

**INVASIVE FUNGAL INFECTIONS OF HEAD AND NECK: A RETROSPECTIVE STUDY**Somu L<sup>1</sup>, Prasanna Kumar Saravanam<sup>2</sup>, A. Ravikumar<sup>3</sup>, Rohini Jose<sup>4</sup>**HOW TO CITE THIS ARTICLE:**

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**ABSTRACT:** Invasive fungal infection of the head and neck is an emerging problem with diverse presentation. It has recently gained clinical importance as it causes considerable morbidity and mortality. It is more common in patients with diabetics, chronic renal disease, patients undergoing chemotherapy etc. Early recognition of this entity will enable treating surgeon to institute appropriate treatment. **AIM OF THE STUDY:** To review the microbiological and clinicopathological profile of patients diagnosed as invasive fungal infections of the head and neck in a tertiary referral hospital. **METHODOLOGY:** In this retrospective study we reviewed the clinical data (Microbiology, clinical manifestations, radiological investigation, diagnosis, therapy and histopathology) of 25 patients diagnosed and treated for invasive fungal infection of the head and neck in our unit in a tertiary care hospital. The period of study was July 2006 to July 2010 (4 years). All cases with a diagnosis of invasive fungal infection of the head and neck region, confirmed either by fungal smear, culture or histopathological examination were included in the study. **RESULTS:** In this study, Of the 25 patients, majority had invasive fungal rhinosinusitis (52%), mucormycosis (32%) and zygomycotic necrotizing fasciitis (12%). One patient had invasive subcutaneous aspergillosis. Most of the patients presented in the fifth decade of life, 86% of these patients had uncontrolled diabetes. The commonest presentation in mucormycosis was head ache or facial pain (100%) along with ptosis (88%). Fungal smear was positive in 81%, fungi were isolated in culture in 54% and histopathological study was positive for fungal hyphae in all these patients (100%). Though all these patients had florid fungal infection of the head and neck only one patient had clinical and radiological evidence of cervical lymphadenitis. **CONCLUSION:** A clinical suspicion of mucormycosis should be kept in mind in an immunocompromised patient with headache and ptosis as these symptoms were present in most of our patients suffering from mucormycosis. Even though lymphadenitis is an indication of florid infection, absence of nodes should raise a high index of suspicion of fungal infection.

**KEYWORDS:** Invasive fungal infection, fungal Rhinosinusitis, zygomycotic necrotizing fasciitis

**INTRODUCTION:** An alarming rise in the incidence of Invasive fungal infections has been noted in recent times. Mostly attributable to the rise in the number of immunocompromised patient who have received an organ transplant or is being treated for malignancy.<sup>[1,2]</sup> The rise in incidence of diabetes mellitus in India has also reflected the increase incidence of invasive fungal infection in this part of the world.<sup>[3]</sup> Managing invasive fungal infection is a challenge because it leaves significant morbidity and mortality. Early diagnosis and aggressive management of this potentially lethal disease results in cure and also reduce morbidity.

Of more than 400,000 known fungal species, approximately 400 are human pathogens and only 50 cause invasive fungal infections. Sinonasal cavity is a potential space for these organisms to

## ORIGINAL ARTICLE

enter the body. The European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) have laid down the revised criteria for diagnosis of invasive fungal infection for the purpose of trial and research in 2008.<sup>[4]</sup>

**MATERIALS AND METHODS:** A retrospective analysis of 25 patients who were diagnosed and treated for invasive fungal infections of the head and neck at our tertiary care institute were analyzed. These were proven cases of invasive fungal infection that had fulfilled the revised criteria for invasive fungal infection EORTC/MSG 2008. In this study we have reviewed the clinical data (Microbiology, clinical manifestations, radiological investigation, diagnosis, and therapy) of each. The period of study was from July 2006 to July 2010 (4 years).

