

A Review on Rhinocerebral Mycosis: Dual Infections

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Submitted: 11 May 2017; Accepted: 18 May 2017; Published: 31 May 2017

Abstract

Rhinocerebral mycosis is an opportunistic infection seen in immune compromised patients, patients with uncontrolled diabetes, organ transplant and malignancies. Zygomycetes and Aspergillus are the commonest causative agents infecting para nasal sinuses and have predilection to invade blood vessels. The infection rapidly spreads to orbit and brain. An early diagnosis and treatment is essential to limit the spread to neighbouring structures. Although, cases of rhinocerebralmucormycosis with dual etiology are rare but their numbers are rising due to increase in the number of people living with diabetes, malignancies and other immunodeficiency disorders. This review emphasis the rising incidence of rhinocerebral mycosis with dual infection and also highlights the importance of early diagnosis and treatment in order to prevent the rapid disease progression.

Keywords: Rhinocerebral mycosis, Zygomycetes, Aspergillus, dual infection

Introduction

The first case of rhinocerebral mycosis was identified by Paltauf in 1885 [1]. It is an opportunistic infection beginning in the nasal mucosa due to inhalation of fungal spores. From the nose the disease rapidly spreads to paranasal sinus, orbit and brain [2]. Though a rare entity, it is associated with poor morbidity and mortality [3]. The predisposing factors for rhinocerebral mycosis are uncontrolled diabetes mellitus, immunosuppressive therapy, organ transplant, malignancies and other immunodeficiency states [4]. Aspergillus and zygomycetes are the two most common etiological agents [5]. The angioinvasive nature causes rapid spread and poor prognosis. Vascular invasion leads to emboli and thrombus formation causing occlusion of the blood vessels. This leads to formation of black necrotic eschar and tissue destruction of the surrounding area. The intravenous antifungal also fail to reach the affected area leading to treatment failure [6]. Early diagnosis, antifungal therapy, surgical debridement along with control of the predisposing factors forms the mainstay of management. Any delay can lead to invasion in the blood vessels causing emboli formation and destruction of the surrounding tissues [5]. There have been few case reports on rhinocerebral mycosis worldwide and even fewer on those having a dual fungal etiology. This review article aims to review the epidemiology, clinical manifestation, diagnosis and management of dual infection in rhinocerebral mycosis.

Epidemiology

Few years back, rhinocerebral mycosis used to be rare entity. But in the recent times, there has been a surge in number of cases worldwide P [7]. In developing countries like India, diabetes, malignancies, transplants and immunodeficiency disorders are

showing a rising trend. India has become second in the list of nations with most number of diabetics [8]. Uncontrollable diabetes, malignancies, immunosuppressive therapies are the risk factors for rhinocerebral mycosis [4]. In India, diabetes emerges as the most common risk factor. In diabetics, uncontrolled diabetes and ketoacidosis are the most important risk factor [7]. Suresh S et al reported a prevalence of fungal etiology to be 30% in 100 patients of chronic rhinosinusitis [9]. Mumbai was reported to have highest incidence of fungal rhinosinusitis in the world by Ferguson et al [10]. The data on epidemiology of the disease is lacking due to inadequate diagnostic facilities, inadequate reporting and lack of clinical suspicion.

Many fungal species are the etiological agents, but the Zygomycetes (Rhizopus, Mucor, Rhizomucor) and species of Aspergillus are the most common etiologic agents [5]. A study done in North India reported Aspergillus to be the most common fungus in 79.17% of cases followed by zygomycetes in 20.83% [5]. Aspergillus is a saprophytic fungi which is ubiquitous in the environment. It affects patients with poorly controlled diabetes and underlying immunodeficiencies. The hot and humid climate of tropical and subtropical countries facilitate the survival of the fungus. Aspergillosis of the CNS spreads via hematogenous route or direct extension from neighbouring areas like paranasal sinuses. However, some studies have reported zygomycetes to be the most common etiological agent.

In a study done by Sita S, et al. on 46 patients with a diagnosis of rhinocerebral mycosis, Zygomycetes and Aspergillus were the commonest organisms found in 18 (47.4%) and 16 (42.1%), respectively cases. Immunocompromised state was noted in 24 (63.2%) and 23 had diabetes mellitus (DM) [11]. In a review by Roden et al, in 929 cases of Zygomycosis, Rhizopus was the most

common organism and paranasal sinus as the most common site. Diabetes was the most common predisposing factor [12].

