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Case Report

Imaging features of perineural and perivascular spread in rapidly progressive rhino-orbital-cerebral mucormycosis: A case report and brief review of the literature

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ABSTRACT

Background: Rhinocerebral mucormycosis (ROCM) is an opportunistic fungal infection originating from the paranasal sinuses with extension to the brain. A delayed diagnosis can rapidly result in a poor prognosis. ROCM commonly affects patients with diabetes or immunocompromised states with a variable progression.

Case Description: We report the case of a 59-year-old patient with an untreated diabetes who developed a ROCM with rapidly progressive neurological symptoms. From the onset of sinus pain, nasal congestion, he rapidly developed facial swelling and masticatory dysfunction. The patient underwent sinus surgery which allowed Rhizopus oryzae to be isolated. Accordingly, a systemic therapy by intensive *intravenous amphotericin B* was started. Nevertheless, the infection rapidly resulted in bilateral cavernous sinuses thrombosis and occlusion of the left internal carotid artery providing the subsequent patient death.

Conclusion: Mucormycosis is a life-threatening fungal infection in diabetic and/or immunosuppressed patients. Our case demonstrates the three main mechanisms for infection spreading that are direct, perineural, and perivascular diffusion. Clear identification of the main risk factors, proper assessment of clinical features, and radiological findings may improve the chance for an early diagnosis and patient survival.

Keywords: Mucormycosis, Perineural spread, Perivascular spread, Rhinocerebral mucormycosis, Zygomycosis

INTRODUCTION

The term "Zygomycosis" describes a wide spectrum of rare infections caused by a group of molds belonging to the class of Zygomycetes, including *Entomophthorales* and *Mucorales*,[25] responsible for Entomophthoromycosis and Mucormycosis (MM), respectively.

The former is a rare mucocutaneous infection restricted to rhinosinusal district often occurring in immunocompetent hosts from developing countries.[4] The latter represents a group of life-threatening angioinvasive infections, more commonly affecting immunocompromised patients with diabetes mellitus (DM) being the main risk factor.[20]

MM typically affects the sinuses or the lungs by inhaling fungal spores from the air, and the skin after the fungus enters through a cutaneous break such as cut or scrape.[7]

Therefore, clinical spectrum of MM is wide including in decreasing order the following:[3,18]

1. Rhino-orbito-cerebral syndrome
2. Pulmonary MM
3. Cutaneous MM
4. Disseminated forms (≥2 noncontiguous sites)
5. Gastrointestinal presentation.

Some authors reported other forms of disease, including isolated cases of tracheal,[24] renal,[15] and temporal bone involvement.[8,16]

Here, we report the case of a 59-year-old patient with an untreated diabetes who developed a rhinocerebral mucormycosis (ROCM) with rapidly progressive neurological symptoms.

CASE REPORT

A 59-year-old man presented with a recent onset of sinus pain, nasal congestion, bilateral periorbital edema, facial swelling, and headache. He was conscious and afebrile.

The patient underwent computed tomography (CT) scan examination showing a widespread sphenoid sinuses effusion with less evident involvement of maxillary and ethmoid sinuses [Figure 1].

Laboratory evaluations revealed decompensated Type 2 DM. Insulin therapy and a broad-spectrum of antibiotic treatment were promptly started. A paranasal sinus magnetic resonance imaging (MRI), performed 3 days after starting antibiotic treatment, showed a low T2W signal effusion in the left maxillary sinus, at the level of ethmoidal air cells and sphenoid sinus, predominantly on the right. It also showed a high T2W signal effusion in the right maxillary sinus, bilateral periorbital soft-tissue swelling, and minimal posterior subluxation of the left crystalline lens and right temporalis muscle swelling. No acute cerebral involvement was observed [Figure 2].

Due to the rapid and marked increase of facial swelling and masticatory dysfunction, 4 days following the initial TC scan, the patient underwent functional endoscopic sinus surgery.

Briefly, following mucosa decongestion by adrenaline instilling, the meatus medium was entered. Uncibullectomy with a large bilateral medium meatotomy was performed, allowing the drainage of the maxillary sinus. Further, bilateral anterior and posterior ethmoidectomy and release of the frontal recess were achieved. Intranasal sphenoidectomy, following the amputation of the tails of sphenoidal conchae and drainage of the sinuses' secretion, was performed.

