to moderate, the pain was exacerbated by postural changes, and at its peak intensity, was accompanied by ipsilateral ocular pain, horizontal diplopia, ptosis, and decreased visual acuity. These symptoms prompted multiple visits to the emergency department and ophthalmology clinics, where he was prescribed naproxen (550 mg three times daily) and pregabalin (75 mg twice daily) without improvement. Due to the lack of resolution and worsening symptoms, he was re-evaluated by an ophthalmologist who identified complete right ophthalmoplegia. This finding prompted his immediate referral to the emergency department for neurological evaluation and subsequent hospital admission.

On admission, the neurological examination revealed complete right ptosis with a fixed, dilated pupil. He presented with total right ophthalmoplegia involving cranial nerves III, IV, and VI, associated with pain during eye movements (see Figure 1). Additionally, there was hypoesthesia in the distribution of the ophthalmic division of the trigeminal nerve (V1) in the right periorbi-

tal region. Fundoscopy showed right optic disc edema. These findings established a syndromic diagnosis of a right-sided orbital apex syndrome, prompting hospitalization for etiological investigation. Elevated blood pressure readings led to a diagnosis of uncontrolled hypertension. Treatment with losartan (50 mg twice daily) was initiated, and adequate blood pressure control was achieved.

Initial laboratory studies revealed leukocytosis (11,000 cells/mm^3) with neutrophilia (65.3%) and a left shift. The erythrocyte sedimentation rate (ESR) was elevated at 30 mm/hr. Blood glucose, as well as liver, renal, and thyroid function tests, were within normal limits. Serologies for HIV and syphilis were negative (see Table 1).

Table 1. Hemogram and serological studies

Parameter	Oct-06-22	Oct-18-22	Oct-19-22	Oct-20-22	Oct-21-22	Oct-23-22	Oct-24-22	Reference values
White Blood Cells								
Leukocytes (x103/mm3)	11.00	9.80						4.23 - 9.07
Neutrophils (%)	65.30	76.30						34.00 - 67.90
Lymphocytes (%)	25.80	13.40						21.80 - 53.10
Monocytes (%)	7.70	9.40						5.30 - 12.60
Eosinophils (%)	0.30	0.10						0.80 - 7.00
Basophils (%)	0.90	0.80						0.20 - 1.20
Immature Cells (%)	3.70	3.30						0.00 - 3.00
Red Blood Cells & Platelets								
Haemoglobin (g/dL)	15.80	16.10						13.70 - 17.50
Hematocrit (%)	47.7	49.4						40.0 - 51.0
MCV (fL)	88.3	88.7						79.0 - 92.2
MCH (pg)	29.3	28.9						25.7 - 32.2
MCHC (g/dL)	33.1	32.6						32.3 - 36.5
RDW (%)	14.50	14.80						11.60 - 14.40
Platelets (x103/µL)	328	263						140 - 400
Inflammatory Markers								
ESR (mm/hr)	30.0	30.0						0.0 - 15.0
C-Reactive Protein (mg/L)			119.80	70.60	90.90	17.60	10.00	0.00 - 10.00
Inmunology (Blood)								
HIV 1 & 2 Antibodies (HIV)	Negative							
Syphilis Serology	Negative							

Source: own elaboration.

Table 2. Key cerebrospinal fluid findings (Oct.-10-2022).

Feature	Result	Typical reference values
Appearance / Color	Clear / Colorless	Clear / Colorless
pH	9.0	7.28 - 7.32
Cell Count	0.00	< 5 (cells/mm3)
Glucose	128.0	40 - 70 (mg/dL)
Protein	32.5	15 - 45 (mg/dL)

