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Case Report

CONCOMITANT MUCORMYCOSIS AND ASPERGILLOSIS OF RHINOCEREBRAL REGION IN A RENAL TRANSPLANT PATIENT – AIR COOLER BEING THE CULPRIT

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ABSTRACT
Invasive fungal infections are associated with morbidity and mortality in immunocompromised patients. Rhinocerebral region infections are mainly due to opportunistic fungal pathogens. Although Zygomycosis and Aspergillosis are two major causes of paranasal infections, reports of combined Mucormycosis and Aspergillosis infections of rhinocerebral region are limited. We report a case of fatal, combined rhinocerebral fungal infection in post renal transplant patient, etiology being an air cooler with old wet pads. Prompt diagnosis is challenging and inspite of aggressive management with a combination of surgical and medical therapies, the outcome is poor. Amphotericin B remains the cornerstone in the medical management of mucormycosis and Voriconazole in Aspergillosis, still we are short of drugs to fight with such a devastating organism (*Mucor*).

Keywords: *Mucormycosis, Aspergillosis, Renal Transplant Recipient and Rhinocerebral Region*

INTRODUCTION
Fungal infections are life-threatening in immunocompromised hosts and it account for 5% of all infections in renal transplant recipients (Patel, 1997). The incidence varies according to the geographical area. Because of environmental exposure and the effects of immunosuppressive regimens, systemic mycosis is a significant problem in transplant patients worldwide and remains the major cause of death. In an Indian study 6.1% of renal transplant recipients were affected by systemic fungal infections and resulted in a 63% mortality rate (Chugh, 1992). The causative agent and the risk factors differ depending on the period after the kidney transplant. Fungal infection caused by rare organism Aureobasidium *pullulans* has also been reported to affect Renal transplant recipient (Eswarappa, 2015). Majority of fungal paranasal sinusitis are non invasive. In diabetics and those on immunosuppressive therapy, it may spread into orbit and central nervous system (Michael, 2008). Zygomycosis and aspergillosis are two major causes of paranasal fungal infections.
Angioinvasive property of fungi causing vascular occlusion with tissue destruction accounts for high mortality and morbidity in rhinocerebral mycosis (Vaidya, 2011).
However, reports of combined infection due to *Zygomycetes* and *Aspergillus* of rhinocerebral region are limited.
We report a case of combined rhinocerebral fungal infection in renal transplant patient recovered from antibody medited rejection, concurred infection from use of an air cooler with old wet pads.

CASES
A 32 year old, non-alcoholic, non-smoker, underwent allograft renal transplantation 40 days back for chronic renal failure, with his mother as donor (HLA- Haploidentical), post transplant on POD 3 he developed acute rejection, kidney biopsy was done and pulse steroid given. Biopsy showed AMR baniff 2b c4d negative.
His DSA came positive. Plasmapheresis initiated, each cycle followed by IVIG (100mg/kg), total 6 cycles given. His renal functions improved and creatinine declined to 1.4 mg/dl. Patient was discharged on triple immunosuppressive drugs and prophylaxis against CMV, PCP and fungal infections (Fluconazole) given. Patient and family was extensively counselled about hygiene (boiled water, ironed clothes, room cleaning).

Case Report

Patient came for follow up 5 days later with complaints of right hemicranial headache, rhinorrhea, swelling and pain over right eye, right facial pain and fever since 1 day. Headache was insidious in onset, continuous and was not associated with nausea and vomiting. Fever was mild without chills. There was no history of trauma, blurring of vision, diplopia, giddiness and convulsions. History revealed exposure to aircooler with old wet pads. ENT examination showed nasal mucosa congested, with blackish discolouration in Right middle turbinate. Right maxillary sinus tenderness with no local deformity. Vestibules were normal. Ophthalmological examination revealed mild ptosis with normal ocular movements, oedema of right eye. Fundus examination was normal.

The patient underwent CT scan of the paranasal sinuses which revealed extensive mucosal thickening involving the frontal, ethmoidal sinuses, sphenoidal sinuses, osteomeatal complex and maxillary antrum on right side (Figure 1). There was erosion of lamina papyracea and extension into the orbit on right side with normal extraconal orbital muscle. Globe was normal. The Left maxillary, ethmoidal and sphenoid sinuses were normal. CT Head was normal.

