

Rhino-Cerebral Mucormycosis: Improving the Prognosis of a Life-Threatening Disease

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Introduction

Rhinocerebral mucormycosis is a rare life-threatening fungal infection particularly jeopardized by delayed diagnosis and initiation of treatment. The incidence could be increasing due to longer survival of immune-suppressed patients. With the advent of newer antifungals, improvements in surgical techniques, and advances in diagnostic technology (both in the microbiology lab and in radiology), we have now the potential to ameliorate the ominous prognosis of this disease. Therefore, early clinical suspicion, diagnosis and empirical initiation of antifungal treatment are of paramount interest, now more than ever. We present a case of Rhinocerebral mucormycosis and review the clinical clues in magnetic resonance imaging and clinical suspicion tips for earlier diagnosis.

Case Report

Mucormycosis is a rare, emerging and life-threatening infection caused by inhaled spores of fungi of the order of Mucorales [1]. The incidence is 1.7 cases/million people/year with prevalence in autopsy series of 1-5 cases per 10,000 [2]. Usually, diagnosis and therapy are performed too late because of low index of suspicion, with up to half of the cases only diagnosed postmortem. The advent of magnetic resonance imaging (MRI), liposomal amphotericin B, and technical advances in surgical debridement, have the potential to improve the prognosis even in severe cases with central nervous system (CNS) involvement.

A 53-year-old woman with poorly controlled diabetes mellitus and treated with azathioprine and metil-prednisone for autoimmune cholangitis, came to our emergency department for having two episodes of tonico-clonic generalized seizures. She had a three-week history of left facial pain and headache, low-grade fever, and occasional epistaxis through the left nose. The physical examination revealed no fever, no meningeal signs, left maxillary sinus pain and three painless, papulo-erythematous scabbing lesions on the scalp of <10 mm diameter.

Laboratory results showed a 732 mg/dl glycaemia with negative ketonuria, normal pH and HCO₃, 7000 leucocytes/ μ L (95% neutrophils), and low hemoglobin (10.1 g/dl). Blood and urine cultures were negative. A MRI (Figure 1) showed an infiltrative lesion T2 hyperintense, with multiple microhemorrhagic foci and peripheral enhancement, with radial strands inside the lesion. Coronal (right) views on T2 and contrast-enhanced T1 showed association with left sinusitis and orbital cellulitis (fat of extraconal compartment). No arterial or venous extension was seen.

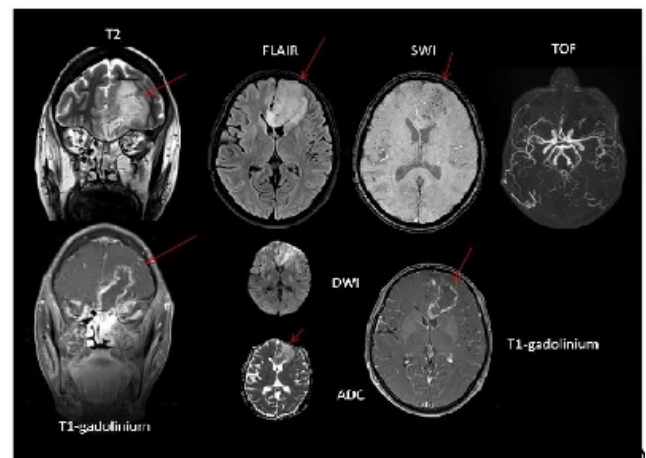


Figure 1: MRI showing an infiltrative lesion hyperintense on T2, with multiple microhemorrhagic foci and peripheral enhancement. Coronal (right) views on T2 and contrast-enhanced T1 show association with left sinusitis and orbital cellulitis.

The patient received high-dose insulin and anticonvulsant treatment with IV levetiracetam. With the suspicion of mucormycosis (high risk immunosuppressed and diabetic patient with sinusitis, altered mentation, seizures and consistent MRI findings), high-dose IV liposomal amphotericin B (6 mg/kg/day) was immediately started, oral metilprednisolone was withdrawn, and azathioprine dose halved. An endonasal biopsy (figure 2) showed extensive ischemic necrosis with abundant hyphae and focal acute inflammatory reaction. Inoculated onto Sabouraud dextrose agar plates at 25°C, after 24 hours a massive growth of a filamentous fungus, non-septated and with wide mycelium, was identified as *Rhizopus* spp.