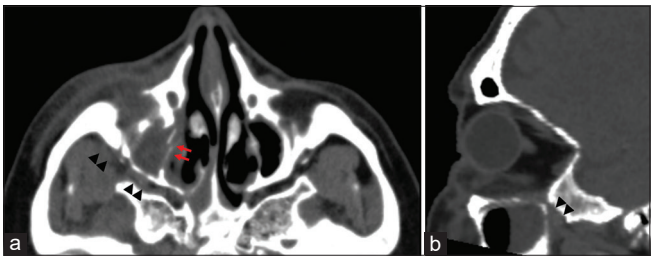

Figure 1: Sinus computed tomography (CT) scan at the clinical onset. Axial (a) and sagittal (b) CT scan examination with soft-tissue algorithm showing right maxillary invasive sinusitis. Note focal sinus medial wall discontinuities (red arrows in a) and partial obliteration of normal fat planes in the pterygomaxillary fissure (arrowheads in a and b).

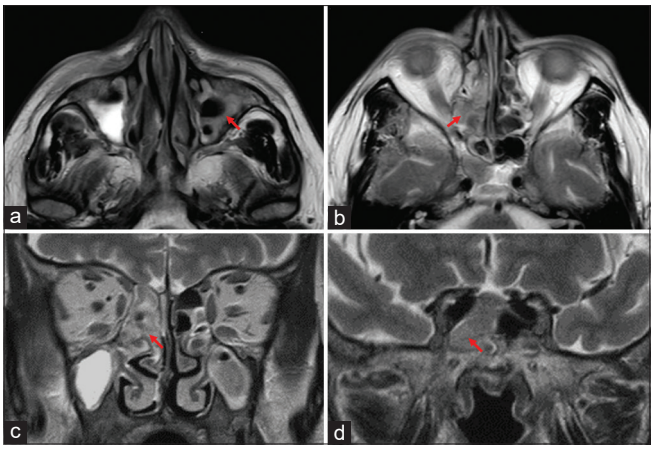

Figure 2: Sinus magnetic resonance imaging. Axial (a and b) and coronal (c and d) fast spin echo T2-weighted images show low signal effusion in the left maxillary sinus, at the level of ethmoidal air cells and sphenoid sinus, predominantly on the right (arrows).

Moreover, the sphenoidectomy was conducted in a transethmoidal fashion until the identification of Onodi's cell was reached. Multiple tissue samples were collected for histological and microbiological analysis. Irrigation with antibiotic solution was performed leaving a drainage for 5 days.

Two days later, *Rhizopus oryzae* was isolated, then MM was diagnosed, and a systemic therapy by intensive intravenous amphotericin B (5 mg/Kg) was started.

A few days after surgery, a sudden onset of bilateral ophthalmoplegia (III, IV, VI cranial nerves palsy) and sensory trigeminal loss (V1–V2 cranial nerves impairment) was observed. These clinical features, suggestive of bilateral cavernous sinus syndrome, were confirmed by an emergency brain MRI [Figure 3]. Main significant MRI findings were bilateral cavernous sinuses thrombosis, more evident on the left side, and slight swelling of the V2–V3 nerve roots on both sides without evidence of contrast

enhancement. Bilateral trigeminal cisternal tract swelling was also demonstrated along with bilateral pontine foci, with evidence of increase in signal intensity on DWI and FLAIR sequences at the level of trigeminal "Root Entry Zone."

The next day, together with a significant worsening of the neurological status, further MRI imaging showed multiple bilateral *watershed* ischemic lesions, more evident on the left, and occlusion of the left internal carotid artery. Last follow-up MRI examination performed a week later, before the exitus, also demonstrated left endophthalmitis with c*rystalline* lens *dislocation* and significant extension of parenchymal ischemic foci [Figure 4].

DISCUSSION

ROCM defines an infection originating from the paranasal sinuses with possible extension to the brain.[27] In these cases, sporangiospores enter the nasal mucosa and paranasal sinuses. The main underlying conditions associated with ROCM are DM[22] and leukemia.[19]

Molds belonging to the order of "*Mucorales*" are saprophytic aerobic microorganisms that grow rapidly and are able to release a large number of airborne spores. They are *ubiquitous in nature* and widely found on organic substrates (e.g. bread, decaying fruits, vegetable matter, or soil).[21]

The genera most commonly responsible for human infections are *Rhizopus*, *Mucor*, and *Absidia* (now reclassified as *Lichthemia)*[29] while *Rhizomucor, Cunninghamella, Saksenaea, Syncephalastrum*, and *Apophysomyces* are less frequently implicated.[14] Overall, *R. oryzae* is the most common pathogen isolated from specimens in MM disease.[25]

It is well known that a regular phagocytic activity is able to kill fungal spores. In this regard, experimental studies have shown that a compromised phagocytic activity and/or neutropenic situations are the two conditions that most favor opportunistic molds infections.[2] According to several studies, the main risk factors for MM[9,22] are the following:

- Poorly controlled DM, with or without ketoacidosis,
- Hematologic malignancies,
- Long-lasting corticosteroids therapies,
- Hematopoietic cell/solid organ transplantation,
- Treatment with deferoxamine and iron overload,
- Illicit intravenous drug use,
- Disruption of mucocutaneous barriers by catheters and other devices,
- Malnutrition.

