Perineural spread of rhino-orbitocerebral mucormycosis caused by *Apophysomyces elegans*

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Abstract

Rhino-orbitocerebral mucormycosis (ROCM) is a fungal infection commonly affecting individuals with diabetes and those in immunocompromised states. However, infections caused by *Apophysomyces elegans* can involve immunocompetent individuals. The invasion pattern of cerebral mucormycosis is somewhat predictable and may occur by direct invasion or hematogenous spread. Perineural spread of the disease is unusual. Here, we report the first case of perineural extension of ROCM caused by *A. elegans* along the trigeminal nerve in a 25-year-old immunocompetent, nondiabetic individual.

Key Words

Magnetic resonance imaging, perineural spread, rhino-orbitocerebral mucormycosis, sinusitis, trigeminal nerve

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Introduction

Mucormycosis is a rare opportunistic infection of the sinuses, nasal passages, and brain caused by saprophytic fungi. Rhino-orbitocerebral mucormycosis (ROCM) commonly affects individuals with diabetes and those in immunocompromised states. However, infections caused by *Apophysomyces elegans* can involve immunocompetent individuals.[1] The invasion pattern of cerebral mucormycosis is somewhat predictable and may occur by direct invasion or hematogenous spread. Perineural spread of disease is unusual.[2] We report a rare case of perineural spread of ROCM along trigeminal nerve in an immunocompetent, nondiabetic individual, caused by *A. elegans*. Only seven cases of ROCM by *A. elegans* have been reported in literature till now.[1] This is the first case report of perineural spread by this organism.

Case Report

A 25-year-old male presented with complaints of gradually increasing painless hard swelling in the right maxillary region and paresthesia on the right side of face along distribution of trigeminal nerve over a period of 1 month. Patient had undergone functional endoscopic sinus surgery 2 years ago. On physical examination, there was no ulceration or induration of overlying skin. Laboratory investigations including hemogram and blood glucose levels were normal, and human immunodeficiency virus (HIV) serology was negative.

Magnetic resonance imaging (MRI) revealed soft-tissue intensity lesion in the right premaxillary region, which was isointense on T1-weighted imaging and hypointense on T2-weighted imaging. Contiguous extension of lesion was noted along infraorbital nerve with widened infraorbital foramen, along the floor of orbit [Figure 1], via the inferior orbital fissure into the pterygo-palatine fossa, through the foramen rotundum into the middle cranial fossa causing widening of foramen rotundum. In the middle cranial fossa, the lesion was limited to extradural space adjacent to cavernous sinus and Meckel's cave, with extension along the trigeminal nerve up to prepontine segment of trigeminal nerve [Figure 2]. Osseous destruction of the anterior wall of right maxillary sinus was seen with minimal mucosal thickening within. On contrast administration, the lesion showed homogenous enhancement [Figure 3].

On imaging, among the differentials of fungal infection, lymphoma, and malignant lesions, fungal infection was favored. Biopsy was performed from premaxillary swelling, and fungal smear, cytology, and fungal culture were done. Histopathologic examination revealed granulomatous inflammation with giant cells. Giant cells showed intracytoplasmic nonseptate fungal hyphae which are highlighted by Grocott's methenamine silver (GMS) stain [Figure 4]. Fungal culture on water agar plate revealed sporangiophores which were long, unbranched, grayish brown, and with funnel-shaped apophyses. This morphology was indicative of *A. elegans*.