**RESULTS:** In this study of the 25 patient who had invasive fungal infections majority, 52% had invasive fungal rhinosinusitis (Aspergillosis) (Fig. 1a & 1b), 32% had rhinocerebral mucormycosis (Fig. 2) and 12% had zygomycotic necrotizing fasciitis (Fig. 3). One had invasive subcutaneous aspergillosis (Fig 4). Most of the patients presented in the fifth decade of life. 86% of these patients had coexisting uncontrolled diabetes. The most common presenting symptom for mucormycosis was head ache, facial pain and ptosis (Table 1). A remarkable feature noted in patients with mucormycosis was the presence of ptosis in 88% of our patients (Fig. 5a). Fungal KOH smear was positive in 81% cases (Fig. 6). Fungi was isolated in culture in 54% of these and histopathological study was positive for fungal hyphae in tissue of all (100%) these patients. Though all these patients had florid fungal infections of the head and neck, only one patient had documented clinical and radiological evidence of cervical lymphadenitis. All patients of invasive fungal infections were managed successfully except one case of zygomycotic necrotizing fasciitis (Fig. 3) in whom *Apophysomyces elegans* (Fig. 7), a rare type of invasive fungi was isolated, this patient later developed embolism of the internal carotid artery and succumbed to the disease in spite of aggressive surgical and medical management.

**DISCUSSION:** Fungal sinusitis is a relatively common, often misdiagnosed disease of paranasal sinuses. Invasive fungal infections are associated with a high rate of morbidity and mortality and hence warrant urgent medical and surgical intervention.<sup>[4]</sup> Fungal sinusitis can be classified in two distinctive categories by Ferguson BJ,<sup>[5]</sup> as shown below.

**Noninvasive Disease Includes:**

1. Saprophytic fungal infection,
2. Sinus fungal ball,
3. Allergic fungal rhinosinusitis.

**Invasive Fungal Sinusitis has been sub Classified:**

1. Acute fulminant invasive fungal sinusitis (AFIFS),
2. Chronic or indolent invasive fungal sinusitis
3. Granulomatous invasive fungal sinusitis

The diagnoses of fungal infections are mainly based on microbiological and histopathological examination. Specimens for fungal smear and culture collected from the wound preferably along with the infected tissue (Exudates, necrotic materials) and sent to the lab within 30 minutes in a sterile container or sterile saline.

## ORIGINAL ARTICLE

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The specimen is examined under light microscopy in 10% potassium hydroxide (KOH) smear (Fig. 6). The walls of the fungi appear light to dark brown and can be easily detected. Exudates as well as tissue can be stained with routine histopathologic preparations,<sup>[6]</sup> such as Hematoxylin and eosin (H&E), Gomori Methenamine silver (GMS) or Periodic acid schiff (PAS).

The GMS and PAS stain are superior to H & E stains, and the fungal wall stain black or red, respectively. The Fontana-Masson melanin stain may be useful in differentiating the dematiaceous fungi from non-melanin containing hyphae such as *Aspergillus*.

Most of our patients with mucormycosis presented with symptom of headache and facial pain (Table 1). Ptosis was seen in 88% and ophthalmoplegia in 66% of our patients with mucormycosis. Bhansali et al.,<sup>[7]</sup> have reported the presence of ptosis in all 35 of their patients with mucormycosis. 97% of these patients had ophthalmoplegia. S. Bhadada et al.,<sup>[8]</sup> has also reported the presence of ptosis in all 6 patients diagnosed to suffer from mucormycosis.

Literature abounds with case reports of cases of mucormycosis presenting with ptosis and ophthalmoplegia.<sup>[7-11]</sup> However we could not find a reasonable explanation as to why patients with mucormycosis with or without orbital involvement have ptosis. A plausible explanation for the same would be that the fungal infection from sinuses spread through the bone either directly by erosion due to angioinvasion and necrosis or indirectly through valveless venous and arterial plexus surrounding the orbit and the sinuses. Hence the inflammation around the venous and arterial plexus affects the oculosympathetic plexus of nerves resulting in features similar to Horner's syndrome. This results ptosis and ophthalmoplegia which is reversible if the disease is appropriately managed. In our study all our patients recovered from ptosis (Fig. 5b).

