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CASE REPORTS

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Apophysomyces elegans rhino-orbitocerebral mucormycosis: atypical cases in immunocompetent patients*

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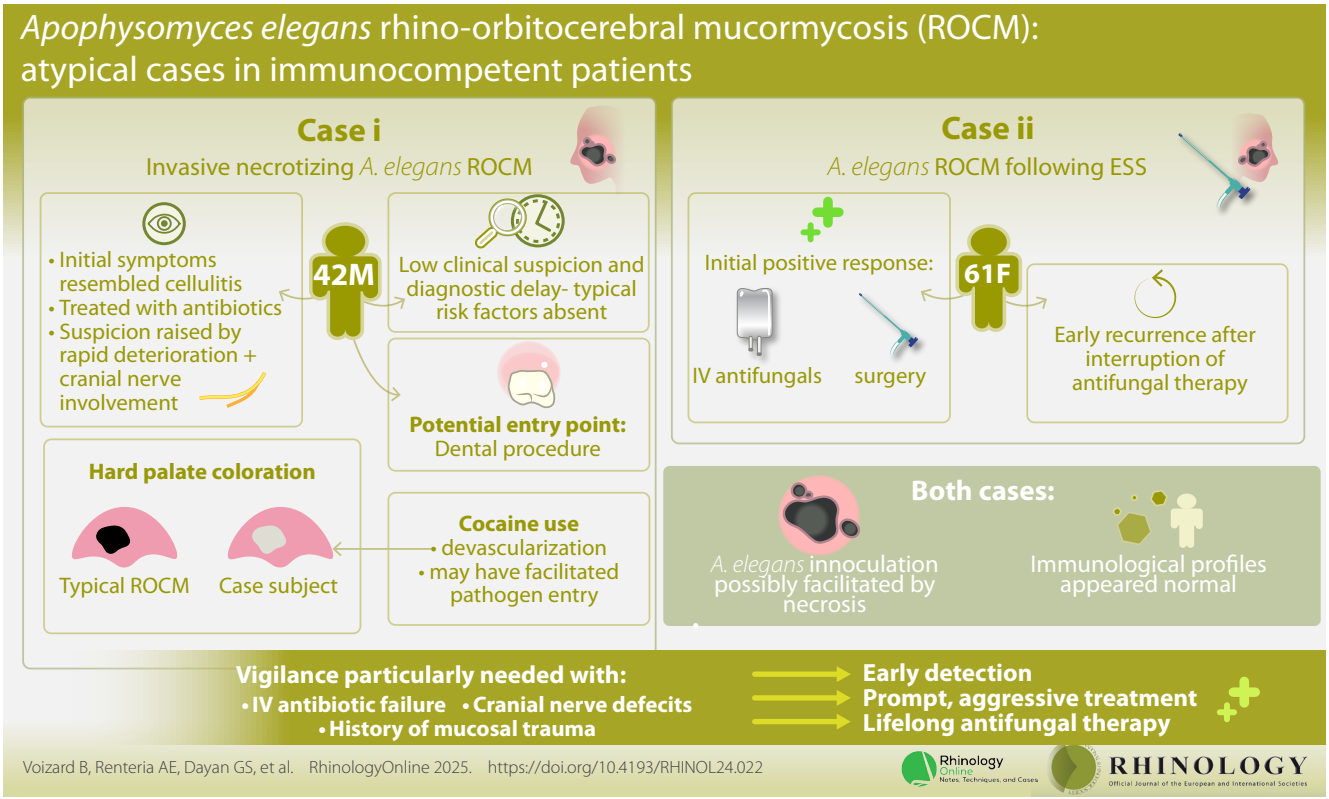

Abstract

Apophysomyces elegans can cause rhino-orbitocerebral mucormycosis in immunocompetent individuals. Awareness of this clinical entity, early recognition, aggressive treatment, and prolonged antifungal therapy are critical for controlling this rare but life-threatening infection.

Key words: mucormycosis, *Apophysomyces elegans*, sinus infection, invasive fungal infections, amphotericin b

Introduction

Mucormycosis are rare but aggressive fungal infections known for neurovascular spread and tissue invasion. Presentations include pulmonary, gastrointestinal, cutaneous, rhino-orbitoce-

rebral (ROCM), and disseminated disease. Most cases occur in immunocompromised individuals, such as those with uncontrolled diabetes [1], but some atypical species like *Apophysomyces elegans* (*A. elegans*) can cause ROCM in immunocompetent hosts. Mortality in immunocompetent patients ranges from 12-17%, with high rates of residual sequelae [1, 2]. Treatment includes high-dose amphotericin B, surgical debridement, and management of underlying causes, such as maintaining blood glucose levels, preventing local trauma, and optimizing oral hygiene [3, 4]. Adjuncts like hyperbaric oxygen and gamma interferon have been proposed, though their use is largely anecdotal [1, 4, 5]. Given the rarity of ROCM in healthy individuals, the objective is to document two cases of *A. elegans* ROCM in immunocompetent adults, highlighting clinical presentations, management, and outcomes to raise awareness and offer insights for future management.