A review of 929 cases of MM between 1940 and 2003, conducted by Roden *et al*.,[22] confirmed that DM was the most common risk factor (36%) followed by hematologic malignancies (17%) and solid organ or hematopoietic cell transplantation (12%).

In diabetic population, phagocytic function seems to be altered, especially in neutrophilic chemotaxis, diapedesis, and hydrogen peroxide production.[1,10] *In vivo* studies on diabetic mice with intrasinus inoculation *R. oryzae*

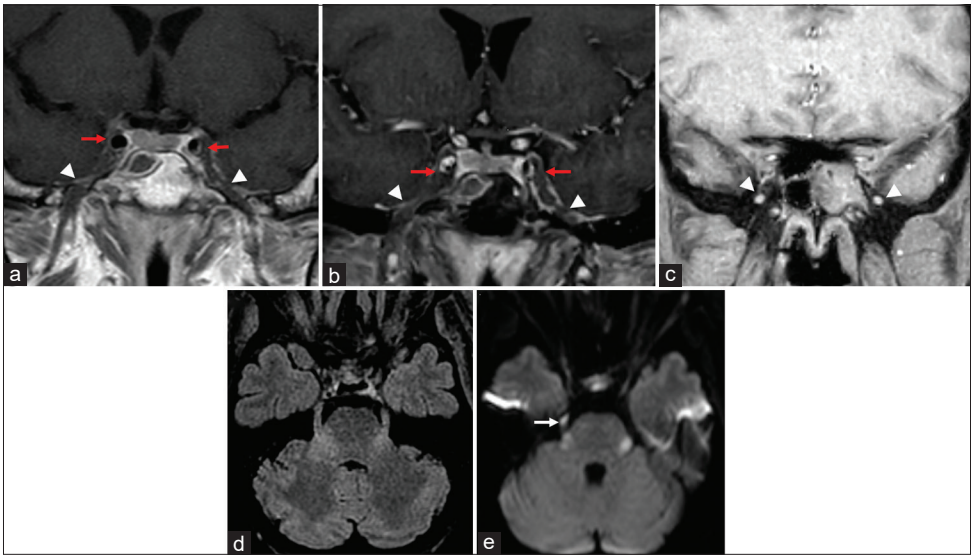

Figure 3: Brain magnetic resonance imaging examination at neurological onset. Coronal contrast-enhanced fat saturation T1-weighted (a and b), coronal basal fat saturation T1-weighted (c), axial fluid-attenuated inversion recovery (d), axial diffusion-weighted (e) images. (a and b): Bilateral cavernous sinus thrombosis (arrows), bilateral V3 swelling without contrast enhancement (arrowheads); (c): bilateral V2 swelling (arrowheads); (d and e): high signal bilateral pontine foci, due to perineural diffusion. Note diffusion restriction at intracisternal tract of right trigeminal nerve (white arrow).