Patients with elevated levels of free iron, which supports fungal (*Mucor*) growth in serum and tissues, are at increased risk for mucormycosis. In iron-overloaded patients as in end-stage renal failure, treatment with deferoxamine predisposes to the development of rapidly fatal disseminated mucormycosis. Deferoxamine used as an iron chelator, serves as a fungal siderophore, directly delivering iron to the Mucorales, hence helping in rapid spread of infection.<sup>[12]</sup>

Patients with diabetic ketoacidosis (DKA) are also at high risk of developing rhinocerebral mucormycosis. 86% of our patients with invasive fungal infection and all patient with mucormycosis were having uncontrolled diabetes mellitus. The acidosis causes dissociation of iron from sequestering proteins in serum, resulting in enhanced fungal survival and virulence. It is likely that hyperglycemia during DKA also contributes to the risk of mucormycosis through its association with poorly characterized defects in phagocytic function.<sup>[13]</sup> Necrotizing fasciitis of head and neck is a rare, highly virulent, life threatening infection primarily involving the subcutaneous tissue and fascia.<sup>[14-17]</sup>

It frequently occurs in uncontrolled diabetics, immunosuppressed patients, intra venous drug addicts, and patients with peripheral vascular disease.<sup>[14-17]</sup> There are only about 68 reported cases in world literature of cervical necrotizing fasciitis. The most common cause of cervical necrotizing fasciitis is dental infections.<sup>[18]</sup>

Necrotizing fasciitis is caused by group A *Streptococcus pyogenes* or as a result of a polymicrobial synergistic infection caused by aerobic, anaerobic, Gram-positive and Gram-negative organisms. Fungal infection although reported,<sup>[15,19-22]</sup> is a rare cause that complicates the outcome of necrotizing fasciitis.

In our study we had 3 cases of necrotizing fasciitis of which invasive *Aspergillus* was isolated in 2 cases which were successfully managed and one case in which *Apophysomyces elegans* was isolated this patient succumbed to the infection after developing internal carotid artery embolism

## ORIGINAL ARTICLE

(Fig. 3). Because of the drastic clinical course and high mortality, a high index of suspicion, rapid diagnosis, and appropriate treatment are key elements of successful management of zygomycetes infection.

Current therapy for the invasive disease includes treating the underlying predisposing factors, antifungal therapy, and surgical debridement of the affected tissues. Early recognition of the disease and treating the underlying cause of mucormycosis, such as diabetes, is a key to improving outcomes. Serum electrolytes and renal parameters should be monitored on regular basis during the treatment of fungal infections. Hypokalemia was seen in most of the patients with mucormycosis which was corrected by giving potassium chloride intravenously as per the requirements.

Intravenous Amphotericin B is the antifungal agent of choice for invasive fungal infections caused by mucorales, but its use is limited by the propensity of the drug to cause renal toxicity and hypokalemia.<sup>[23]</sup> We had to use other oral antifungals such as Voriconazole and Itraconazole in patients who could not tolerate Amphotericin B or for cases in which invasive *Aspergillus* was isolated. Extensive endonasal endoscopic wound debridement was done for 2 patients with mucormycosis, maxillectomy was required of two, and palatectomy was done for one patient. One of them required orbital decompression.

In our study we have observed that majority of the patient with mucormycosis present with ptosis (88%), with or without ophthalmoplegia and though all these patients had invasive fungal infections, cervical lymphadenitis was seen only in 1 out of the 25 cases. Further large scale study or Meta-analysis will be required to evaluate the cause of ptosis and its implication on invasive fungal sinusitis in head and neck.

