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CASE REPORT

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A treated case of rhinocerebral zygomycosis with aspergillosis: a case report from India

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Abstract

Zygomycosis and aspergillosis are two serious fungal infections that are commonly seen in immunocompromised patients. Since both of these infections involve fungi that invade vessels of the arterial system, an early and rapid diagnosis by direct examination of KOH mounts of the relevant clinical sample can clinch the diagnosis. Here, we present a case of a 60-year-old diabetic patient who presented with swelling and pain over the nose and left eye for 7 days with loss of vision in the left eye. After investigation, the patient was diagnosed as having rhinocerebral mucormycosis and aspergillosis, and was initially treated with amphotericin B (1 mg kg^{-1} day^{-1} intravenously), followed by endoscopic debridement under general anaesthesia. The patient gradually improved after surgery, and treatment with intravenous amphotericin B was continued along with the addition of 200 mg oral voriconazole twice daily (for the aspergillosis). With prompt diagnosis and treatment, the patient survived these fatal fungal co-infections and finally was discharged.

INTRODUCTION

Mycotic infection of the paranasal sinuses was first described in 1893 by Mackenzie [1]. Mucormycosis is a difficult to diagnose disease with high morbidity and mortality [2], which is caused by one of the members of the family Mucoraceae [3]. Rhinocerebral mucormycosis is generally associated with an immunocompromised state, haemochromatosis, desferrioxamine therapy, malignancy, diabetes mellitus with or without ketoacidosis, organ transplantation, severe burns, trauma and prolonged corticosteroid therapy [4]. This infection occurs infrequently, and poses diagnostic and therapeutic problems for those who are not familiar with its clinical presentation [5].

Aspergillus is a ubiquitous ascomycete mould that belongs to the family Aspergillaceae [6, 7]. *Aspergillus* sinusitis occurs in both normal and immunocompromised hosts, with invasive and fulminant types of infection more prevalent in immunocompromised patients [8].

Co-infection of aspergillosis and mucormycosis in sinuses is apparently a rare entity that is difficult to diagnose, posing clinical dilemmas, and very few such cases have been reported with recovery in the literature [9]. Here, we report an unusual case of rhinocerebral zygomycosis with aspergillosis in a 60-year-old diabetic patient, who recovered completely from this fatal co-infection due to timely diagnosis and treatment .

CASE REPORT

A 60-year-old female patient, resident of Moradabad, India, was referred to the Otorhinolaryngology Department of the Dr Ram Manohar Lohia Hospital and PGIMER, New Delhi, India, with complaints of insidious onset of swelling for 7 days, which had progressed gradually leading to nasal blockade. The patient also complained of swelling followed by loss of vision in the left eye for 7–10 days. There was no history of any purulent nasal discharge nor bleeding. There was no previous history of photophobia, diplopia, squint nor vision abnormality in the left eye. No facial weakness nor impaired facial expression was present. There was no family history of any similar clinical condition. The patient was a known diabetic for the previous 5 years and also gave history of hypertension for the previous 10 years, and was taking on and off treatment for both conditions (Table 1).

The general physical examination of the patient was normal, with no obvious external deformity except localized swelling on the left side eye and nose. The blood pressure of the patient was noted as 140/70 mmHg. On local examination, a blackish crust was observed in the left nasal cavity when examined

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Keywords: aspergillosis; mucormycosis; Amphotericin B.

Abbreviations: LPCB, lactophenol cotton blue; MALDI -TOF, matrix-assisted laser desorption/ionization-time of flight; MRI, magnetic resonance imaging.

Table 1. Clinical presentation of the patient

Symptom	Sign	Past history
Swelling and pain (throbbing) over the nose and left eye for 7 days	Blackish crust in the left nasal cavity	Patient was a known diabetic for the previous 5 years and a known hypertensive for the previous 10 years
Loss of vision in the left eye for 7 days	Perception of light was absent in the left eye with chemosis, proptosis and ptosis	No family history of any similar clinical condition
Progressive left sided nasal blockage due to swelling for 7 days		

by anterior rhinoscopy. On ocular examination, perception of light was absent in the left eye, and chemosis, proptosis and ptosis were present (Table 1). Laboratory investigation revealed: 11.2 g/dl haemoglobin, 12 100 cells mm^{-3} total leukocyte count and 177 mg/dl random blood sugar, with the rest of the biochemical parameters within normal limits. Magnetic resonance imaging (MRI) and contrast enhanced magnetic resonance imaging (CEMRI) showed altered heterogeneously enhanced oedema involving the left periorbital soft tissue, including the left eyelid, with left proptosis and sinusitis (Fig. 1, Table 2).