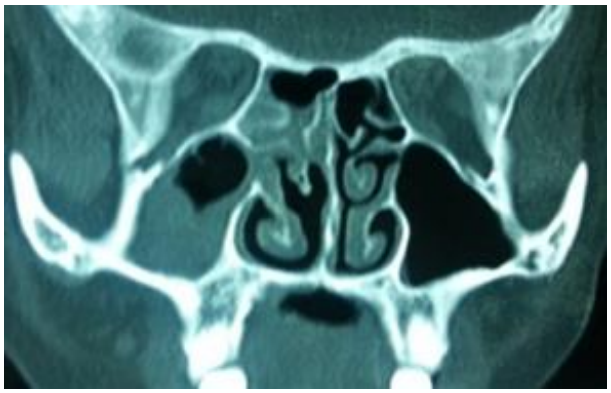

Figure 1: Mucosal Thickening Involving Maxillary Antrum with Extension into the Orbit

Laboratory investigations showed leucocytosis. Based on clinical and radiological findings, provisional diagnosis of acute invasive rhino sinusitis with right eye ptosis with probable fungal aetiology was suggested. Patient was started on antifungal treatment with Liposomal Amphotericin B (5 mg/Kg /day).

Functional endoscopic sinus surgery (FESS) was done. Tissue after debridement was sent for histopathological and mycology examination. On gross examination, tissue was black in colour and necrotic (Figure 2). 10% potassium hydroxide (KOH) examination demonstrated two different types of fungal hyphae. Predominantly hyphae were thin, slender and septate while other were broad aseptate ribbon like with collapsing walls.

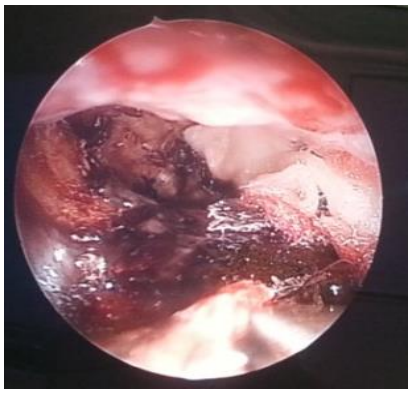

Figure 2: Endoscopic Gross Appearance of Sinuses Showing Black, Necrotic Tissue

Case Report

Specimens were inoculated on Sabouraud's dextrose agar (SDA) and incubated at 25 °C and 37 °C. After 48 h, it showed wringled colonies with brown powdery pigmentation (Figure 3) and white cottony filamentous growth in test tube. It was identified as *Apergillus* and *Zygomycetes*.
Mycophenolate stopped and tacrolimus reduced by 50% steroid continued.
Despite antifungal therapy, the headache and right ptosis persisted with development of right proptosis and ophthalmoplegia. MRI brain done which excluded any cranial extension at this point. The infection spread to the left sided sinuses also.
Post FESS on left side and histopathologically proven coinfection with *Aspergillus fumigates* and *Zygomycetes* was documented. FESS repeated, crusts cleared from left and right side, eroded nasal septum removal and tissue sample was again sent for mycological examination after extensive debridement. The tissue again revealed septate fungal hyphae in KOH examination. Culture on SDA showed white wringled colonies with brown powdery pigmentation (Figure 3). Fungi were identified. Confirmed with LCB lactophenol cotton blue stain which showed mixed picture of ruptured sporangium with developing vescicle in the field. These findings suggested a coinfection of *Zygomycetes* and *Aspergillus*. Patient was operated under general anaesthesia and exenteration of the sinuses on right side was done and Voriconazole for aspergillus was added.

Figure 3: Sabouraud's Dextrose Agar with Wringled Colonies with Black Powdery Pigmentation

Three days later Left Cheek Swelling appeared, with no involvement of Left Eye. Neurological examination revealed, anosmia, complete right sided ophthalmoplegia. Repeat MRI scan of brain and sinus was done, sinuses were clear but right frontal lobe showed inflammation. Repeat FESS revealed clear sinuses with healthy mucosa. After one week he developed left hemiplegia.