Case reports

We present two cases of *A. elegans* ROCM from a tertiary center in Montreal, both affecting immunocompetent adults.

Fist case

A 42-year-old male with a history of hypothyroidism and dyslipidemia presented with increasing erythema and pain on the left cheek. One month prior, he had undergone a dental procedure and consumed cocaine in Guatemala. An initial facial CT scan was normal, and he was discharged with amoxicillin for suspected cellulitis. Four days later, his condition progressed with fever, leukocytosis, and suspicion of left preseptal cellulitis of odontogenic origin. IV piperacillin-tazobactam was initiated.

Despite treatment, his condition deteriorated with severe torticollis, hypoesthesia of the maxillary branch of the trigeminal

Table 1. Antifungals used for treatment of rhino-orbito-cerebral mucormycosis caused by *Apophysomyces elegans*.

Source	Antifungals / Antibiotics	Dosage	Other treatments	Outcome
Radner, 1995 [6]	Amphotericin B	1 mg/kg (IV) daily until total dose of 3.5g	Orbital exenteration, Multiple endoscopic sinus debridement, Maxillectomy	Cure
Chakrabarati, 1997 [7]	Amphotericin B	1 mg/kg (IV) daily x 15 days	Orbital exenteration, Multiple endoscopic sinus debridement	Death
Sdralis, 1997 [8]	Amphotericin B	-	Orbital exenteration, Multiple endoscopic sinus debridement	Cure
Brown, 1998 [9]	Amphotericin B	1 mg/kg (IV) daily x 5 days	Bilateral Cadwell-Luc, Multiple endoscopic sinus debridement	Cure
Fairley, 2000 [10]	Amphotericin B	Amphotericin B packing	Orbital exenteration, Multiple endoscopic sinus debridement	Cure
Chakrabarati, 2003 [11]	Amphotericin B	Total dose between 1.06 and 1.8g	Orbital exenteration, Multiple endoscopic sinus debridement	Cure
Schütz, 2006 [12]	Amphotericin B	1 mg/kg (IV) daily + Interticial perfusion continuous amphotericin B solution (5 mg/ 100 mL water at 40 mL/hour).	Orbital exenteration, Multiple endoscopic sinus debridement	Death
Rao 2006 [13]	Amphotericin B	Average total dose 1.8g	Orbital exenteration, Multiple endoscopic sinus debridement	4 cures, 1 death
Liang, 2006 [14]	Liposomal Amphotericin B, Cefepime, Metronidazole	5 mg/kg (IV) daily x 70 days	Orbital exenteration, Multiple endoscopic sinus debridement	Cure
Papadogeorgakis, 2010 [15]	Amphotericin B	1 mg/kg (IV) daily x 10 days	Orbital exenteration, Multiple endoscopic sinus debridement	Death
Cornely, 2013 [4]	Amphotericin B, Clindamycin	1 mg/kg (IV) daily x 5 days	Bilateral Caldwell-Luc procedures	Cure
Singh, 2017 [2]	Liposomal systemic and local Amphotericin B, tobramycin, penicillin	Total dose: 27.5 g x 14 days + "brief" course for relapse	Orbital exenteration, Multiple endoscopic sinus debridement, Hyperbaric oxygen, Granulocyte colony-stimulating factor (G-CSF)	Cure
Medina, 2017 [16]	Liposomal Amphotericin B	5 mg/kg (IV) daily x 42 days	Orbital exenteration, Multiple endoscopic sinus debridement	Cure
Skiada, 2018 [17]	Amphotericin B, Ceftazidime, Clindamycin	1.5 mg/kg (IV) daily	Orbital exenteration, Bilateral maxillectomy, Multiple endoscopic sinus debridement	Cure

Abbreviations: IV, intravenous.