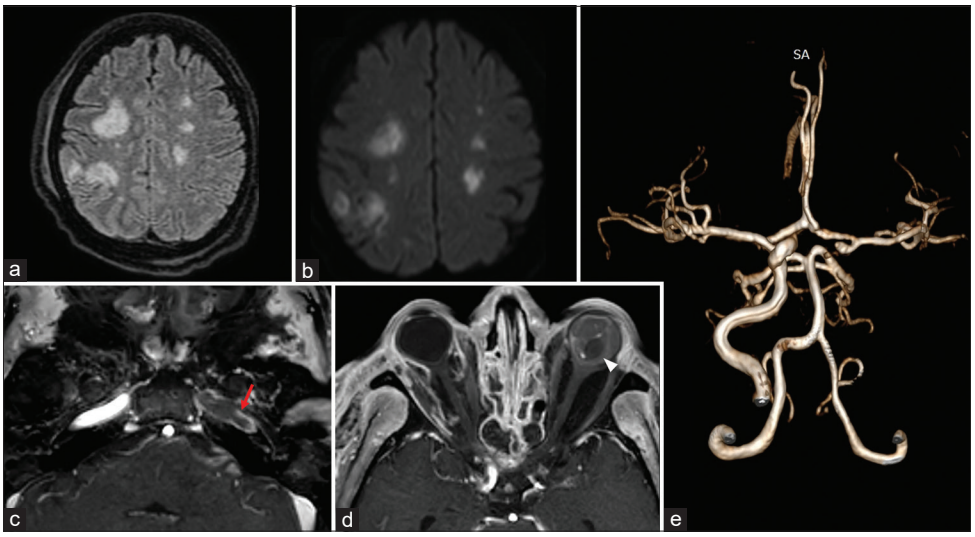

Figure 4: Follow-up brain magnetic resonance imaging examination Axial fluid-attenuated inversion recovery (a), axial diffusion-weighted (b), axial contrast-enhanced fat saturation T1-weighted (c and d) images. Volume rendering technique (VRT) time-of-flight magnetic resonance angiography. (a and b) Bilateral acute frontoparietal watershed infarction; (c): left internal carotid artery (ICA) wall enhancement, due to mucormycosis vasculitis (arrow); (d): left endophthalmitis with crystalline lens dislocation (arrowhead) VRT angiography well depicts left ICA thrombosis.

confirmed the rapid progression to intracerebral MM and high rate mortality within 11 days.[28]

Our case suggests all the possible common complications of ROCM in both endocranial and orbital sites, by three main mechanisms of infection that is direct diffusion, perineural, and perivascular spreading.

Direct diffusion

Nasal cavity and paranasal sinuses are usually the first site of involvement by fungal sporangiospores inhalation. Main CT findings include mucosal thickening, endosinusal high-density soft tissues, sinus wall thinning, and bone destruction.[11]

On MRI imaging, the compacted fungal hyphae present low signal intensity on T2-weighted sequences. Characteristic low T2 signal of MM is also caused by associated tissue necrosis phenomena due to mucosal angioinvasion.

On contrast-enhanced T1-weighted sequences, devitalized tissue demonstrates a characteristic lack of enhancement, also known as "black turbinate sign," feature that itself could easily lead to an early and reliable diagnosis.[23]

Direct extension beyond slight anatomical boundaries of rhinosinusal cavities results in involvement of the pterygopalatine fossa, periantral fat, nasolacrimal duct and the lacrimal sac, and less commonly of the nasopharynx.[11]

Rarely, orbital invasion[16] can be observed, with variable patterns of preseptal, postseptal cellulitis or endophthalmitis, as well as direct invasion of the brain (typically at the frontal lobes) through the cribriform plate of the ethmoid bone, with variable patterns of meningoencephalitis or brain abscess.[23]

Perineural spread (PS)

In the past, PS was considered unusual. However, emerging studies have demonstrated possible PS both microscopically and macroscopically. Particularly, Sravani *et al*.[26] demonstrated a peripheral PS on biopsy specimens in 15 out of 30 patients affected by ROCM, even for considerable distance from primary focus of infection. Other authors depicted a macroscopic PS on large caliber nerves, also visible on MRI imaging, for instance along the three branches of trigeminal nerve. Margo *et al*.[12] described a V1 trigeminal branch division involvement in the anterior orbit in a patient with invasive MM. A retrograde V2 trigeminal root involvement, from the infraorbital nerve and diffusion to the pterygopalatine fossa through the inferior orbital fissure, and to middle cranial fossa through the foramen rotundum, was also reported.[17] Again, cavernous sinus, Meckel's cave, and the intracisternal tract of the trigeminal nerve involvement have also been reported,[13,17] with a variable pontine localization.[6]

Perivascular spread

The hallmark of *Mucorales* infection is its vascular tropism. Without a prompt therapy, fungal spores, by escaping phagocytosis, tend to invade vessels with efficacious adherence to endothelial cells. Moreover, *R. oryzae*

synthesizes an alkaline protease allowing dissection of the internal elastic lamina from the media by cleaving elastin.[5] These phenomena may be responsible for vasculitis, thrombosis with infarction, and necrosis of involved tissues.[6]

Arterial intracranial mucorthrombosis could easily lead to a mucormycotic vasculitis, cavernous sinus thrombosis, and septic strokes. Onset of mycotic aneurysms with subarachnoid hemorrhage was also reported.[5]

CONCLUSION

MMs are life-threatening fungal infections in patients with DM, cancer, and organ transplantation.

Clear identification of the main risk factors, careful assessment of clinical features, and radiological findings may improve the chance for an early diagnosis and patient survival.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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