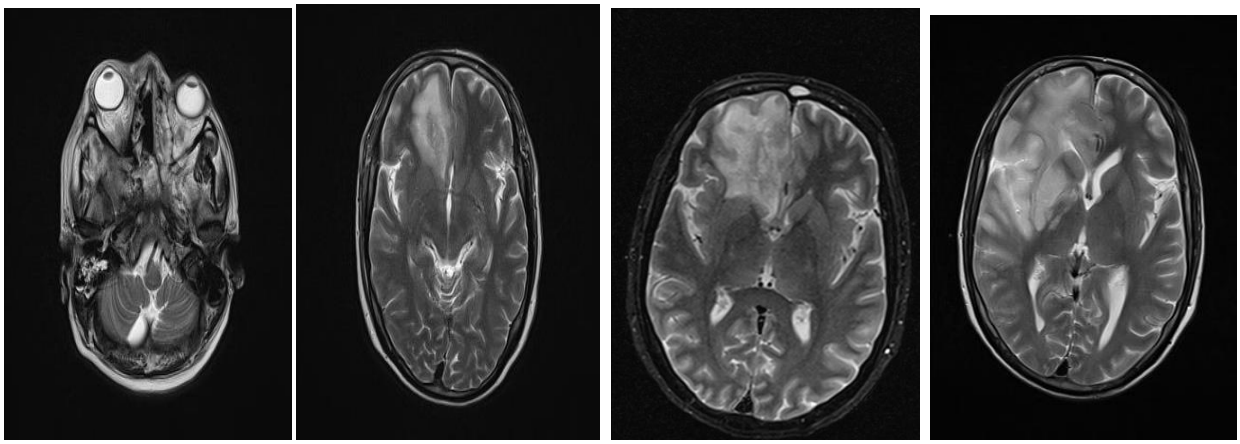

Figure 4 : Progressively Extending Intracranial Lesions

MRI brain with contrast revealed Right MCA territory infarct. Disease extended intracranially even with multiple debridement and antifungal drugs. Anticoagulation therapy initiated. During his illness his renal functions remained stable. His immunosuppressives were reduced to 5 mg of prednisolone and Tacrolimus 0.25 mg twice a day. On 28th day of hospitalization, the patient went into septic shock with respiratory failure and died on day 29th of his hospital stay.

DISCUSSION

Rhinocerebral infection usually originates from paranasal sinuses and extends into orbit and or brain. Zygomycosis and aspergillosis are two fatal rhinocerebral fungal infections.

Zygomycosis is an opportunistic fungal infection belonging to the class *zygomycetes*. It mainly infects immunocompromised patients. Most common route of transmission is inhalation of spores. Pathogenesis involves angioinvasion leading to thrombi formation in the vessels followed by ischaemic necrosis of the affected region producing characteristic nasal black eschar in cases of nasal mucormycoses (Petrikkos, 2012).

The fungus also possesses the property of systemic spread and passes to other parts of the body like cranium through nasal ethmoid bone. It has emerged as one of the most important pathogen for fungal rhinocerebral infection (Carmine, 2006).

Aspergillosis is a common fungal infection caused by the saprophytic fungus *Aspergillus*. It causes pulmonary and extra pulmonary infections in both immunocompetent and immunocompromised individuals. The frequency of invasive aspergillosis (IA), the second highest cause of invasive fungal infection in renal transplant recipients after candidiasis, ranges from 0.5% to 2.2%, with a mortality rate up to 88% (Alangaden 2006, Ergin 2003 and Morgan 2005). In rhinocerebral infection, invasive aspergillosis first manifests as localized sino-nasal infection and then may spread to adjacent region leading to tissue destruction (Carmine, 2006).

Combined aspergillosis and mucormycosis of a single region has been reported by few authors. To best of our knowledge Vidya and Shah (2011); Carmine *et al.*, (2006) and Maiorano *et al.*, (2005) published cases of combined mucormycosis and aspergillosis infection. This is probably the first case of concomitant infection of rhinocerebral region in renal transplant patient concurred from air cooler with old wet pad.

In our case, patient was renal transplant recipient on prolonged immunosuppressive therapy. Although provisional diagnosis was made based on clinical and radiological findings, definitive fungal aetiology was confirmed only after laboratory investigations. Microscopic examination of the tissue revealed two types of fungal morphology.

Culture initially yielded only *Mucor*. This might be due to rapid and luxuriant growth of *mucor* which have overgrown *Aspergillus*. Subsequent tissue samples yielded both *Mucor* and *Aspergillus*. This may be attributed to decreased load of *Mucor* owing to initial Amphotericin B treatment (Russell, 2011). Addition of voriconazole along with repeated extensive surgical debridement could not save our patient.

Thus, due to rapid progressive nature of rhinocerebral fungal infection with associated mortality, any immunocomopromised patient with headache and visual changes should be promptly evaluated with the help of imaging studies and laboratory investigations to rule out fungal aetiology.

Combined antifungal treatment coupled with extensive surgical debridement is hallmark for treatment of rhinocerebral fungal infection. For Mucormycosis, adding Posaconazole to Liposomal Amphoterecin has been proved to be more efficacious over monotherapy (Singh 2009).

The reduction of environmental exposure (air cooler exposure) remains main preventive measures against the fungal infection particularly in immunocompromised patients. Special attention needed in countries like India where use of air coolers with wet pads is quite common.

To conclude laboratory identification of combined fungal pathogens may help in prompt institution of treatment with favourable outcome without any undesired sequelae. In certain clinical situations and pathogens like Mucorales (Forrest, 2007), the decision to withdraw the immunosuppression and forgo the graft might be the call of the hour.

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