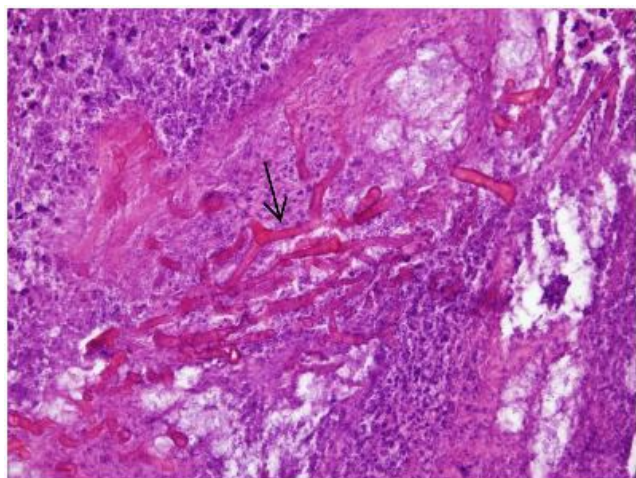


Figure 2: Massive growth of a filamentous non-septated fungus with wide mycelium into a Sabouraud dextrose agar plate, identified as *Rhizopus* spp.

A debridement of inflammatory tissue in left ethmoid, maxillary antrotomy and drainage of the single brain collection through frontal craniotomy was performed. A 6-week course of full dose IV liposomal Amphotericin B was completed and the patient was successfully switched to oral posaconazole with clinical resolution and complete solving of MRI signs at 10 weeks.

Many sites of infection have been described in mucormycosis including pulmonary, cutaneous, gastrointestinal, disseminated and rhinocerebral, which is the most common in diabetics [3]. The pathogenic mechanism is vascular invasion resulting in tissue infarction, necrosis and thrombosis. Hyperglycemia and acidosis are known to impair the ability of phagocytes, which are by means of oxidative and non-oxidative mechanisms the principal host defence against mucor [3].

The mycological culture of a biopsy is only diagnostic if the fungus is cultured from sterile tissues, or repeatedly or massively isolated from non-sterile sites in large numbers of colonies, because mucosal colonization can exist in patients without infection and it is a relatively common contaminant in laboratories [4]. The definitive diagnosis is therefore better supported by a biopsy showing the presence of extensive ischemic necrosis with abundant hyphae and focal acute inflammation. Hyphae are characteristically wide, non-septate with right angles [5].

We could not carry out the biopsy on the erythematous papular lesions because they were solved with earlier treatment. Cutaneous lesions in disseminated rhino-cerebral mucormycosis must be deliberately searched, because they can be a helpful clue in the diagnosis, as it happens with many fungal infections.

The sinus contents have a variety of MRI signal characteristics, including T2 hyperintensity or marked hypointensity ("black turbinate") on all sequences, possibly due to the presence of iron and manganese in fungal elements [6]. For rhino-orbito-cerebral mucormycosis, thickening and lateral displacement of the medial rectus muscle are characteristics of orbital invasion from the ethmoid sinuses. A lack of enhancement of the superior ophthalmic vein or

ophthalmic artery and internal carotid artery may be seen, related to vasculitis and thrombosis [7]. The lesions have variable enhancement patterns with gadolinium, ranging from homogeneous to heterogeneous or non-enhancing at all. Contrast-enhanced T1-weighted images are helpful in delineating the parenchymatous, meningeal or cavernous spread.

The CNS may be invaded directly through the cribriform plate, superior orbital fissure or basal foramina, but also indirectly via the invasion of vessels. In these cases infarcts may be added to the cerebritis [8]. Thus, it is also recommended to include in the study the main intracranial and cervical vessels (Figure 1).

Proper debridement of infected sinus and orbital space leads to high cure rates (>85%) [9]. In a case series of 49 patients with rhinocerebral mucormycosis, mortality with antifungal agents alone was 70% compared to 17% when surgery was associated. However, these data could be biased, indeed favouring the performance of surgery in individuals with better prognosis and surviving the first days of treatment [10].

Early initiation (within 5 days after strong suspicion or diagnosis) of polyene therapy is of paramount importance, usually with high dose liposomal amphotericin B (5 to 8 mg/kg). 3 Doses and duration of antifungal therapy are not well established due to the lack of comparative studies, but should be continued until clinical resolution of signs, symptoms of infection and radiographic signs on serial imaging [1]. The combination of a polyene and an echinocandin has not proven to increase outcomes yet, even though *Rhizopus* expresses the target enzyme for echinocandins [1].

Therefore, in diabetic or immunosuppressed patients with epistaxis, acute/subacute history of headaches, maxillary pain or sinusitis, neurological deficits or seizures, rhino-orbito-cerebral mucormycosis must be included in the differential diagnosis. Early diagnosis, reversal of underlying predisposing factors, correct antifungal therapy, and early surgical debridement are the four steps required for healing this deadly fungal disease, with an ominous prognosis that could improve significantly with the recent advances in antifungal treatment and diagnostic techniques.

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Declaration of interest:

The authors declare that they have no conflicts of interest.

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