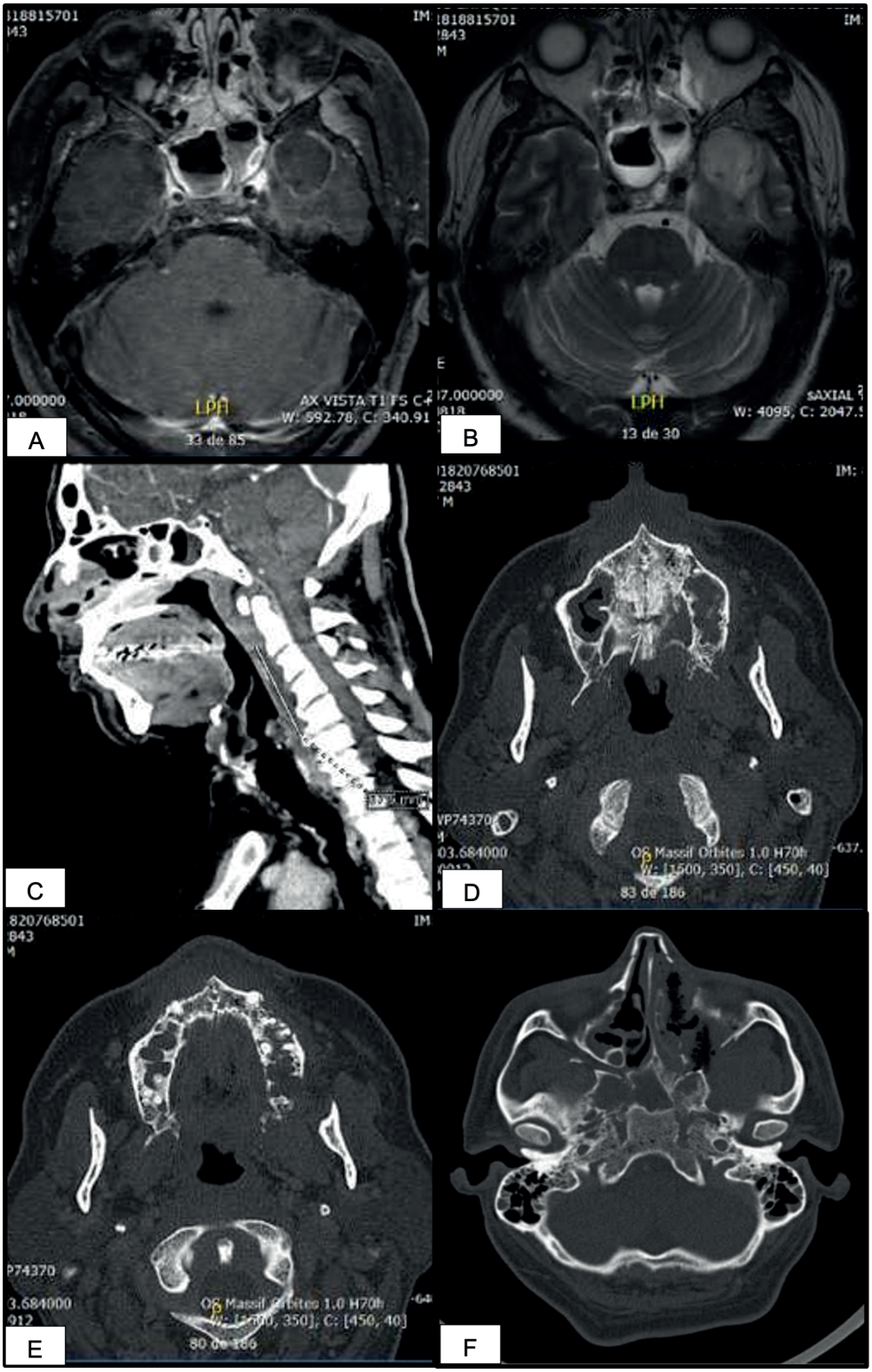

Figure 1. A and B: Cerebral MRI (axial) showing left temporal abscess in formation with minimal hemorrhagic degeneration. C: CT-scan (sagittal) of the neck showing an organized retropharyngeal collection from C2 to C6 (36 x 40 x 56 mm). D and E: Cerebral CT-scan (axial) showing osteolysis of the left maxillary alveolar ridge, resorption of teeth #11 to #15 along with moth-eaten appearance of the hard palate and fistula between the right maxillary sinus and oral cavity. Bilateral moth-eaten appearance of the greater sphenoidal wings, bilateral involvement of the foramen rotundum and vidian nerves as well as infiltration of pterygopalatine fat and left masticatory space were also noted. F: Bone erosion and destruction of the left temporal bone, clivus, bilateral petrous apices, occipital condyles, and bilateral pterygoid processes.

