JMID/ 2017; 7 (4):207-212
Journal of Microbiology and Infectious Diseases doi: 10.5799/jmid.369276

CASE REPORT

Apophysomyces elegans Caused Rhino-Orbito Mucormycosis: An Emerging Infection in Immunocompetent Individuals

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ABSTRACT

Mucormycosis is a rare necrotizing angioinvasive infection caused by fungi of the class Zygomycetes (order Mucorales). It predominantly occurs in immunocompromised/ predisposed individuals. Recent surge in its incidence in healthy individuals has emphasized the need to reconsider our age-old presumption of 'mucormycosis as a classical opportunistic infection'. *Apophysomyces elegans* has emerged as a pathogen causing invasive Rhino-Orbitocerebral Mucormycosis (ROCM), mostly in immunocompetent individuals. Mostly resistant to commonly used azoles and echinocandins, management of *A. elegans* associated ROCM solely depends on radical debridement and Amphotericin B. Recent reports of Amphotericin B resistant *A. elegans* strains is disturbing. Till date only 12 cases of ROCM in immunocompetent/ otherwise healthy individuals attributable to *A. elegans* has been reported.

Our main objective is to delineate the clinical characteristics and treatment outcome of immunocompentent/ otherwise healthy individuals suffering from *A. elegans* caused ROCM. We also report four new cases of A. elagans caused ROCM. *J Microbiol Infect Dis 2017; 7(4):207-212*

Keywords: Mucormycosis, *Apophysomyces elegans*, Rhino-Orbitocerebral Mucormycosis, Immunocompetent

INTRODUCTION

Mucormycosis is a rare necrotizing angioinvasive infection caused by fungi of the class Zygomycetes and order Mucorales. Generally considered an opportunistic infection, it occurs predominantly in immunocompromised and predisposed individual eg. Diabetes, leukemia, receiving antineoplastic agents or prolong steroid therapy and solid organ recipients. The genera most commonly reported to cause invasive infection are Absidia, Mucor, Rhizomucor and Rhizopus. Still rare, the incidence of mucormycosis in immuno-competent individuals has been reported to be increasing in recent year emphasizing the need to reconsider our age-old presumption of mucormycosis as a classical opportunistic infection [1].

Apophysomyces elegans, a ubiquitous saprophytic soil fungus of the class Zygomycetes (order Mucorales) has recently emerged as a pathogen causing invasive Rhino-Orbitocerebral Mucormycosis (ROCM), mostly in immunocompetent individuals [2]. Infection usually begins in the nose, as inhalation is the natural route of entry, from where it spreads into the paranasal sinuses and the orbit, eventually reaching intracranial through blood vessels or by direct spread, and possibly by perineural spread [3,4]. Traumatic implantation is also considered a common cause of infection; specifically with the *A. elegans* [5]. Till date 12 cases of ROCM in immunocompetent/ otherwise healthy individuals attributable to *Apophysomyces elegans* has been reported (Table I).

The main objective of this review is to delineate the clinical characteristics and treatment outcome of *A. elegans* caused ROCM in immunocompentent/ otherwise healthy individuals for better understanding this rare condition. Our secondary objective was to update the limited current literature by adding 4 new cases.

STUDY DESIGN

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Received: 03 March 2017 Accepted: 28 October 2017

Retrospective case review conducted at a tertiary referral center.

Our retrospective review of medical records for ten years (2005-2015) revealed 19 cases of ROCM in immunocompetent/otherwise healthy individuals. ROCM was defined as infection, which originates in the nose & paranasal sinuses and involve the orbit, palate, face with or without intracranial spread. Out of these, 4 cases were found associated with *A. elegans*. The diagnosis was accepted only after confirming by histologic examination or a positive tissue culture.

Immunocompetence/ otherwise-healthy status of the patients were assumed following a detailed medical history and examination, routine blood tests, Hb1AC, VDRL, ELISA for HIV and Electrocardiogram reveal no abnormalities predisposing the individual to invasive fungal infections.

A review of the literature pertaining to 'sinonasal mucormycosis', particularly *A. elegans* caused ROCM in otherwise healthy individuals were done.