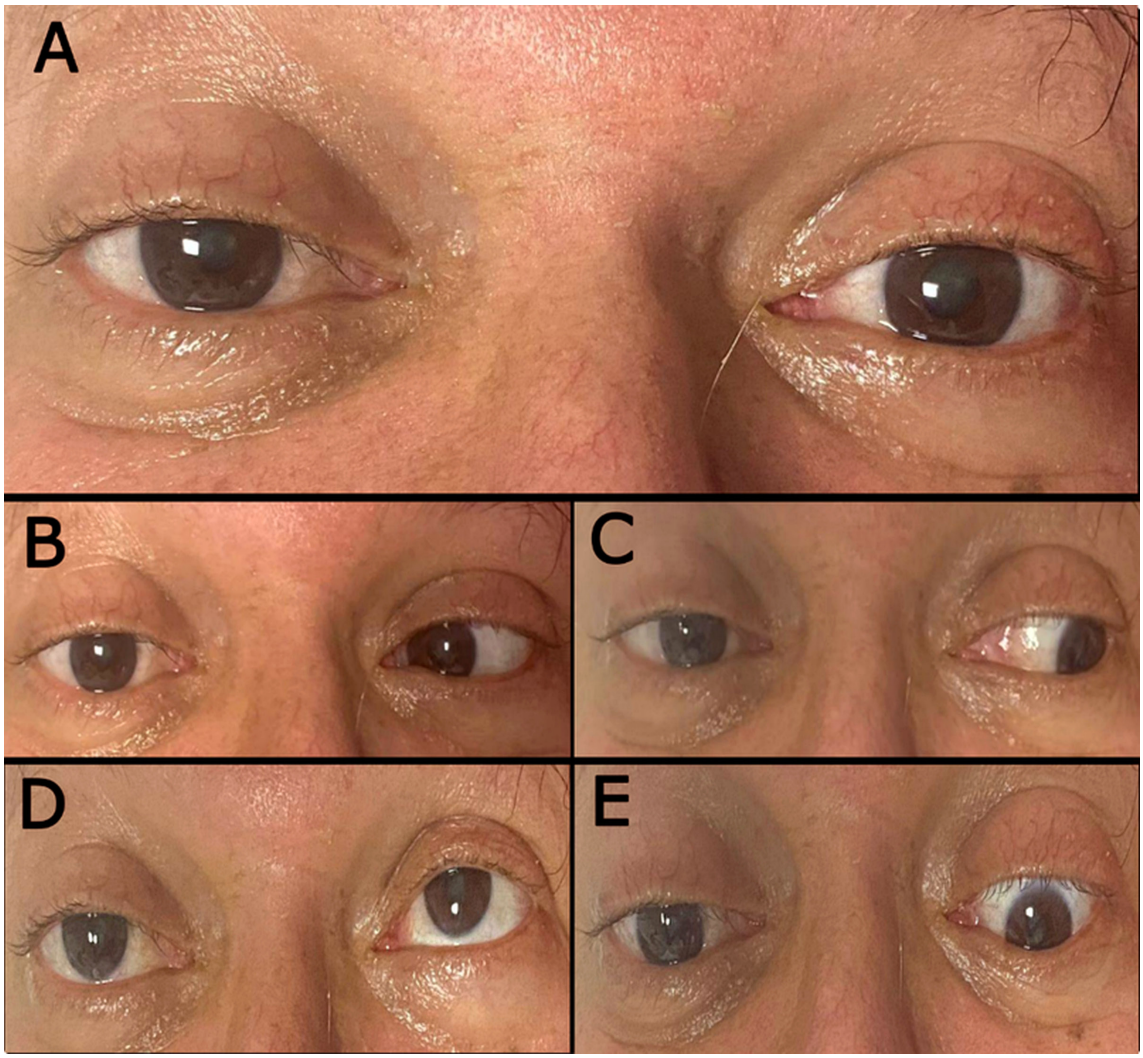
Source: own elaboration.