Although dual infections are known to occur but are very rare. Lack of awareness amongst clinicians and poor diagnostic facilities makes the diagnosis tough. Very few case reports/ series

have been published worldwide (Table 1) but more research is needed. Fungal co-infection of rhinocerebral mycosis are difficult to diagnose and treat. Since, the most common causative agents like aspergillus and zygomycetes are ubiquitous in environment and can cause contaminate the cultures.

Table 1: case reports on rhinocerebral mycosis (co-infections)

Study	Year	Risk factor	Site	Diagnosis	Isolate	Treatment	Outcome
Maiorano, E et al. [13]	2005	Castleman's disease Chemotherapy	Orosino-nasal	Culture	Aspergillus spp. Zygomycetes	antifungals	Survived
Alfano C [14]	2006	Diabetes mellitus	rhinocerebral	Culture histopathology	Aspergillusfumigatus Mucoraceae	Voriconazole Caspofungin Amphotericin B	Survived
Gupta R, et al. [15]	2006	Diabetes mellitus	Sino-nasal orbit	Culture histopathology	Aspergillus spp. Rhizopus spp.	Liposomal Amphotericin B	Survived
Malhotra S, et al. [16]	2008	Diabetes mellitus	Rhinocerebral pulmonary	KOH mount Culture	Aspergillusflavus zygomycetes	Liposomal Amphotericin B	Died
Vaidya D, et al. [17]	2011	hypertension	Rhinocerebral	Culture	Rhizopusarrhizus Aspergillusflavus	Liposomal Amphotericin B	Survived
Malhotra S, et al. [18]	2012	Diabetes mellitus	Rhinocerebral	KOH mount Culture	Aspergillusflavus Rhizopus	Liposomal Amphotericin B Itraconazole	Survived
Bajpai T, et al. [19]	2014	Renal transplant	Sinonasal	Culture	Aspergillusniger Mucor Rhizopus	Liposomal Amphotericin B Voriconazole	Survived
Rit K, et al. [20]	2014	Malignancy Diabetes mellitus	Rhinocerebral	Culture	Aspergillusflavus Mucor	Liposomal Amphotericin B Voriconazole	Died
Sharma B, et al. [21]	2016	Diabetes mellitus	Sino-nasal orbit	Culture	Alternaria alternate Rhizopusarrhizus	Amphotericin B	Survived

Pathogenesis and Clinical manifestation

Rhinocerebral mycosis is an opportunistic infection with high rate of morbidity and mortality. Phagocytes are the major defence mechanism against Mucorales and kill by generation of oxidative metabolites. Patients with neutropenia or dysfunctional phagocytes are at greater risk of developing mycosis. Phagocyte functioning is also hampered by hyperglycemia, acidosis and corticosteroid therapy [22,23]. The infection begins after inhalation of fungal spores and hyphae. Nasal / sinus mucosa is the site of origin of infection. Due to angioinvasive property of the fungal hyphae, the disease rapidly spreads to adjacent sinuses, orbit and into cranium via ethmoid bone [6]. The disease begins with headache, fever, nasal congestion, discharge, epistaxis and anosmia. As the infection progresses and spreads to orbit, symptoms such as proptosis, ptosis, chemosis and orbital cellulitis appear. Complications such as vision loss, ophthalmoplegia, facial paralysis result due to cavernous sinus thrombosis and internal carotid artery thrombosis [24,25,26]. Due to vascular invasion, there is black necrotic eschar and perforation in nasal and oral cavities which is characteristic of

mucormycosis [27,28]. Spread into brain can occur either through orbit or via ethmoid bone leading to cavernous sinus thrombosis and internal carotid artery thrombosis. Thus, resulting in cerebral infarction with hematogeneous dissemination of the infection [26].

Mucormycosis has a strong affinity to patients with uncontrolled diabetes. In diabetics, neutrophils and macrophages become dysfunctional with impaired killing. Patients with diabetic ketoacidosis are more prone due to low serum pH and increased free iron which supports the fungal growth. Patients on deferoxamine have increased susceptibility to mucormycosis. Rhizopus is known to utilise deferoxamine as a siderophore to supply iron to fungus [23].

