Annals of Case Reports
Boynes AC, et al. Ann Case Rep: 8: 1148
www.doi.org/10.29011/2574-7754.101148
www.gavinpublishers.com

Case Report

Rhino-Orbital-Cerebral-Mucormycosis: The Importance of Urgent Assessment

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Citation: Boynes AC, Schuringa R, Hickey DG, Reynolds G, Khong JJ (2023) Rhino-Orbital-Cerebral-Mucormycosis: The Importance of Urgent Assessment. Ann Case Report. 8: 1148. DOI:10.29011/2574-7754.101148

Received: 12 January 2023, **Accepted:** 30 January 2023, **Published:** 01 February 2023

Abstract

A case report highlighting the importance of early assessment and intervention in treating ROCM. This paper is particularly relevant as we are seeing a concerning increase in the incidence of ROCM associated to COVID-19.

A 67 year-old female had a delayed diagnosis of ROCM confirmed with radiological and microbiological findings. Her predisposing risk factors included end-stage renal disease, aplastic anaemia with neutropenia, and iron overload requiring deferoxamine infusions. Management included surgical debridement of paranasal sinuses, orbital exoneration and systemic antifungal treatment. The disease progressed despite this management, with the development of multifocal fungal cerebritis and superimposed ischaemic infarcts. The patient died five days after the cessation of treatment. ROCM is a life-threatening emergency. ROCM should be considered in all at risk patients who present with common sinus symptoms and disproportionate facial pain, especially when associated with red flags such as ophthalmoplegia, vision loss and facial numbness.

Introduction

This case report adds to current knowledge by highlighting less well-known risk factors for poor prognosis in rhino-orbital-cerebral-mucormycosis (ROCM) such as end-stage renal failure and deferoxamine infusions. It describes recent changes in the evidence-based management of ROCM including topical amphotericin B, which is gaining increasing popularity. This report is particularly relevant as we are seeing a concerning increase in the incidence of ROCM associated to COVID-19. Written patient consent was provided and this report adhered to the tenets of the Declaration of Helsinki.

Case Presentation

A 67-year-old female presented to an Emergency Department with two days of left-sided facial pain and headache. She was diagnosed with acute-on-chronic sinusitis based on computerized tomography (CT) and treated with oral Augmentin duo (500/125mg BD). Her medical history included end-stage renal disease secondary to polycystic kidney disease, requiring haemodialysis; transfusion-dependent aplastic anaemia and associated iron overload, treated with deferoxamine infusions; and left middle cerebral artery (MCA) aneurysm clipping. She suddenly deteriorated two days later whilst an inpatient, developing left ptosis, proptosis, periorbital discolouration, ophthalmoplegia, and an absent corneal reflex. Her best corrected visual acuity (BCVA) was 6/9 in both eyes. A CT showed enlargement of the left medial and inferior rectus muscles alongside early orbital fat stranding and left maxillary and ethmoidal sinus opacification. Her medical care was transferred to our hospital with a provisional diagnosis

of orbital cellulitis. On the initial ophthalmology assessment, her BCVA was 6/6 in the right eye and light perception in the left eye. She had a left relative afferent pupillary defect and complete ptosis. Examination revealed 3mm of proptosis in the left eye and complete ophthalmoplegia (Figure 1). In addition, reduced sensation in the V1 distribution had resulted in an absent corneal reflex. The posterior segment examination in both eyes was grossly normal. Otorhinolaryngology assessment identified necrotic tissue underlying the sphenoid and ethmoid sinuses, and throughout the left turbinate's. Magnetic resonance imaging (MRI) showed inflammatory changes compatible with acute invasive fungal sinusitis involving the left optic nerve. There was significant artefact over the cavernous sinus due to previous MCA aneurysm clipping (Figure 2). A provisional diagnosis of mucormycosis was made, and she was commenced on intravenous amphotericin, ceftazidime and flucloxacillin. That same day, paranasal sinus debridement and orbital exploration were performed, during which extensive tissue necrosis including the left turbinate's, maxillary/ethmoid sinuses, internal maxillary artery, extraconal fat and medial rectus were noted. Intraoperative tissue samples were consistent with mucor species showing angioinvasive fungal hyphae with extensive necrosis extending to the orbital apex (Figure 3). A diagnosis of ROCM was made, as was a decision to proceed to left orbital exoneration with amphotericin onlay at the orbital apex and orbital fissures, alongside further debridement of left paranasal sinuses. Postoperatively she experienced ongoing fever and became increasingly confused. A postoperative MRI showed features consistent with multifocal fungal cerebritis with superimposed ischaemic infarcts. As this represented a terminal event, active treatment was withdrawn, and the patient died five days later.

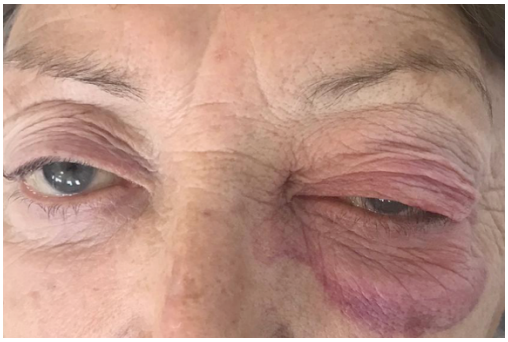

Figure 1: Patient photograph on initial ophthalmology assessment with evidence of left ptosis, proptosis and periorbital discolouration.