Table 3. Microbiological and serological studies for differential diagnosis

Sample Type	Test	Date	Result
Serology (Blood)			
	HIV 1 & 2 Antibodies (HIV)	Oct-06-22	Negative
	Syphilis Serology	Oct-06-22	Negative
Cerebrospinal Fluid			
	Gram Stain	oct-10-22	No microorganisms observed
	India Ink (for Cryptococcus)	oct-10-22	No fungal structures observed
	VDRL	oct-10-22	Non-Reactive
	Culture (Common organisms)	oct-13-22	No growth after 72 hours
Lesion Samples			
Cranial Base Lesion	Gram Stain	oct-20-22	No microorganisms observed
	Culture (Common organisms)	oct-24-22	No growth after 5 days
Nasal Lesion	KOH Smear	oct-21-22	No fungal structures observed
	India Ink (for Cryptococcus)	oct-21-22	No fungal structures observed
	AFB Stain (for Mycobacteria)	oct-21-22	Negative

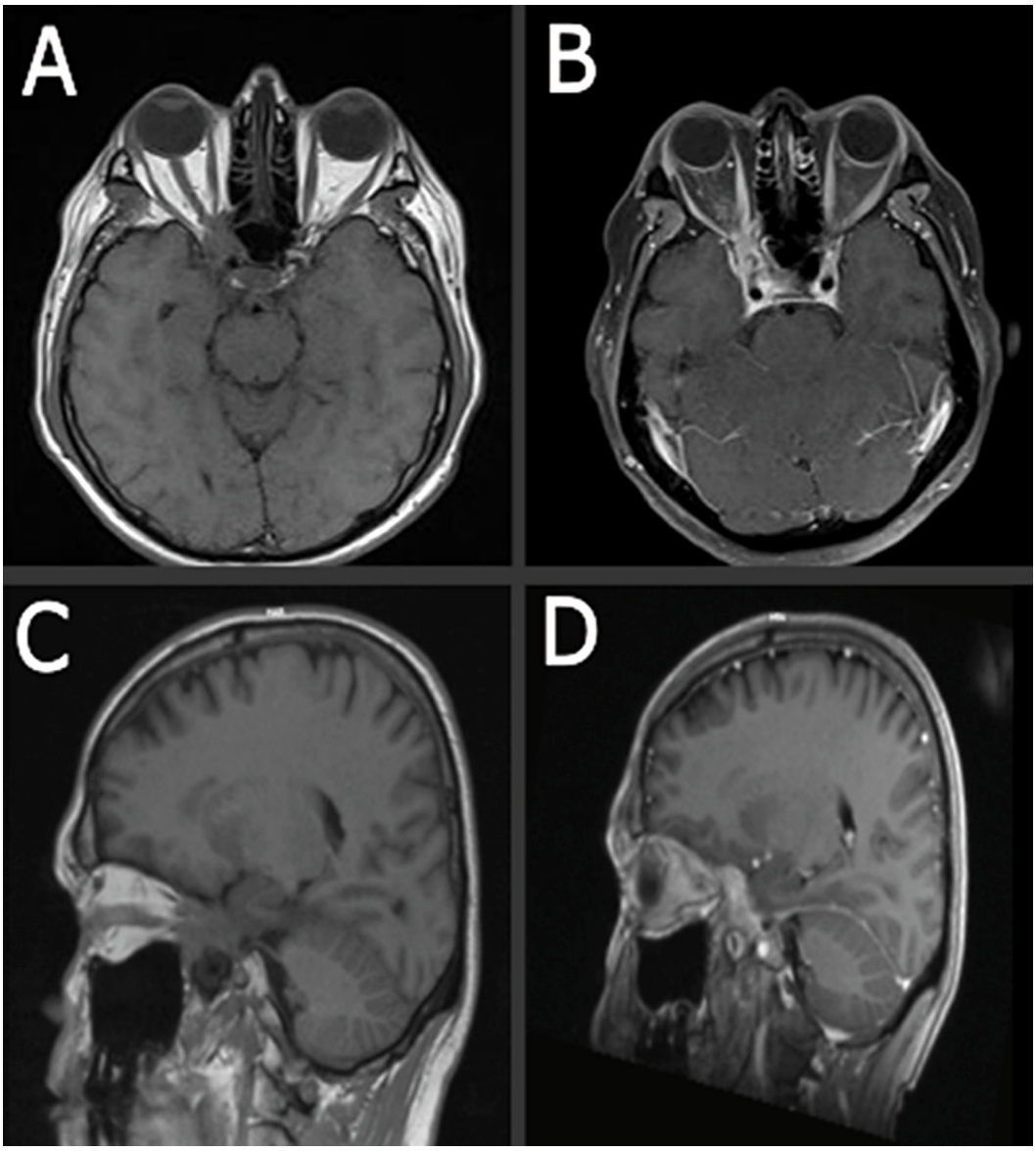
Note. Gadolinium-enhanced Magnetic Resonance Imaging (MRI) of the brain and orbits revealed thickening and pathological enhancement of the soft tissues in the right orbital apex, with extension into the ipsilateral cavernous and sphenoid sinuses. These findings were consistent with an inflammatory or infiltrative process (see Figure 2). A lumbar puncture revealed an opening pressure of 20 cmH_2O, and cerebrospinal fluid (CSF) analysis was unremarkable (see Table 2).