Based on the above findings, a provisional clinical diagnosis of fungal sinusitis was made and the patient was started on 1 mg kg^{-1} day^{-1} intravenous amphotericin B. After a few days of treatment, the patient was subjected to endoscopic debridement of the nasal crest under general anaesthesia. A clinical specimen obtained during this procedure was sent for both microbiological and histopathological examination. In the microbiology laboratory, 10% KOH mount analysis was performed, which initially showed branched septate hyphae of 3–6 µm in diameter with characteristic dichotomous branching, along with a few broad non-septate hyphae (Fig. 2). Cultures were plated on Sabouraud dextrose agar (SDA) with and without antibiotics at 25 and 37 °C. After 1 week of incubation on SDA without antibiotic at 25 °C, a velvety greenish growth was observed. After 3–4 days of further incubation, a scanty white cottony growth was also observed. A lactophenol cotton blue (LPCB) mount of this mixed growth showed both septate hyphae with phialides, and broad non-septate hyphae

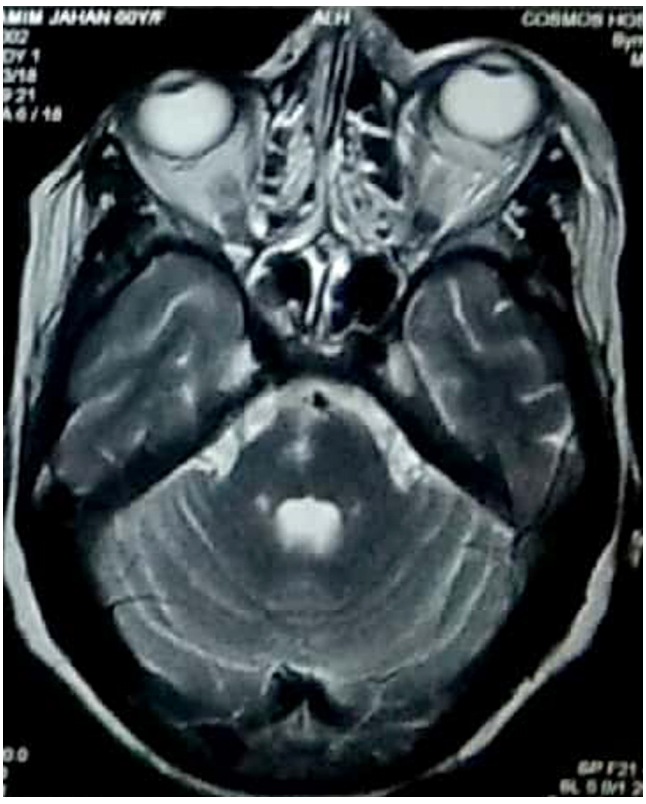

Fig. 1. MRI showing altered heterogeneously enhanced oedema involving the left periorbital soft tissue, including the left eyelid, with left proptosis and sinusitis.

Table 2. Investigations

On admission – haemoglobin, 11.2 g /dl; total leukocyte count, 12 100 cells mm^{-3}; random blood sugar, 177 mg/dl.

MRI – altered heterogeneously enhanced oedema involving the left periorbital soft tissue, including the left eyelid, with left proptosis and sinusitis.

Microbiological examination – specimen of nasal crest obtained from endoscopic debridement was subjected to 10% KOH mount, which initially showed branched septate hyphae of 3–6 µm in diameter with characteristic dichotomous branching, along with a few broad non-septate hyphae.

SDA without antibiotic at 25 °C showed velvety greenish growth and on further incubation a scanty white cottony growth was also observed.

LPCB examination of the greenish velvety colonies revealed branched septate hyphae with conidiophores.

LPCB mount of the cottony white colony showed broad (7–10 µm) non-septate, ribbon-like, hyaline hyphae that were of varied sizes bearing unbranched sporangiophores. Nodular rhizoids were visualized at the base of these sporangiophores.

MALDI-TOF MS analysis – confirmed the isolates as *Aspergillus flavus* and *Rhizopus arrhizus*.

Histopathological examination – showed a mixed inflammatory infiltrate with necrotic debris. It also showed both acute angle branching septate hyphae with spores and ribbon-like aseptate broad hyphae.