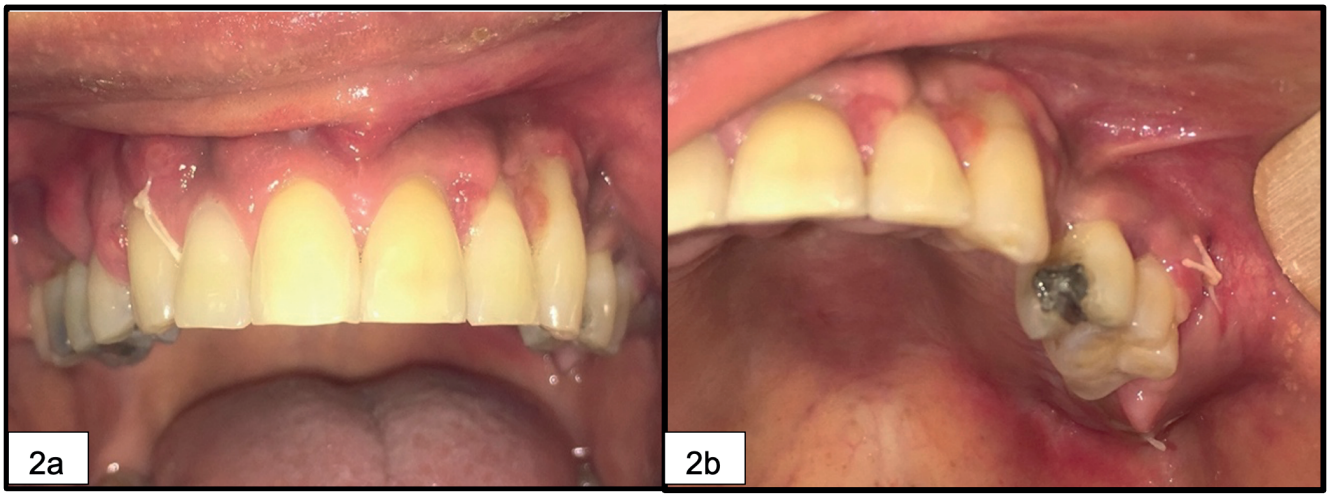

Figure 2. Intra-oral necrosis: discrete necrotic changes can be seen on the gingiva, along with a softened alveolar bone and teeth mobility which increased suspicion of acute osteonecrosis. Patient's written consent was obtained prior to taking these pictures.

nerve, and decreased left eye abduction. Repeat CT scan revealed infiltration of the masticatory, intra-orbital, and retropharyngeal spaces. Oral examination showed osteolysis of tooth #27 and a whitish aspect of the soft palate. Antibiotics were escalated to IV ceftriaxone, vancomycin, and metronidazole. Biopsy and culture of new necrotic lesions on left gum revealed broad filamentous fungi with hyphae, suspicious for mucormycosis. IV liposomal amphotericin B (8mg/kg/day) was initiated, followed by tooth extraction and debridement.

A cerebral MRI showed left temporal lobe abscess (Figure 1). Left craniotomy for abscess drainage was performed and endoscopic sinus surgery (ESS) with pterygomaxillary fossa debridement. IV posaconazole (300mg) and meropenem were added. Progression of gingival infection (Figure 2) required combined open and endoscopic infrastructural maxillectomies. Cultures from maxillectomy confirmed *A. elegans*, as well as coagulase negative *staphylococcus*, *enterococcus*, and *lactobacillus*. There may have been contamination of the specimen considering the surgical approach. Terbinafine and anidulafungin were added. The patient developed chronic kidney failure due to nephrotoxic medications.

Further complications included clival extension. After two additional debridement procedures, a prolonged treatment with amphotericin B, terbinafine, isavuconazole, hyperbaric oxygen, and IFN-gamma injections, the patient improved. He was discharged with a 2-year antifungal regimen, with follow-up showing no residual disease.

Second case

A 61-year-old female, who had undergone ESS for nasal polyposis two weeks prior, presented with right orbital pain and visual disturbances. Initial imaging suggested orbital cellulitis. Despite IV antibiotics, her condition worsened. ESS revealed necrosis along the ethmoid roof, right peri-orbital fat and orbital muscles after removing the lamina papyracea. Surgical debridement and right orbital exenteration were performed, and IV liposomal amphotericin B was initiated. Gene sequencing later confirmed *A. elegans*. Treatment was switched to posaconazole due to hypokalemia. Antifungal treatment was discontinued one-month post-exenteration after clinical and radiological improvement. Recurrent symptoms prompted the reinstatement of amphotericin B and posaconazole. CT showed moth-eaten frontal bone and anterior skull base. After subsequent surgical debridement, the patient quickly recovered. She was discharged on lifelong posaconazole.