Source: own elaboration.



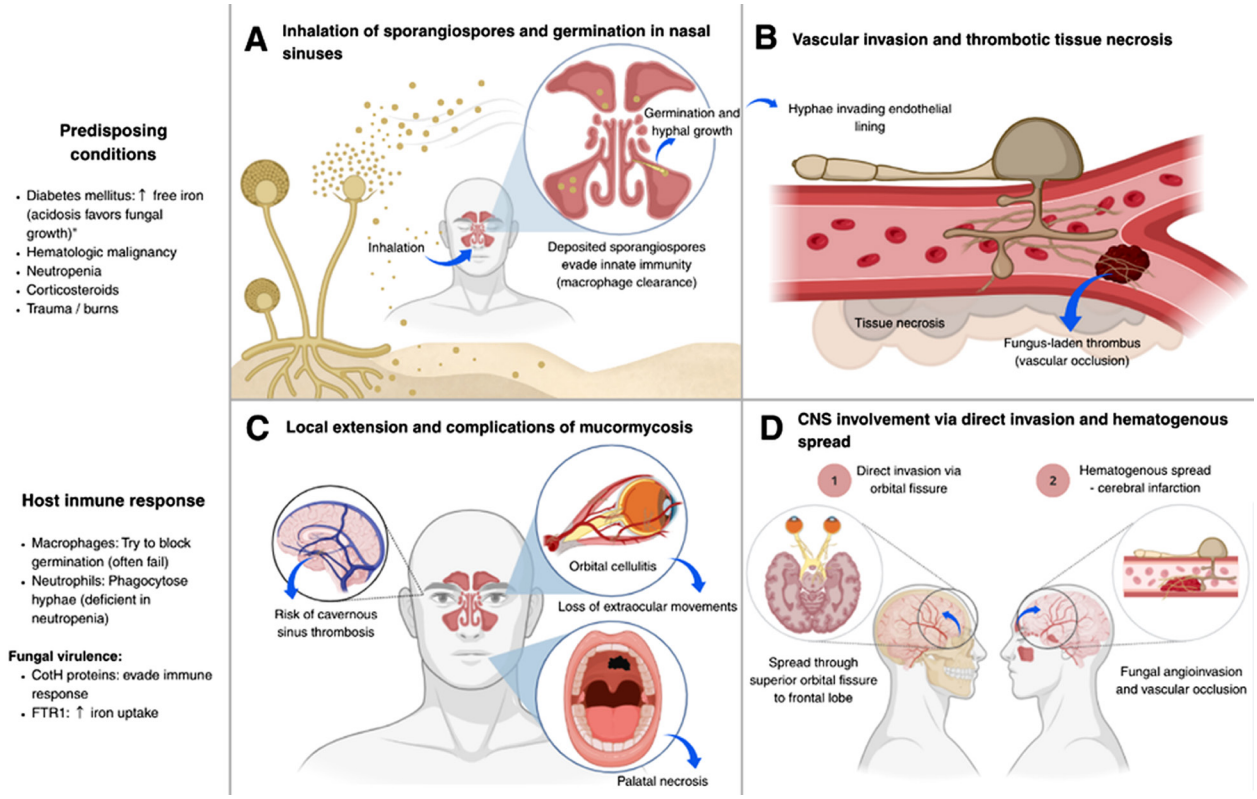
Source: own elaboration.

