Rhinocerebral mucormycosis: an update

A. MALLIS, S.N. MASTRONIKOLIS, S.S. NAXAKIS, A.T. PAPADAS

ENT Department, University Hospital of Patras (Greece)

Abstract. – Background and Objectives: Mucormycoses are a group of invasive infections caused by filamentous fungi of the Mucoraceae family, with the rhinocerebral form of the disease being the most common in large case series. In the present paper we review the characteristics of the rhinocerebral form of the disease.

Evidence and Information Sources: The present review is based on the analysis of the current literature on rhinocerebral mucormycosis.

State of the Art: Rhinocerebral mucormycosis is associated with immunocompromised patient state, haemochromatosis, desferrioxamine therapy and prolonged corticosteroid therapy. Uncontrolled diabetes and increased serum iron are regarded as the two leading predisposing factors for the development of the disease. Currently, treatment for the disease is based on three main principles; rapid reversal of underlying predisposing factors, antifungal therapy with amphotericin B and timely surgical intervention.

Perspectives: Antifungal drugs of the azole group and new iron chelating agents – deferasirox, deferiprone – have been supported as alternative options to amphotericin B or as salvage therapy.

Conclusions: Rhinocerebral mucormycosis requires a high level of awareness if early diagnosis and treatment is to be achieved. Large scale evaluation of arising treatment options is a mandatory course of action in the future research of the disease.

Key Words: Rhinocerebral mucormycosis, Treatment, Otorhinolaryngology, Fungal infections.

Introduction

Mucormycoses are a group of invasive infections caused by filamentous fungi of the Mucoraceae family. Throughout the present paper we will refer to infections caused by Mucorales as mucormycosis in contrast to the term zygomycosis. The latter is sometimes used in the relative literature due to the previous classification of the involved fungi1 and encompasses infections by both Mucorales and Entomophthorales4.

Mucormycosis is an invasive fungal infection first described by Paultaufl A in 1885. Based on the clinical presentation and particular site of involvement six manifestations of the disease can be described: rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated and localized infections not otherwise belonging in the previous categories1.

The causative agents of mucormycosis are the filamentous fungi of the Mucoraceae family of the order Mucorales, subphylum Mucormycotina1. The most frequently isolated species is Rhizopus oryzae followed by Rhizopus microsporus, and Absidia corymbifera2. The remaining five families of the Mucorales order have rarely been reported as causes of mucormycosis4, with the exception of the Cunninghamellaceae family whose members have been isolated in a number of case reports. The infection is acquired through the aerodigestive tract, giving rise to various forms of the disease, with no person to person spread reported5.

Rhinocerebral mucormycosis is also referred to as rhino-orbito-cerebral mucormycosis in the respective literature to denote involvement of the orbital structures.

In the present paper we review the characteristics of the rhinocerebral form of the disease. Table I provides a quick overview of rhinocerebral mucormycosis.

Epidemiology and Risk Factors

Infections by members of the order Mucorales are primarily opportunistic infections and represent the third leading cause of invasive fungal infections following Aspergillus and Candida species6.

Comprehensive incidence data, however, are not available and reports on the incidence of mucormycoses among the general population vary, with Rees et al7 reporting an annual incidence rate of 1.7 cases per million people in the United States and Bitar et al8 reporting an average annual incidence rate of 0.9 per million people in
Diabetic Ketoacidosis

Diabetic ketoacidosis is uniformly recognized as the commonest underlying condition in the majority of rhinocerebral mucormycosis cases although its role is not fully understood\(^3\).

Early studies by Chinn et al.\(^{17}\) and Artis et al.\(^{18}\) have proven that diabetic ketoacidosis impairs chemotaxy and phagocytic activity of neutrophils and increases available serum iron respectively. These findings, however, do not adequately explain clinical data as neutropenic patients are predisposed to pulmonary mucormycosis and disseminated mucormycosis seems to be more common in the presence of deferoxamine treatment\(^3\).

Available Serum Ion

Iron is required for the growth of a variety of microorganisms, with its availability being especially important in the case of mucormycosis\(^9\) as has been proved by the studies of Boelaert et al.\(^{20}\) on *Rhizopus oryzae* models. In particular Boelaert et al. have shown a marked growth increase of *Rhizopus oryzae* in iron enriched serum. Of particular clinical importance are studies by de Locht et al.\(^11\) and Boelaert et al.\(^{22}\) showing that deferoxamine treatment for iron overload in fact induces *Rhizopus* spp. growth as it is utilized by the fungi as a siderophore. These results are further supported by the works of Anand et al. on their animal models of rhinocerebral mucormycosis\(^{23}\).