LPCB, Lactophenol cotton blue; MALDITOF MS, Matrix associated laser desorption ionization time of flight Mass spectrometry; MRI, Magnetic resonance imaging; SDA, Sabouraud Dextrose Agar.

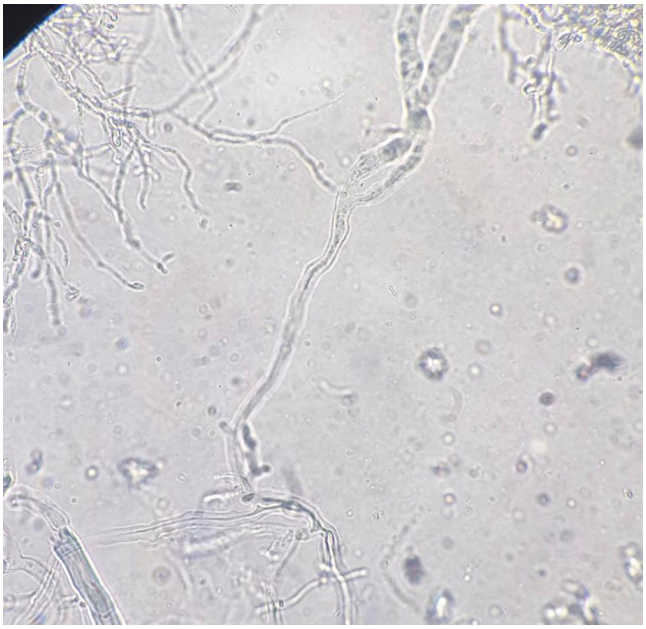

Fig. 2. 10% KOH mount showing branched septate hyphae with characteristic dichotomous branching, along with a few broad non-septate hyphae (under 400 X magnification).

with sporangium and rhizoids (Fig. 3). The mixture of this fungal growth was subcultured on separate SDA slants to isolate individual fungal colonies. After 3 days of incubation at 25 °C, greenish velvety growth appeared in one slant. The other slant showed cottony white dense growth after 8–10 days of incubation (at 25 °C) (Fig. 4). On LPCB examination of the greenish velvety colonies, branched septate hyphae with

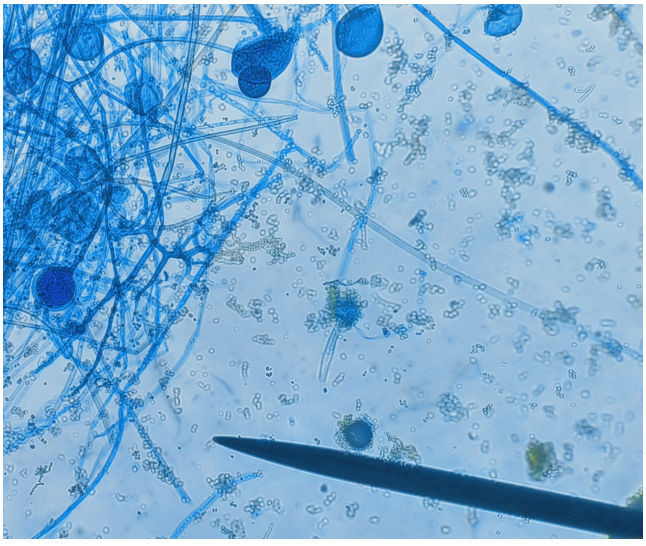

Fig. 3. LPCB mount showing both hyphae with phialides and broad non-septate hyphae with sporangium and rhizoids (under 400 X magnification).