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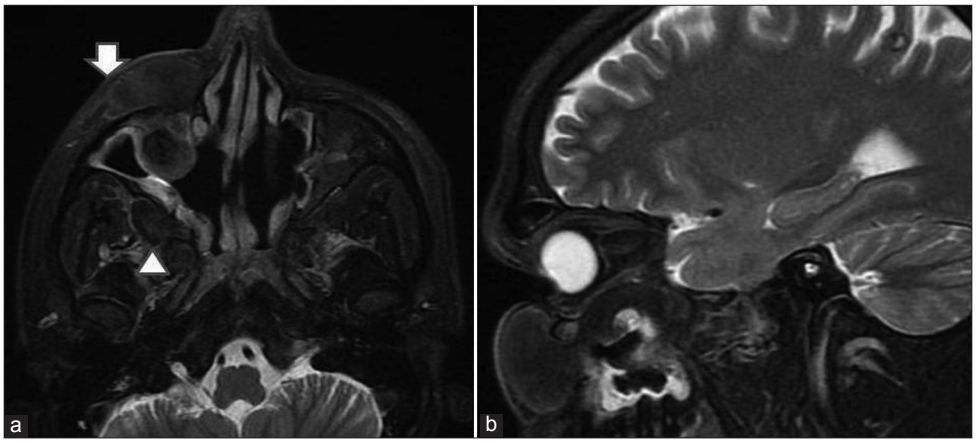

Figure 1: Fat-suppressed T2-weighted axial (a) and sagittal (b) images show hypointense lesion in right premaxillary region, extending into infraorbital foramen (short arrow), floor of orbit, and into pterygopalatine fossa (arrowhead)

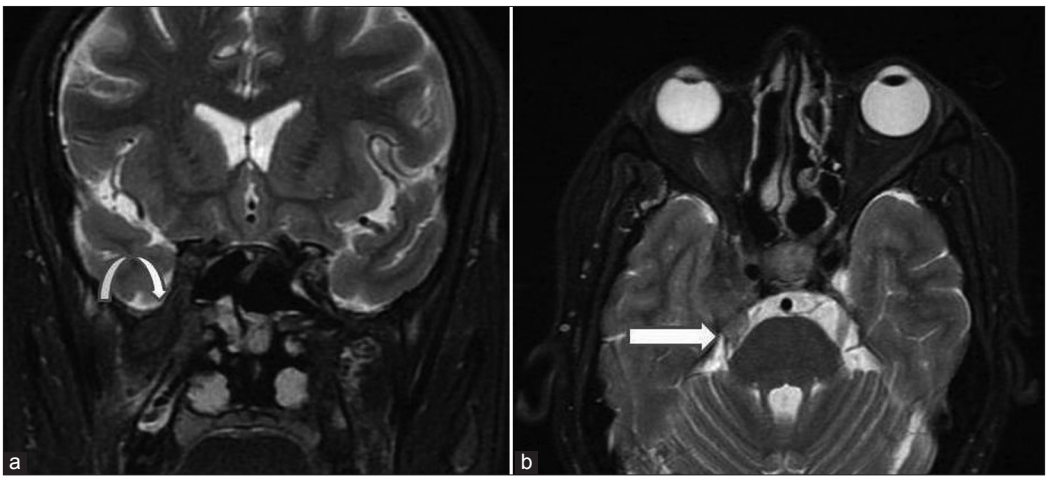

Figure 2: Fat-suppressed T2-weighted coronal (a) and axial (b) images show hypointense lesion extending from pterygopalatine fossa into middle cranial fossa through widened foramen rotundum (curved arrow). In middle cranial fossa, the lesion is seen in Meckel's cave and extends into prepontine segment of the right trigeminal nerve (long arrow)

Surgical debridement of the maxillary component was performed and systemic amphotericin B was administered. Follow-up MRI after 2 months revealed significant reduction of the lesion [Figure 5].

Discussion

ROCM caused by more common zygomycetes (e.g. *Mucor*) is known to cause rapidly fatal infections in immunocompromised patients and diabetics. *A. elegans* is an emerging zygomycete that has been reported to cause invasive cutaneous and rhino-orbitocerebral infections in immunocompetent individuals, unlike the other members of Mucorales.[3]

Zygomycosis is caused by sparsely septate filamentous, saprophytic fungi belonging to the class Zygomycetes *and the order* Mucorales. The species of the genera *Absidia, Rhizopus*, *Rhizomucor, Mucor* and *Apophysomyces* have been reported to cause invasive infections. However, species of the genera *Rhizopus, Absidia*, and *Rhizomucor* are the more commonly reported pathogens.[4] *A. elegans* is a relatively newer agent in this order, being first isolated from the soil in India in 1979 by Misra *et al*.[5]