Figure 1. A. Primary gaze. B. Impaired abduction of the right eye. C. Impaired adduction of the right eye. D. Impaired elevation of the right eye. E. Impaired depression of the right eye



Note. (A-B) T1-weighted sequences without and with contrast showing altered signal intensity in the right orbital apex, characterized by thickening of the soft tissues within the superior and inferior orbital fissures, with avid heterogeneous enhancement following contrast medium administration. (C–D) The T1-weighted sequences with and without contrast in sagittal reconstructions show a clear mass effect on the orbital apex, with involvement and pathological enhancement of the oculomotor, abducens, ophthalmic (V1), and trochlear nerves.
Source: own elaboration.

Figure 2. Magnetic resonance imaging of the brain and orbits with contrast



Note. This diagram illustrates the progression of mucormycosis, initiated by the inhalation of fungal sporangiospores (A) that germinate into hyphae, leading to aggressive angioinvasion, thrombosis, and subsequent tissue necrosis (B). The infection spreads contiguously from the nasal sinuses to the orbits (orbital apex syndrome) and then to the central nervous system (C, D) via direct invasion or hematogenous dissemination, resulting in severe local destruction and CNS involvement. Predisposing factors include diabetes mellitus and immunosuppression, while fungal virulence factors such as CotH proteins and FTR1 aid in host immune evasion and survival.
Source: own elaboration.

Figure 3. Pathophysiology of mucormycosis

Given the suspicion of an infiltrative infectious or neoplastic process, the case was discussed in a multidisciplinary team meeting involving the Neurosurgery, otorhinolaryngology (ENT), and neurology departments. Considering the involvement of the sphenoid sinus on MRI, the ENT service requested a computed tomography (CT) scan of the paranasal sinuses. The CT confirmed opacification of the right sphenoid sinus with soft-tissue density material. This finding significantly raised the clinical suspicion for rhino-orbito-cerebral mucormycosis (ROCM). Based on this high

clinical suspicion and pending histopathological confirmation, the infectious diseases service recommended initiating empiric combination therapy. A regimen of liposomal amphotericin B (250 mg daily IV) was initiated to cover invasive fungal etiologies, and trimethoprim/sulfamethoxazole (160/800 mg IV every 6 hours) was initiated as part of a broad-spectrum antibiotic coverage for atypical pathogens considered in the initial differential diagnosis, albeit with low probability, such as Nocardia.

Twelve days after admission, the patient underwent an endoscopic ethmoidectomy and sphenoidotomy for tissue biopsy. The procedure was well-tolerated. Specimens were sent for bacterial, fungal, and mycobacterial cultures, as well as for histopathological analysis with special stains. While all microbiological cultures were negative (see Table 3), the pathology report, received two weeks later, described broad, aseptate hyphae with right-angle branching—morphological features characteristic of a fungus from the order Mucorales. This result definitively confirmed the diagnosis of invasive mucormycosis. It is noteworthy that histopathological confirmation was obtained 14 days after the biopsy was taken. Although this interval may reflect hospital logistics, it highlights the critical importance of basing empirical treatment on a high level of clinical and radiological suspicion, as any delay in initiating specific antifungal therapy is directly associated with increased mortality.

The clinical course was favorable, with no progression of neurological deficits or treatment-related complications. The patient completed a 21-day course of antibiotics and, following the diagnosis, continued liposomal amphotericin B until clinically stable. He was discharged on an oral regimen of isavuconazole, starting with a loading dose (200 mg three times daily for 48 hours) followed by a maintenance dose (200 mg once daily). A multidisciplinary outpatient follow-up plan was established, including neuro-ophthalmology, Neurosurgery, ENT, and Neurology. Oral isavuconazole was planned for a total duration of 12 months, with periodic clinical and neuroimaging assessments to be conducted at regular intervals. A follow-up MRI of the brain and orbits performed in November 2023 (13 months after presentation) showed only stable postsurgical changes in the right ethmoid region, with no evidence of active disease. Consequently, given the excellent clinical and radiological response, antifungal therapy was discontinued. It is worth noting that the patient experienced partial recovery of ocular movements and, as a sequela of

the pathological process, remained with right-sided visual loss—an outcome that, given the high mortality rate of the disease, could be considered successful.