### Disease Spread

The locoregional spread pathway of rhinocerebral mucormycosis has not been adequately described. Thorough research of the relevant literature revealed only one study by Hosseini et al.\(^{24}\) on their animal models of rhinocerebral mucormycosis.
tients, Hosseini et al regard the pterygopalatine fossa as a reservoir of the disease through which it can spread to neighboring structures including the retroglobal space of the orbit and infratemporal fossa.

On the contrary angioinvasion by the fungi has been studied to a greater extent and is considered central to its ability to cause tissue necrosis and dissemination. Of special interest are findings by Ibrahim et al indicative of possible endothelial cell damage even by dead *Rhizopus oryzae*, although the mechanism remains unknown.

**Clinical Presentation**

Rhinocerebral mucormycosis most commonly presents in an acute setting, reminiscent of sinusitis or periorbital cellulitis. Facial pain and unilateral facial swelling are also important parts of the clinical picture of the patient with variable grade fever being present although not in all cases. The only disease specific finding described in the relative literature is blackened necrotic eschars of the nasal mucosa or palate. However, in large case series it has been noted in less than half of the patients. Furthermore, it should be noted that initial appearance of the inflamed nasal mucosa may be normal. An erythematous phase develops at a later stage and the formation of necrotic eschars rather represents local disease progression with blood vessel thrombosis and tissue infarction. Moreover, ulceration of the hard palate should be interpreted as a sign of disease extension from the sinus rather than expected as an early sign of the disease.

The clinical picture may further progress to include unilateral ophthalmoplegia representing involvement of the orbital contents either by infection or vascular compromise. Contralateral ophthalmoplegia suggests cavernous sinus thrombosis, although bilateral rhinocerebral mucormycosis albeit rare should be considered.

Progression of the infection to central nervous system is heralded by development of confusion and disorientation, with bloody nasal discharge also reported as a potentially early sign of disease extension to the brain. Central nervous system damage may also result from cavernous sinus thrombosis and internal carotid artery encasement leading to cerebral infarctions and hematogenous dissemination of the disease to other organ sites.

Contrary to the aforementioned clinical presentation, the few cases of chronic rhinocerebral mucormycosis that have been described most commonly present with ophthalmologic complaints and a clinical course varying from weeks to months. Furthermore, internal carotid artery and cavernous sinus thrombosis seem to be more common in this group of patients.

**Diagnosis**

Early diagnosis of rhinocerebral mucormycosis is considered a step of grave importance for the appropriate management of the patient. Symptoms compatible with mucormycosis in a predisposed patient call for prompt initiation of treatment while appropriate steps are taken towards confirmation of diagnosis, a course of action unanimously supported in the relevant literature.

Histopathological examination of surgical specimens can confirm the clinical diagnosis with the appearance of right-branching aseptate hyphae, which are considered typical of mucor species, along with evidence of angioinvasion and tissue necrosis. Fungal cultures can provide further confirmation. However, a large number of false negative results have been reported compared to direct histopathological examination. Speciation and susceptibility tests can also be ordered, although this information is more of scientific and epidemiologic interest with no clinical implications as the treatment plan is uniform in all cases.

Other laboratory diagnostic modalities include molecular detection of zygomycetes which has been available for some time now. However, the results so far have been less than promising. Cerebrospinal fluid analysis has also been reported as helpful in the diagnosis in few reports, however isolation of the fungi from blood cultures and cerebrospinal fluid should not be considered the norm.

Imaging methods are of little help during the early stages of rhinocerebral mucormycosis with thickening of the sinus mucosa or extraocular muscles being described as an early sign suggestive of the disease.

CT scans can be used to evaluate the progression of disease although correlation with the clinical findings may not always be accurate. MRI scans may be more accurate in evaluating the extent of disease due to fungal invasion of soft tissues. Both CT and MRI scans, however, should be frequently obtained due to the rapidity
of disease progression and are indispensible for appropriate planning of surgical interventions

**Treatment**

Treatment for rhinocerebral mucormycosis is based on three main principles: reversal of underlying predisposing conditions, prompt initiation of antifungal therapy and surgical intervention when appropriate\(^3\).