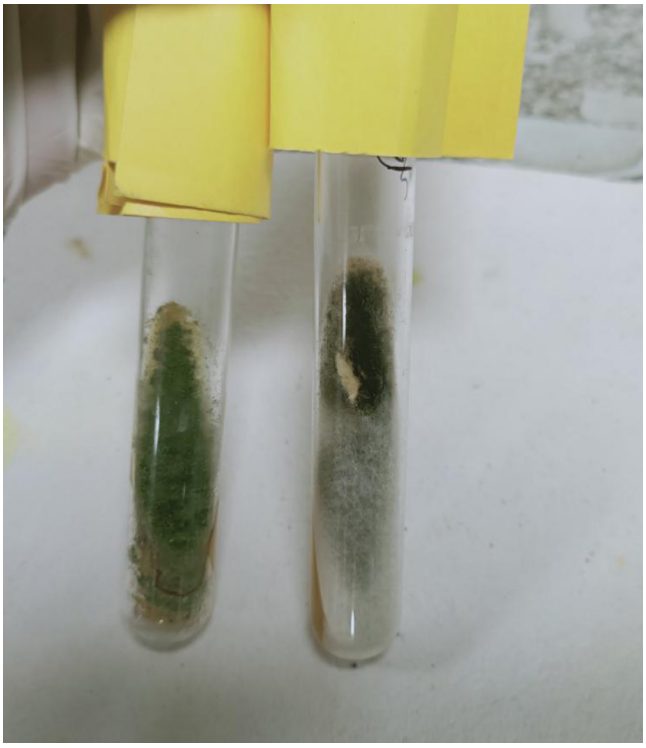

Fig. 4. Subculture on SDA showing greenish velvety growth in the slant on the left and cottony white dense growth in the slant on the right.

conidiophores arising from them were seen. The conidiophores terminated in vesicles, where biseriate phialides covered all around a whole vesicle, suggestive of *Aspergillus flavus*. The LPCB mount of the cottony white colony showed broad (7–10 µm) non-septate, ribbon-like, hyaline hyphae of varied sizes, bearing unbranched sporangiophores. Nodular rhizoids were visualized at the base of these sporangiophores. Sporangia were round, dark brown, with a flattened base, up to 175 µm in diameter and contained many spores suggestive of *Rhizopus* sp. Histopathological examination showed mixed inflammatory infiltrate with necrotic debris. It also showed both acute angle branching septate hyphae with spores and ribbon-like aseptate broad hyphae (Fig. 5).

Based on the KOH mount report suggestive of septate along with aseptate hyphae, oral voriconazole at a dose of 200 mg twice daily was added to ongoing parenteral amphotericin B treatment. The patient started responding well to the treatment and there was a gradual decrease in the swelling over the left eye. After 2.5 months of treatment another MRI was carried out, which showed a significant decrease in the soft tissue problems. Fluid noted in the sphenoid sinus was labelled as likely postoperative collection (Fig. 6). Treatment continued for another 15 days, after which the patient was discharged with 200 mg oral voriconazole twice daily for 15 days, with advice for further follow-up every fortnight in the Otorhinolaryngology Outpatient Department. The patient attended for 3 months, and showed complete recovery of the facial and nasal swelling and sinusitis (Table 3). The fungal

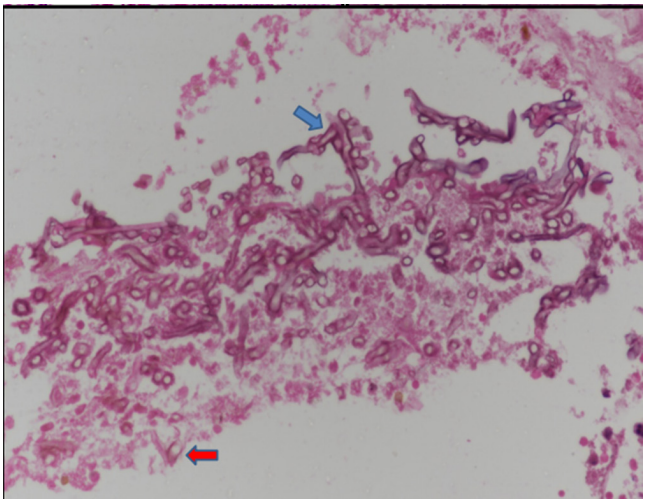

Fig. 5. Histopathological examination showing many acute angle branching septate hyphae of aspergillus (blue arrow) along with a few aseptate ribbon-like hyphae of mucor fungus (red arrow). (Under 1000X magnification).