DISCUSSION

Mucormycosis is a fulminant, angio-invasive fungal infection with high mortality, predominantly affecting immunocompromised individuals. This report describes an exceptionally rare presentation of rhino-orbito-cerebral mucormycosis (ROCM) manifesting as an isolated orbital apex syndrome (OAS) in a seemingly immunocompetent 57-year-old male. Consequently, this favorable outcome underscores the critical importance of a high index of suspicion, prompt diagnosis, and aggressive multidisciplinary management.

Orbital apex syndrome, characterized by dysfunction of cranial nerves II, III, IV, V1, and VI at the orbital apex, constitutes a formidable diagnostic challenge owing to its myriad etiologies, encompassing inflammatory, neoplastic, vascular, and infectious processes. Among infectious causes, fungal sinusitis due to Aspergillus or, as in this instance, Mucorales, is a recognized, albeit infrequent, cause, particularly in the absence of classical risk factors such as uncontrolled diabetes mellitus, hematological malignancies, or immunosuppressive therapy [12], [15]the pattern of infection, the surgical and antifungal treatments, and survival were described. Results. The mean age of patients was 38.8 years; 65% were male. The prevalence and overall mortality were 36% and 44%, respectively, for diabetes; 19% and 35%, respectively, for no underlying condition; and 17% and 66%, respectively, for malignancy. The most common types of infection were sinus (39%. Notably, our patient's presentation, lacking these classical risk factors, underscores the importance of including mucormycosis in the differential diagnosis of OAS, even in patients considered immunocompetent.

The pathophysiological cornerstone of mucormycosis is angio-invasion, whereby hyphae breach vessel walls, precipitating thrombosis, ischemia, and profound tissue necrosis [6]. This angio-invasive nature explains the contiguous spread from the paranasal sinuses, in this case the sphenoid sinus, to adjacent structures like the orbit and cavernous sinus. In immunocompetent hosts, it has been postulated that local factors, such as subclinical chronic sinusitis, may disrupt the mucosal barrier, thereby facilitating the inoculation and germination of inhaled spores [8], [9].

Although our patient had no documented history of sinusitis, the initial involvement of the sphenoid sinus supports this as the most probable portal of entry.

As demonstrated in our case, cultures from cerebrospinal fluid, blood, or nasal secretions are typically unrevealing, requiring a diagnosis based on clinical and radiological suspicion, with ultimate confirmation by histopathology [8]. Neuroimaging is paramount; magnetic resonance imaging was pivotal in delineating the extent of the infiltrative process, while computed tomography of the paranasal sinuses guided the surgical approach. This case reinforces that when high clinical and radiological suspicion for ROCM exists, a deep tissue biopsy should be performed without delay. Direct microscopic identification of broad, aseptate hyphae with right-angle branching remains the diagnostic gold standard.