CASE REPORTS

We report four cases of *A. elegans* caused sinoorbital mucormycosis in immunocompetent/ otherwise healthy individual. All were male with an average age of 41 years (range 24 and 62 years). None of these patients had history of trauma or any invasive procedure. The presenting symptoms were unilateral hemifacial pain, fever, rapidly progressive vision loss, headache, proptosis, diplopia, nasal obstruction and nasal discharge. One of our patients had hemi facial numbness. The symptom-duration varied from 10 days to 2 months. All patients were treated with antibiotics before referral to our hospital.

Diagnostic nasal endoscopy demonstrated a variously inflamed nasal mucosa with necrotic debris. Two of the patients had purulent exudates. Ophthalmologic examination revealed orbital cellulitis along with unilateral orbital apex syndrome in three of our patients. Fundoscopy of these patients showed a pale retina with attenuated central retinal artery. Contrast enhanced CT scan demonstrated heterogeneous density lesion in the frontal, maxillary, ethmoid and sphenoid sinuses. Erosion of bony medial-orbital wall with thickening of extra ocular muscles was seen in three patients. One patient showed isolated sphenoid sinus opacity with lateral wall erosion and involvement of adjacent middle cranial fossa. Intraorbital mass or collection was not found in any of the patients. The clinical, radiological, and therapeutic parameters of our patients are summarized in Table II. All patients underwent multiple radical endoscopic sinonasal debridements which included endoscopic medial-maxillectomy in two of them. Three of our patients underwent orbital exenteration (OE), of which two were performed during the first sinonasal debridement. One patient subsequently underwent OE with his third endoscopic debridement. Debridement was repeated until intraoperative and histopathological study showed no necrosis or residual infection. They received injectable amphotericin B up to an average dose of 2.2 gm. One patient succumbed on 11th postoperative day due to cerebrovascular accident. Remaining three patients were discharged and maintained on oral itraconazole 200 mg once daily for an average duration of 55 days (range 30 to 90 days). In follow-up (a period ranging from 2 to 24 months) all three were asymptomatic and no residual disease seen in CT evaluation.

Histopathological evaluation showed sparsely distributed broad, thin-walled aseptate hyphae. Multiple giant cells with fungal hyphae and angioinvasion with thrombosis was seen in all our patients. Fungal culture showed growth of sparsely septate hyphae. Unbranched sporangiophores bearing characteristic funnel-shaped apophysis were noted.

DISCUSSION

Mucormycosis is a rapidly fatal angioinvasive infection caused by fungi of the order mucorales and class mucormycetes. Despite of recent advances in its diagnosis and treatment, mucormycosis still has a high mortality rates.

Clinically, the most common form of mucormycosis, comprising almost half of all reported cases, is rhino-orbito-cerebral disease. Other reported presentations are cutaneous (10–16%), pulmonary (10%), disseminated (6-12%) and gastrointestinal (2-11%) [13].

Interestingly, geographic distribution of mucormycosis in immunocompentent or otherwise healthy individuals shows maximum cases coming from India (45%) and USA (20%). And over 60% of these have been reported in last 10 year possibly indicating a definite rising trend [1].

The fact that India has the highest number of reported cases might probably be related to its warm humid climate favoring fungal growth. Other influencing factors may be its low socio-economic status, poor hygienic conditions, and limited health awareness. This peculiar uneven geographic distribution probably indicates a predisposed genetic pool.

Table 1. Details of previously published twelve otherwise healthy individuals diagnosed with *A. elegans* ROCM.