Diagnosis

Clinical suspicion is considered a step of utmost importance for early management of the patient. The presence of signs and symptoms in a patient with the predisposing factors warrants a high index of suspicion of rhinocerebral mycosis. The general

laboratory findings include raised total leucocyte count, raised C reactive protein, elevated erythrocyte sedimentation rate and iron deficiency.

Analyses of tissue samples from nasal/sinus extraction, debridement tissue on potassium hydroxide mount often demonstrate the presence along with morphology of fungus. If the fungus is in the order Mucorales then broad, aseptate, ribbon-like, hyaline hyphae are seen [29]. Otherwise, branched and septate hyphae are seen in *Aspergillus* or other non-Mucorales fungi [30]. Early primitive diagnosis of fungal infection can be made on the basis of direct KOH mounts and the patient can be started on empirical therapy until confirmation by culture methods. But due to the ubiquitous nature of the fungus, contamination of the specimen is common.

Histopathological examination of surgical specimens can confirm the clinical diagnosis with the appearance of typical morphology of the fungus as well as other suggestive findings such as angioinvasion and tissue necrosis [31].

Imaging methods are nonspecific during the early stages of disease. Changes such as thickening of sinus mucosa or extra ocular muscles can be detected on CT scan [23]. MRI prove to be more useful in evaluating the extent of the disease spread. It is useful in identifying intracranial extension, cavernous sinus thrombosis and perineural spread of the disease [32]. Imaging techniques are frequently needed for assessing the disease progression and planning surgical intervention.

Molecular techniques like PCR can be used to determine the exact etiology but their high cost and non-availability in most of the centres in developing countries are the major drawbacks. Molecular test must always be used along with other conventional methods like direct KOH mounts and culture. Some serological test like glactomannan or beta glucan can be used but they are only done in few centres [23].

Treatment

Rhinocerebral mycosis is a rapidly progressing, highly invasive and life threatening infection. Widespread tissue necrosis results in poor penetration of antifungal agents at the site of infection. Even if the causative fungi is sensitive to the antifungals, but poor penetration leads to treatment failure. Hence, surgical debridement of the infected tissue become highly essential [33]. Repeated debridement is necessary to remove the necrosed infected tissue and prevent the spread of infection to the nearby structure [14]. Amphotericin B is the basic drug for the treatment of rhinocerebral mycosis. It has a good action against zygomycetes. The conventional form of the drug has many side effects such as hypokalemia and nephrotoxicity. This limits its use amongst patients with renal impairment. Liposomal formulations have low risk of side effects and high concentration maintained in infected tissue [34,35]. The total dose of conventional amphotericin B estimated at 3–4 g should be given with- in 6–12 weeks. The daily dose of intravenous dose is usually 1 mg/kg. The lipid form is administered by infusion at a dose of 5 mg/kg/day [34]. Resistant strains can be treated with posaconazole [36]. Infection due to *aspergillus* can be treated with voriconazole. But due to its high cost, Amphotericin B or itraconazole are being used instead [26,36].

Apart from surgery and antifungals, it is very essential to treat any

co-existing co-morbidities. Additional supportive therapies include glucose homeostasis, hyperbaric oxygen, GM-CSF (granulocyte-macrophage colony-stimulating factor) and G-CSF (granulocyte colony-stimulating factor) [23,32].

Delayed diagnosis and treatment can greatly increase the mortality. Intracranial extension, immunocompromised state, elderly age, co-infection are few factors for predicting a poor prognosis.

Conclusion

Rhinocerebral mycosis is a serious opportunistic infection that is commonly seen in immunocompromised patients, diabetics and patients with malignancies. Due to the rapid progression of the disease into the surrounding tissues and intracranial extension, an early diagnosis and treatment is needed. Clinical suspicion and adequate diagnostic techniques can help in clinching the diagnosis. Antifungal pharmacotherapy, surgical debridement and correction of co-morbidities form the basis of management. Although several case reports/series on dual fungal etiology of rhinocerebral mycosis have been reported, there have never been a review article in the literature to the best of our knowledge. This review emphasis the rising incidence of rhinocerebral mycosis with dual etiology due to increase in the number of people living with diabetes, malignancies and other immunodeficiency disorders. This review also highlights the importance of early diagnosis and treatment in order to prevent the rapid disease progression.

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