The management of mucormycosis involves a three-pronged approach: the rapid initiation of systemic antifungal therapy, extensive surgical debridement of necrotic tissue, and control of underlying predisposing factors. Adhering to current guidelines, empiric treatment was initiated with liposomal amphotericin B, the drug of choice for first-line therapy owing to its potent activity against Mucorales [14]. The subsequent transition to oral isavuconazole for long-term treatment represents a significant therapeutic advance, offering an effective and better-tolerated option for consolidation and maintenance therapy [2]. The role of surgery, in turn, cannot be overstated, as it is crucial for reducing the fungal burden and improving drug penetration. The decision to avoid radical debridement was clinically appropriate given the imminent risk of injuring the internal carotid artery, thereby reducing the likelihood of catastrophic hemorrhage. Nevertheless, this limitation in surgically controlling the infectious focus likely influenced the patient's clinical course. It is reasonable to infer that the persistence of necrotic tissue necessitated prolonged systemic antifungal therapy and contributed to the persistence of residual ophthalmoplegia, possibly secondary to ischemic or compressive neuropathy affecting the oculomotor nerve and adjacent structures. This case highlights the delicate balance between the surgical aggressiveness required to eradicate invasive fungal infection and the need to preserve critical neurovascular structures, particularly at the orbital apex, where multiple functionally relevant nerve pathways converge. Indeed, although radical debridement was not performed in this patient due to involvement of the internal carotid artery within the cavernous sinus, endoscopic biopsy and sinus drainage were essential both for diagnosis and for initial source control [16].

A review of the literature confirms the profound rarity of this clinical picture. While reports of ROCM in immunocompetent hosts exist, their manifestation as an isolated orbital apex syndrome without evident predisposing factors such as trauma or diabetes is seldom documented. This case therefore provides valuable evidence, serving as a critical reminder that mucormycosis can mimic other orbital pathologies and must be actively considered to prevent diagnostic delays that can lead to permanent visual loss or mortality, with case-fatality rates for mucormycosis reported as high as 60% [4], [17].

Although the patient was classified as immunocompetent based on the absence of classical co-morbidities, the development of such an aggressive fungal infection challenges this definition. It raises the possibility of underlying, subtle immune deficiencies not routinely assessed in clinical practice, such as phagocytic dysfunction or impairments of the innate immune system (e.g., polymorphisms in pattern recognition receptors). This case underscores the necessity to include mucormycosis in the differential diagnosis of orbital apex syndrome even in patients without apparent immunosuppression, particularly when the clinical progression is rapid and atypical.

CONCLUSIONS

Mucormycosis is a fulminant, angio-invasive fungal infection with high mortality, predominantly affecting immunocompromised individuals. This report describes the case of a 57-year-old male, considered immunocompetent, with an exceptionally rare presentation of rhino-orbito-cerebral mucormycosis, manifested as an isolated orbital apex syndrome. The favorable outcome underscores the critical importance of a high index of suspicion, prompt diagnosis, and aggressive multidisciplinary management.

Author Contributions

- K.S.-C., A.V.-D., A.K.C.-Z., D.R.-P., V.B., and J.V.-M. contributed to the conceptualization of the study.
- K.S.-C., A.V.-D., A.K.C.-Z., and J.V.-M. conducted the investigation.
- K.S.-C., A.V.-D., A.K.C.-Z. were responsible for data curation.

- K.S.-C., A.V.-D., A.K.C.-Z. prepared the original draft.
- D.R.-P., V.B., and J.V.-M. reviewed and edited the manuscript.
- D.R.-P. and V.B. contributed to visualisation.
- V.B. acquired the funding for the study.
- All authors read and approved the final manuscript.

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Institutional Review Board Statement: This study was conducted following the Declaration of Helsinki and approved by the BIOS Institutional Review Board from Clínica la Misericordia Internacional, protocol CEI BIOS-26 - 13 June 2025.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient to publish this paper.

Data Availability Statement: Data sharing is restricted due to privacy and ethical considerations. The clinical data supporting the findings of this case report are not publicly available to protect the confidentiality of the patient.

Conflicts of Interest: The authors declare no conflicts of interest.

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Abbreviations

AFB: Acid-Fast Bacillus

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CRP: C-Reactive Protein

CSF: Cerebrospinal Fluid

CT: Computed Tomography

ENT: Otolaryngology

ESR: Erythrocyte Sedimentation Rate

HIV: Human Immunodeficiency Virus

IV: Intravenous

KOH: Potassium Hydroxide

MRI: Magnetic Resonance Imaging

OAS: Orbital Apex Syndrome

ROCM: Rhino-Orbito-Cerebral Mucormycosis

VDRL: Venereal Disease Research Laboratory

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