Both patients underwent comprehensive immunocompetency evaluations, including a primary immunodeficiency genetic panel, with all results negative.

Discussion

This case series highlights critical learning points from two cases of *A. elegans* ROCM in immunocompetent individuals, emphasizing the importance of early recognition and aggressive treatment, even in those without classic predisposing factors. Table 1 summarizes the different prior cases and treatment regimen described in literature.

In Case 1, a healthy 42-year-old male suffered invasive necrotizing *A. elegans* ROCM. The absence of typical risk factors led to low clinical suspicion and diagnostic delay. Initial symptoms resembled cellulitis and were treated with antibiotics until rapid deterioration and cranial nerve involvement raised suspicion for invasive fungal infection. A dental procedure may have

Table 2. Clinical pearls.

Diagnosis and clinical suspicion
• Mucormycosis primarily affects immunocompromised individuals, but ROCM can also occur in healthy patients. • Mucosal trauma, including dental or sinonasal procedures, as well as drug use, can serve as potential entry points for mucormycosis infections. • It is important to have higher clinical suspicion for invasive fungal infection when medical and antibiotic treatments for orbital cellulitis or sinusitis fail. • Early neurological symptoms, such as cranial nerve deficits, should heighten clinical suspicion for invasive fungal infections. • Some species of mucormycosis (such as Apophysomyces sp.) may be difficult to cultivate or to visualize on biopsy. Treatment should be initiated before histopathological confirmation of the infection. • Diagnostic delays can lead to more extensive infection, requiring multiple surgical interventions and increasing morbidity.
Management
• Management principles are similar for immunocompetent and immunocompromised patients. • Initiate amphotericin B early upon any suspicion of ROCM. • Surgical debridement may need to be repeated multiple times to control infection. • Long-term antifungal therapy is crucial to reduce the risk of recurrence or disease progression. • A multimodal treatment approach is essential, incorporating aggressive antifungal therapy, surgical debridement, and supportive measures like hyperbaric oxygen therapy and immune modulation (e.g., IFN-gamma injections). Infectious disease specialists should be involved early in the management process.

served as an entry point. Notably, the whitish aspect of the hard palate deviates from the typical black coloration associated with mucormycosis. This whitish devascularized aspect may be attributed to the patient's cocaine use, potentially facilitating pathogen entry. In Case 2, a 61-year-old immunocompetent female developed *A. elegans* ROCM following ESS. Despite initial positive response to IV antifungals and surgical debridement, she experienced early recurrence after antifungal therapy was interrupted. This case highlights the necessity of prolonged or lifelong antifungal therapy and vigilant follow-up to achieve sustained disease control and ensure survival. Key clinical pearls are highlighted in Table 2.

In both cases, necrosis—likely due to cocaine-induced mucosal damage and surgical trauma—may have facilitated *A. elegans* inoculation. Given the rarity of invasive fungal infections in immunocompetent individuals, comprehensive immunological profiling was conducted, including serum glucose monitoring, immunoglobulin levels, and lymphocyte immunotyping, all of which were normal. This suggests that either these patients harbor an immune deficiency not detectable with current methods or, as we propose, *A. elegans* possesses intrinsic pathogenicity capable of causing severe infection even in immunocompetent hosts. Another unknown co-factor may also be implicated.

Conclusion

Although classically associated with immunocompromised individuals, clinicians should maintain vigilance for atypical Mucorales, like *A. elegans*, ROCM in immunocompetent patients, particularly when IV antibiotics fail, cranial nerve deficits emerge, and there is a history of mucosal trauma. Early detection and prompt aggressive surgical and antifungal treatments are critical to limiting disease progression and reduce the need for highly morbid surgical debridement, particularly in the head and neck region. Patients likely require prolonged or lifelong maintenance antifungal therapy to sustained disease control.

List of abbreviations

A. elegans: *Apophysomyces elegans*; ESS: endoscopic sinus surgery; ROCM: rhino-orbitocerebral mucormycosis.

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Authorship contribution

Supervision: MD, FL; Conception and design: MD, FL, BV, AER; Materials: MD, FL; Data collection: BV, GD, SD; Analysis: BV, AER, GD, CH, LME; Literature review: BV, GD, LME; Writing of manuscript: BV, GD, AER; Critical review: MD, FL, SD, CH, LME.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent for publication of their clinical details and clinical images was obtained from the patients. A copy of the consent form is available for review by the Editor of this journal.

Availability of data and material

Not applicable.

Conflict of interest

The authors declare that they have no competing interests.

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