**The Role of Surgery**

Surgical intervention has been associated in large series with favorable outcome\(^1^3,3^9\). However, no formal guidelines have been formulated as to the timing and extent of appropriate surgical management\(^4^0\).

Reed et al\(^4^1\) advocate an “aggressive-conservative” approach with frozen section guided surgical exploration, sparing uninvolved orbital structures while Nithyanandam et al\(^1^3\) support a more aggressive approach with early excision of infected structures. Although orbital exenteration has been reported as helpful even in the context of intracranial spread\(^2\), the topic of orbital exenteration has not been adequately studied\(^4^1\) thereby necessitating individualization of surgical intervention.

Irrigation of the surgical site with amphotericin B solution has also been proposed based on the vaso-occlusive nature of the infection which leads to reduced delivery of antibiotics to infected areas\(^2^7\).

**Antifungal Therapy**

Although amphotericin B deoxycholate (AMP) remains the only licensed antifungal agent for mucormycosis, lipid formulations of amphotericin B are considered a safe and efficient alternative\(^4^0\). Liposomal amphotericin B (LAMP) in particular has been proved superior to AMP in a retrospective study\(^5^\), while amphotericin B lipid complex (ABLC) has been reported to be effective as part of a combination treatment with caspofungin\(^4^1\).

Members of the azoles drug group have also been used in the treatment of mucormycosis infections with varying results. Itraconazole has known *in vitro* activity against the Mucorales order, however in vivo its effectiveness is limited to the Absidia species thus limiting its clinical use\(^4^0\). On the contrary the clinical role of posaconazole as primary treatment has been supported by a number of researchers\(^4^2\) despite mixed laboratory evidence of its effectiveness\(^4^0\) and is generally regarded as salvage therapy for mucormycosis\(^4^3\).

**Iron Chelation Therapy**

Deferasirox and deferiprone are new iron chelators, which in contrast to deferoxamine cannot be utilized by the fungi as siderophores\(^1^9\). According to the research of Ibrahim et al both deferasirox and deferiprone have been proved to be effective agents against mucormycosis in animal models. Furthermore deferasirox has also been used successfully as salvage therapy in a case of rhinocerebral mucormycosis\(^4^4\) opening up new areas of clinical research.

**Adjunctive Therapies**

Case reports support the role of granulocyte stimulating factor\(^4^5\) and hyperbaric oxygen\(^4^6\) in treating patients with mucormycosis although further research is required to determine their place in a comprehensive treatment plan.

**Treatment Strategy**

Reversal of underlying predisposing conditions is of paramount importance. Euglycemia should be restored rapidly and any immunosuppressive conditions reversed if possible\(^4^0\). The surgical approach should be based on the clinical state of the patient with timely interventions for appropriate debridement of infected areas\(^4^1\).

Absence of supportive clinical evidence on the effectiveness of various combination treatments\(^4^7\), elevates polyene based therapy as the main course of action. Recommended starting doses for the lipid formulation of amphotericin are 5-7.5 mg/kg/day with higher dosages (up to 10 mg/kg/day) recommended for CNS involvement\(^4^0\). Iron chelation therapy and posaconazole should be considered in cases of refractory infection or polyene intolerance\(^4^0\).

Regarding the duration of treatment, Spellberg et al\(^4^8\) specify the resolution of immunosuppression, radiographical signs and clinical symptomatology as the objectives of treatment.

**Prognosis**

Cases of localized sinonasal rhinocerebral mucormycosis have been reported to have low mortality rate (10%)\(^1^3\). Progression of the disease is associated with worse prognosis, with CNS involvement considered fatal\(^3^8\).

The overall prognosis however has improved considerably over the past fifty years\(^4^9\), with reported mortality rates of about 40%\(^3^8,5^0\).
In conclusion, rhinocerebral mucormycosis remains still a poorly understood disease with high mortality rate. Presently, the triad of clinician’s awareness, prompt initiation of treatment and timely surgical intervention represent the monus operandi against the disease. Continued research into the pathology of the disease and large scale evaluation of arising treatment options are mandatory future directions in the area of rhinocerebral mucormycosis.

References