The main route of infection is inhalatory. However, there may be traumatic transmission in polytraumatized patients, mainly with *A. elegans*.[6]

Clinical spectrum ranges from noninvasive sinusitis in immunocompetent patients to fulminant invasive forms in immunocompromised patients In its invasive form, fungal infection typically spreads by osseous erosion or vascular invasion, with perineural extension being an unusual mode of spread.[7]

After inhalation into the nasal cavity and paranasal sinuses, the fungi infect the host by causing necrotizing vasculitis of the nose and sinuses, and rapidly extend into the orbits, deep face, meninges, and cranial cavity.[8] This results from perivascular, perineural, or direct soft-tissue invasion by the fungi, causing suppurative arteritis, vascular thrombosis, and infarction of the surrounding tissues.

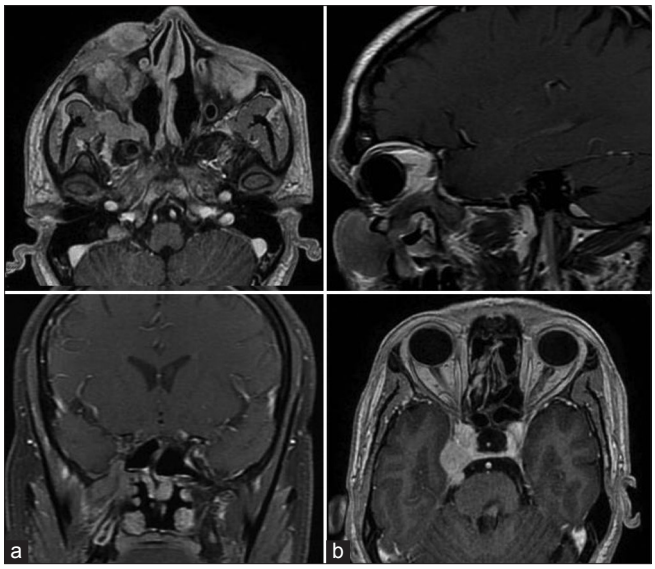

Figure 3: Fat-suppressed contrast-enhanced T1-weighted axial (a), sagittal (b), coronal (c), and axial (d) images show homogenous enhancement of the lesion

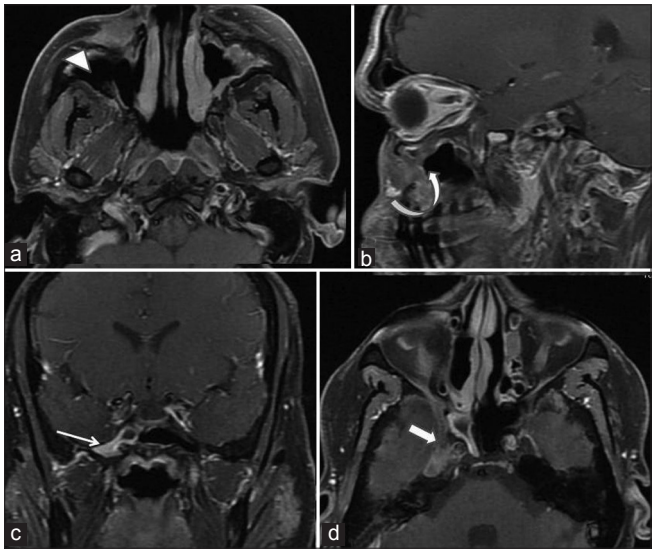

Figure 5: Follow-up images after 2 months. Fat-suppressed contrast-enhanced T1-weighted axial (a) sagittal (b) coronal (c) and axial (d) images show significant reduction of lesion in right premaxillary region (arrowhead), floor of orbit (curved arrow), foramen rotundum (arrow), and Meckel's cave (block arrow)