**CONCLUSION:** Invasive fungal infections of the head and neck are more common than reported. It has diverse presentation making the diagnosis difficult. Fungal smear and culture should be done in all immunocompromised hosts with head and neck infection. A high index of suspicion will result in early diagnosis and management. Invasive fungus will require aggressive surgical debridement and appropriate antifungal therapy.

The key points of note are the presence of ptosis with or without ophthalmoplegia and absence of cervical lymphadenitis in spite of florid infection in nose and paranasal sinuses should raise the suspicion of mucormycosis.

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## ORIGINAL ARTICLE

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## ORIGINAL ARTICLE

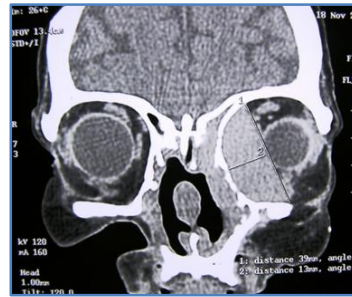
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**Fig. 1a:** Frontal view of a case of invasive fungal rhinosinusitis (Aspergillosis), showing proptosis of left eye.

**Fig. 1b:** CTscan with contrast, coronal section showing the orbital involvement in a patient with invasive fungal rhinosinusitis (Aspergillosis).



**Fig. 1a**



**Fig. 1b**

**Fig. 2:** Necrosis and ulceration seen in the right side of the hard palate in a case of mucormycosis.

**Fig. 3:** Zygomycotic Necrotizing fasciitis involving the left temporo-parietal region and neck after wound debridement.



**Fig. 2**



**Fig. 3**

**Fig. 4:** Frontal view of a case of invasive subcutaneous aspergillosis showing swelling in the right side of the face.

**Fig. 5a:** Frontal view of a patient with mucormycosis with left eye ptosis.



**Fig. 4**

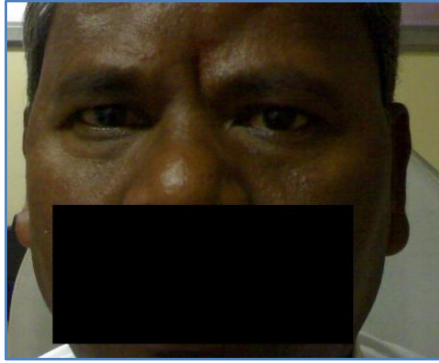


**Fig. 5a**

## ORIGINAL ARTICLE

**Fig. 5b:** Frontal view of the same patient 3 year post treatment, showing complete recovery from ptosis and ophthalmoplegia.

**Fig. 6:** KOH mount showing broad aseptate hyphae (200x).

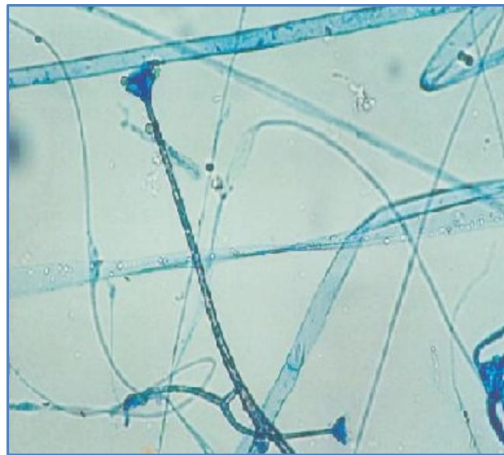


**Fig. 5b**



**Fig. 6**

**Fig. 7:** Lactophenol cotton-blue mount of *Apophysomyces elegans* showing sporangiophores having funnel-shaped apophyses and pyriform sporangia ( $\times 200$ )



**Fig. 7**

Symptom	Frequency	Clinical sign	Frequency
Headache/ facial pain	83.30%	Ptosis	88%
Diplopia	16.60%	Restriction of Extra ocular movements	66.60%
Nasal discharge/block	33.30%	Proptosis	33.30%

Table 1: Showing the commonest presenting symptom and sign of rhinocerebral mucormycosis

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