Ref. no.	Age/Sex	Presenting symptoms	Physical findings	Radiological findings	Treatment and outcome
4	31/M	Red painful eye. proptosis and progressive visual loss, headache	Orbital apex syndrome, congested nasal mucosa	Proptosis, orbital cellulitis, temporal meningitis, cavernous sinus thrombosis with infratemporal, pterygopalatine and parapharyngeal fossa involvement	Sys steroid, SxD and Amp B Died
7	19/M	Pain upper palate and decreased vision after RTA	Dark necrotic tissue on palate, proptosis	Opacification of Lf maxillary sinus and periorbital swelling	OE, palatectomy, B/L maxillectomy, SxD. Amp B (3.5 g) Cured
8	54/M	Fever, nasal congestion, frontal headache, Lf cheek swelling	Congested inf. turbinates, pus discharging sinus tracts in upper alveolar ridge	Extensive mucoperiosteal thickening of both maxillary sinuses with bony resorption.	Bilateral Caldwell-Luc procedures, Amp B (1 mg/kg/day) Cured
9	59/M	Retro-orbital pain and fever after water jet injury.	Marked periorbital edema, erythema, and proptosis	Proptosis & chemosis; mucosal thickening in PNS; thicken extraocular ms, involvng infratemporal fossa	OE, SxD, Liposomal Amp B (14.7 g) Cured
10	20/F	Painful cheek swelling, rhinitis, headache, fever	Rt proptosis, erythema, and cheek swelling	Mass extending across nasal septum, displacing right orbital tissue with retro-orbital extension	OE, SxD . Amp B (1.5 g) Cured
11	(5 pts) 45/M, 26/F, 16/F, 55/M, 26/M	Unilateral facial pain, proptosis, nasal discharge, nasal obstruction, and vision loss	Dilated unreactive pupil, orbital apex syndrome with features of orbital cellulites and proptosis. Central retinal artery occlusion.	Marked proptosis, chemosis, thickening of the extra ocular muscles, heterogeneous density lesion involving all PNS, parapharyngeal abscess in one pt.	OE, SxD. Amp B (avg.- 1.8 g), Drainage of Parapharyngeal abscess in 1 pt. 1 pt. died due to CVA, four recovered.
12	24/M	Head trauma with Le Fort II complex fracture post RTA	Periorbital ecchymosis, proptosis. Skin necrosis, opacified cornea	Opacification of all PNS	OE with multiple SxD, HBO2, AMB (27.5 g) Cured
13	25/M	Rt cheek painless, hard swelling. Numbness along distribution of CN-V.	Rt cheek swelling	Soft-tissue intensity lesion Rt premaxilla extending into pterygopalatine & middle cranial fossa. Extension along the CN-V up to its pre-pontine segment.	SxD. Amp B Reduced.

SxD =surgical debridement; OE=orbital exenteration; Amp B=Amphoterecin B; RTA=Road traffic accident; HBO_2=Hyperbaric oxygen

Table 2. Details of four patients with *A. elegans* caused Rhino-Orbito Mucormycosis.

Case no.	Age/ sex	Presenting symptoms	Physical findings	Radiological findings	Treatment & outcome
1	32/M	Decrease vision, orbital pain, hemifacial numbness, headache, fever	periorbital edema, erythema, proptosis and chemosis	Isolated sphenoid sinus opacity with lateral wall erosion, Middle cranial fossa involvement	Sphenoidotomy, sx-debridement, lipo-Amp B. Died.
2	62/M	Headache, nose block, hemifacial pain, progressive loss of vision, proptosis	Congested nasal mucosa, necrotic debris, purulent nasal discharge, proptosis	Heterogeneous density lesion involving ethmoid sinus, orbital cellulitis with marked proptosis.	ant & post ethmoidectomy, sphenoidectomy, OE, Amp-B Cured
3	25/M	Nose block, discharge, proptosis, headache, red painful eye, vision loss. Diplopia, fever	Ophthalmoplegia, proptosis, Congested inf. turbinates	Opacified Ethmoid sinus, orbital cellulitis with anterior skull base erosion	Extensive SxD, MM, OE, Amp-B. Cured
4	47/M	Nasal obstruction and discharge, facial pain, vision loss	Ophthalmoplegia, purulent nasal discharge	Opacified Ethmoid and Maxillary sinus with orbital cellulitis	SxD, MM, OE, Amp- B, Cured

M=Male, Amp-B=Amphotericin B, SxD=Surgical Debridement, OE=Orbital Exenteration, MM=Medial Maxillectomy

Apophysomyces elegans, a saprophytic soil fungus of the class Zygomycetes and the order Mucorales, is an emerging agent causing mucormycosis especially in immunocompetent individuals. Numerous series of cutaneous / subcutaneous and renal mucormycosis caused by A elegan has been published worldwide.