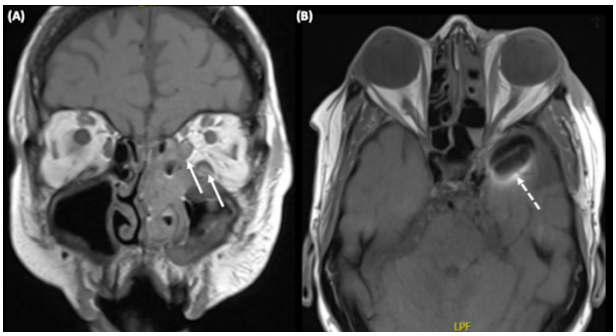

Figure 2: Pre-operative MRI brain/orbits (A) T1 coronal view showing opacification of the left maxillary and ethmoid sinuses as well as thickening of the inferior and medial rectus muscles (white arrows). (B) MRI brain/orbits T1 axial view showing inflammatory changes involving the intraconal optic nerve and thickening of the left medial rectus muscles. Image quality at the cavernous sinus and orbital apex is degraded by artefact related to middle cerebral artery metallic clip (dashed arrow).

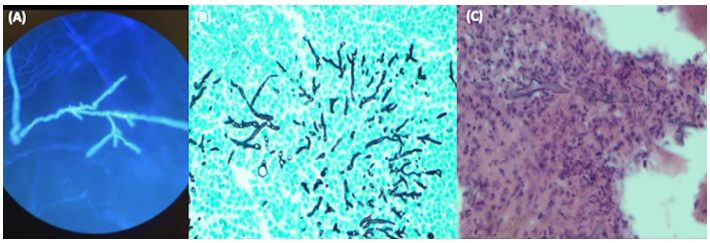

Figure 3: (A) Calcofluor stain demonstrating broad non-septate hyphae with right angle branching. (B) Grocott's meth enamine silver stain highlighting fungal elements. (C) Haematoxylin and eosin stain demonstrating broad non-septate fungal ribbons.

Discussion

This case highlights the importance of understanding risk factors for ROCM and the need for urgent assessment and management. Rhino-orbital-cerebral-mucormycosis is a rapidly progressive disease with a mortality rate between 15 to 85% [1]. Clinicians need to be aware of the warning symptoms and signs of ROCM as highlighted in Table 1 [2,3]. In the setting of the COVID-19 pandemic there has been a concerning increase in the global incidence of ROCM [2,4] Globally, diabetes is the single most important risk factor for ROCM [5]. In our case, predisposing risk factors that warrant early suspicion of ROCM included a history of renal failure, haematological disorder-associated

pancytopenia, and iron overload requiring deferoxamine therapy [1]. Antifungal medications and controlling the underlying disease are the mainstay of initial treatment in ROCM. Amphotericin B, 5-10mg/kg/day has been shown to effectively treat mucormycosis [5]. In cases with predominant sinonasal manifestation with no or limited involvement of the orbit and preserved vision, early and aggressive debridement of paranasal sinuses is indicated, and retro bulbar amphotericin B injections (3.5mg/ml) and sinus irrigation with amphotericin has been advocated [2]. Adjuvant orbital amphotericin B injections have been increasingly used in early-stage ROCM, especially during COVID-19 pandemic where 22% received injections in an Indian series [4]. Orbital exenteration is considered when early management fails with progressive orbital involvement, and in late stages with extensive orbital involvement with visual loss and intracranial extension [2]. While it was shown previously that orbital exenteration did not significantly change survival in ROCM [1] recent analysis of large series of over 2000 COVID-19 related ROCM cases suggested orbital exenteration was associated with mortality reduction from 52% to 39% in ROCM stage 4 disease with intracranial extension [4]. Decision on globe survival is based on aggressiveness of presentation, type of underlying disease process and response to initial therapy [1].

Anatomical structure involved	Clinical feature	Assoc. mortality rate (%)
Sinus / Non-specific	Epistaxis	50
	Headache	47
	Fever	44
	Nasal or oral necrosis	41
	Nasal congestion	38
	Facial pain	33
	Nasal discharge	29
Orbit	Periorbital/orbital pain	53
	Periorbital oedema	47
	Ptosis	47
	Periorbital discoloration	47
	Afferent pupillary defect	45
	Ophthalmoplegia	44
	Facial nerve palsy	43
	Proptosis	38
	Trigeminal anesthesia	37
	Decreased vision	35
	Diplopia	31
Cerebral	Seizures	67
	Internal carotid occlusion	67
	Mental status change	66
	Hemiplegia or Stroke	61
	Cavernous sinus thrombosis	57
† Mortality rate reported by Vaughan et al1; Mortality data extracted from Honavar et al [2]		

Conclusion

Rhino-orbital-cerebral-mucormycosis is a life-threatening emergency and should be considered in all at risk patients with diabetes, renal failure, and those on deferoxamine therapy who present with sinus symptoms and pain. Red flags such as ophthalmoplegia, vision loss or facial numbness are late-stage features that warrant immediate attention.

Disclosure statement: There are no conflicts of interest to disclose.

Financial support: We have received no funding from any organizations for this work.

Patient consent: Written patient consent was provided

Ethical statement: This report adhered to the tenets of the Declaration of Helsinki

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