In the appropriate clinical context, the imaging findings of rhinocerebral mucormycosis on computed tomography (CT) and MRI are diagnostic. These include soft-tissue opacification of sinuses with hyperdense material, nodular mucosal thickening, and an absence of fluid levels in the maxillary, ethmoid, frontal, and sphenoid sinuses, in decreasing order of incidence.[9]

Sinus contents have a variety of MR signal characteristics, including T2 hyperintensity or marked hypointensity on all sequences, possibly secondary to the presence of iron and manganese in the fungal elements.[10] Soft-tissue infiltration of the deep face and obliteration of the normal fat planes in the

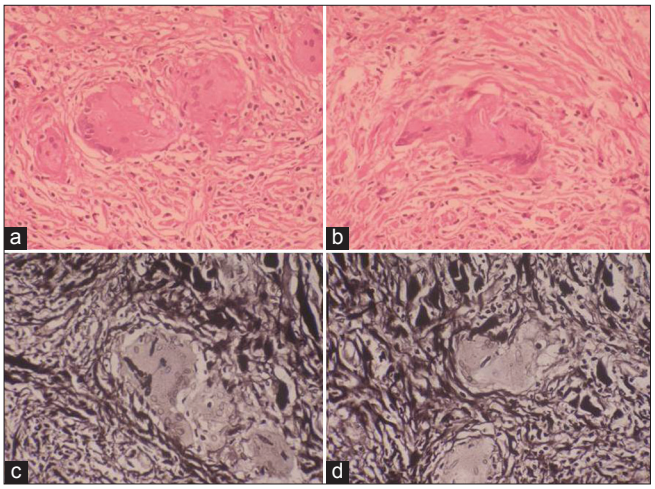

Figure 4: Histopathologic examination (a, b) reveal granulomatous inflammation with giant cells. (c, d) Giant cells show intracytoplasmic nonseptate fungal hyphae which are highlighted by GMS stain

infratemporal fossa, pterygopalatine fossa, pterygomaxillary fissure, and periantral fat are often present.[9,10] Spread can occur from orbit to cavernous sinus and perineurally along the trigeminal nerve up to pons and along foramen rotundum into the maxillary division of trigeminal nerve.[11]

In our case, the mucosal thickening in sinuses was minimal. However, there was marked T2-hypointense signal and perineural extension of lesion along the maxillary division of trigeminal nerve and prepontine cisternal portion of the trigeminal nerve, which suggested fungal infection.

Perineural spread of disease is commonly described in head and neck malignant neoplasms, particularly adenoid cystic carcinoma, squamous cell carcinoma, lymphoma, and rhabdomyosarcoma. The trigeminal nerve and its branches are common sites of perineural spread of malignancy.[12]

On MRI, direct findings suggestive of perineural spread are enlargement, irregularity, and excessive enhancement of a cranial nerve or its branch (either within the cisternal portion or within a canal or foramen), loss of the normal fat pad adjacent to a foramen, or widening/excessive enhancement within the pterygopalatine fossa, Meckel's cave, or the cavernous sinus.[12] In our patient, there was thickened and enhancing maxillary division of the trigeminal nerve, enlargement of foramen rotundum, and thickened and enhancing cavernous and cisternal portions of the trigeminal nerve on MRI, further confirming perineural involvement.

In the largest series describing invasive fungal infection in immunocompetent patients, 25 patients were assessed; however, none of these had perineural extension.[13]

Prompt and aggressive surgical debridement and therapy with an amphotericin B formulation are necessary for successful treatment. Posaconazole therapy may be an effective alternative to the use of amphotericin B in these patients. Survival in ROCM caused *A. elegans* is favorable.[1]

Our case is unique because of the rare occurrence of ROCM by *A. elegans* in an immunocompetent individual and its perineural spread along the trigeminal nerve. It is important to consider fungal infection even in an immunocompetent individual so as to institute early and appropriate treatment.

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