Earlier to our report only 12 cases of *A. elegans* related Rhino-orbitocerebral mucormucosis in otherwise healthy individuals has been reported. Two similar cases of ROCM reported earlier as otherwise healthy individuals had predisposing systemic conditions and were omitted from our review [14,15].

Commonly observed presenting signs and symptoms of *A. elegans* caused ROCM which include fever, headache, orbital pain, proptosis, orbital cellulitis, ophthalmoplegia, progressive loss of vision, sinusitis, nasal congestion, mucosal ulceration and necrosis, and central retinal artery occlusion, are similar to the classical features of ROCM caused by other mucorales [4-16]. Skin or mucosal necrosis, and necrotic echar in nasal cavity, though reported in *A. elegans* caused ROCM in diabetic patients, are unlikely in immunocompetent / otherwise healthy individuals [10]. Radiographic findings including proptosis, sinus thickening or opacification, intraorbital inflammation and presence of bony wall erosion are also similar to other forms of ROCM [1-3,10-16].

Histopathological finding of large sparsely septate or nonseptate, right-angle branching hyphae with features of angioinvasion is suggestive of *A. elegans* as the causing agent. It is desirable to isolate of the organism by culture to identify the specific causing mucorale [17].

Regarding pathogenesis of ROCM in otherwise healthy individuals in absence of a definite history of trauma or surgery, it is believed that a chronic insult of a localized body part (e.g. chronic sinusitis) may result to a localized immunocompromission, thus fostering the growth and invasion by fungus. Any history of injury/ surgery or local predisposing factor e.g. Sinusitis, were absent in our patients hinting at acquisition of infection through spore inhalation.

Kimura et al observed the strains of *A. elegans* in their study were mostly resistant to commonly used azoles and echinocandins. They concluded that the management of *A. elegans* associated ROCM solely depends on radical surgical debridement, administration of Amphotericin B and correction of the underlying predisposing comorbidities [16]. Chakrabarti et al reported a trend of increasing Amphoterecin B resistance in isolated strains of *A. elegans* in vitro with MIC_{50} and MIC_{90} of 2 and 4 μg/ml respectively, much higher than earlier studies. Noting a better prognosis for patients with Amphotericin B MIC <1 μg/ml, they demonstrated a correlation between in vitro strain susceptibility and in vivo outcome. Accordingly they suggested Posaconazole, Itraconazole and Isavuconazole

as good alternative drugs [18]. Biswas et al reported a strain of *A. elegans* completely resistant to Amphotericin B (MIC 16 μg/ml), Voriconazole (MIC 32 μg/ml) and Fluconazole (MIC 64 μg/ml) [14]. These reports warn us of a possible surge in the incidence and a poorer prognosis for A.elegans associated ROCM in coming days.

All forms of ROCM, irrespective of the associated mucorale, have similar presenting complains, clinical findings and radiological features. Recent emergence of Amphotericin B resistant *A. elegans* strains has made identification of the causing mucorale and determining its susceptibility to antifungal drugs indispensable in managing ROCM.

From a reported mortality of 88% in 1961 to the present range of 15 to 34%, the prognosis of ROCM has improved markedly [8]. As ROCM caused by *A. elegans* is rare, the rate of mortality is not known. However, among the 17 reported cases, only 3 patients (17%) died indicating a better prognosis compared to other forms of ROCM.

Conclusion

Although classically defined as an opportunistic infection affecting immunosuppressed or diabetic patients, mucormycosis particularly *A. elegans*-associated ROCM, can affect immunocompetent hosts as well. So its possibility should be considered while evaluating patients presenting with severe acute headache, sinusitis, or orbital cellulites irrespective of thier immune status. One should have a high level of suspicion to identification this condition promptly, for with early intervention this potentially fatal condition has a favorable prognosis.

ACKNOWLEDGMENTS

Conflict of interest: The authors declare no personal or financial conflict of interest.

Funding disclosure: Non to declare

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