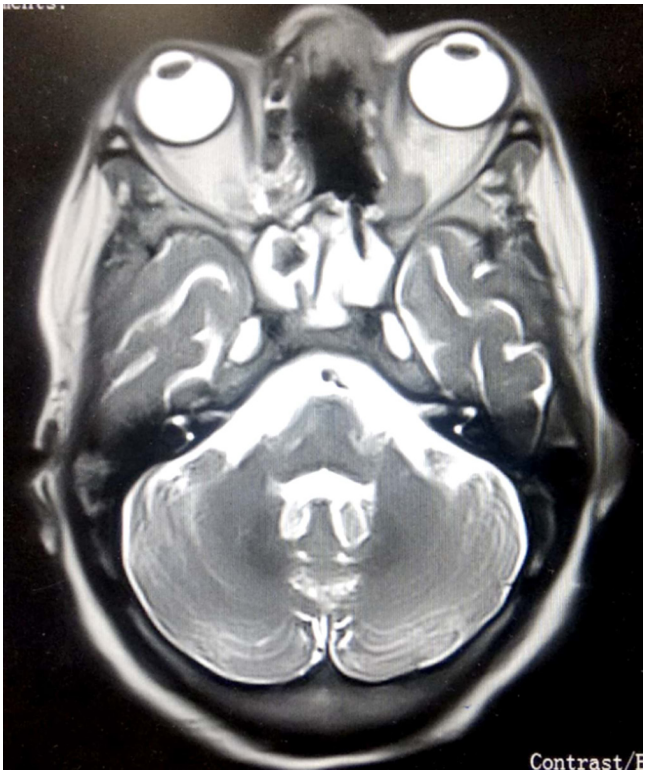

Fig. 6. After 2.5 months of treatment another MRI was carried out, which showed a significant decrease in the soft tissue problems. Fluid noted in the sphenoid sinus was likely postoperative collection.

Table 3. Management

Patient was started on intravenous amphotericin B at 1 mg kg^{-1} day^{-1} for 15 days.
Endoscopic debridement of the nasal crest was performed under general anaesthesia.
Based on culture reports, oral voriconazole at a dose of 200 mg twice daily was added to ongoing amphotericin B treatment after surgery.
After 2.5 months of treatment another MRI was carried out, which showed a significant decrease in the soft tissue problems. Fluid noted in the sphenoid sinus was labelled as postoperative collection.
The patient was discharged with a treatment of 200 mg oral voriconazole twice daily for 15 days, with advice for further follow-up every fortnight in the Otorhinolaryngology Outpatient Department.
After 3 months of follow-up, the patient showed complete recovery of the facial and nasal swelling and sinusitis.

isolates of *Rhizopus* species and *A. flavus* were sent to the Vallabhbhai Patel Chest Institute and All India Institute of Medical Sciences (AIIMS), Delhi, India, for molecular confirmation. Matrix-assisted laser desorption/ionization-time of flight (MALDI -TOF) MS confirmed the fungi as *Rhizopus arrhizus* and *A. flavus*.

DISCUSSION

Zygomycosis and aspergillosis are two serious fungal infections that generally present with a high case fatality rate, especially among immunocompromised patients [2, 10]. Our patient was known to have been suffering from diabetes for the previous 5 years with poor compliance to treatment, leading to a hyperglycaemic state. Such a state causes alteration in neutrophil chemotaxis, promoting opportunistic fungal infection, and was responsible for the state of the patient [11].

Co-infection of *Aspergillus* species and *Rhizopus* species was first reported in a case of fungal pneumonia in the year 2004 after the patient faced a near-drowning incident in The Netherlands [12]. Another case was reported from South Africa in 2015, where a case of oro-rhinocerebral disease caused by mucormycosis and aspergillus co-infection was found in a 54-year-old insulin-dependent diabetic patient. Although the patient was successfully treated with parenteral amphotericin B followed by oral posaconazole, she was left with irreversible blindness of the right eye and multiple cranial nerve palsies [13].

In India, a dual infection of invasive pulmonary aspergillosis and rhinocerebral zygomycosis was reported in 2009. Unfortunately, that patient did not respond well to treatment and succumbed to his illness, probably due to a delay in diagnosis and treatment [14]. Another case was reported from India in Gujarat in 2011, where co-infection of *Aspergillus* species and *Rhizopus* species in rhinocerebral sinusitis was contained by antifungal treatment and the patient made a full recovery [9]. In the current case, prompt diagnosis and treatment also controlled the fatal fungal co-infection, leading to complete recovery of the patient with no sequelae.

Thus, we can conclude that although there is no particular preventive measure available to curtail fungal infection in diabetic patients, with early diagnosis, proper treatment and good collaboration between surgeon and clinical microbiologist, the morbidity and mortality rates due to fungal sinusitis, especially dual infections, can be kept under control.

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Conflicts of interest
The authors declare that there are no conflicts of interest.

Ethical statement
Consent to publish has been obtained.

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