

## A case series of mucormycosis and *aspergillus* coinfection in post-covid-19 patient with uncontrolled diabetic

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### ABSTRACT

Mucormycosis is an angioinvasive infection caused by fungi Mucorales which mainly occurs in immunocompromised patients. Aspergillosis is also an opportunistic fungal infection caused by *Aspergillus* species. Coinfection with mucormycosis and aspergillosis is very rare and very few cases were published in the literature till now. There is an increase in the incidence of mucormycosis infection in post-COVID-19 patients. Here, we are going to report a case series of three cases of combined infection of mucormycosis with *Aspergillus*. All three patients were treated with extensive surgical debridement and intravenous liposomal amphotericin B. Even after aggressive treatment, the mortality rate is high in these types of patients.

**Keywords:** Aspergillosis, Coinfection, COVID-19, Mucormycosis

**M**ucormycosis is a rapidly destructive necrotizing fungal infection caused by fungi Mucorales and is mostly seen in diabetics and immunocompromised patients [1]. Among *Mucoraceae*, *Rhizopus oryzae* is the most common cause of infection [2]. Aspergillosis is a clinical condition caused by *Aspergillus* species, most often caused by *A. fumigatus* [3]. They occur mostly in immunocompromised patients like uncontrolled diabetics, those on chemotherapy, organ transplantation, and steroids [4]. Phagocytes are the major host defense mechanism against mucormycosis [5]. In addition, corticosteroid treatment affects the ability of macrophages to prevent the germination of the spores of these fungi. A hallmark of mucormycosis infection is the presence of extensive angioinvasion with resultant vessel thrombosis and tissue necrosis [6].

Reports of combined mucormycosis with *Aspergillus* infection are very rare. In the era of the COVID-19 pandemic, we have noticed that there is an increase in the incidence of invasive mucormycosis infections in COVID-19 patients. Here, we are going to share our experiences of three cases of combined mucormycosis and *Aspergillus* infection in patients with COVID-19 infection.

### CASE SERIES


#### Case 1

A 53-year-old male patient having diabetes and hypertension for the past 10 years was admitted to the emergency department with

complaints of fever associated with cough and headache for the past 18 days. Then, he developed swelling over the left cheek and the left side ptosis for the past 6 days. Initially, fever and headache subsided after the medication but reappeared when the medication was stopped.

On general examination, the pulse was 104 bpm, mouth temperature was 102°F, blood pressure was 126/86mm/Hg in the right arm in the supine position, and oxygen saturation was 96% on room air. Local examination of the face showed swelling over the left maxillary area which was around 4 × 3 cm in size. On initial investigation, random blood sugar level was 295 mg/dl, total leukocyte count (TLC) was 5540/cu mm, neutrophil was 77%, lymphocyte was 16%, monocyte was 5%, eosinophil was 02%, and basophil was 0%. Hemoglobin was 7.9 g/d and erythrocyte sedimentation rate (ESR) was 112 mm in the 1<sup>st</sup> h. Liver function and kidney function tests were within normal limits. After evaluation, computed tomography (CT) scan of the brain, orbit, and paranasal sinus (PNS) was advised which showed invasive fungal sinusitis of the left PNS with the left orbital involvement (Fig. 1).

After all pre-operative evaluation, extensive surgical debridement (medial maxillectomy +Lt-sided ethmoidectomy with sphenoideotomy) was done under general anesthesia by the surgical team. Necrotic tissues and fungal balls were removed from all approachable areas and some removed tissues were sent for microbiological and histopathological examination. On the KOH mount of the direct specimen, broad aseptated/septated hyaline hyphae with wide/acute angle branching were present (Fig. 2a).

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The specimen was also inoculated on Sabouraud dextrose agar (SDA) plate and incubated at 25°C and 37°C. On the 3<sup>rd</sup> day, two types of growth were seen in the culture plate (Fig. 2b and c). The growth was subjected to lactose phenol cotton blue (LPCB) mount preparation which showed *Rhizopus* spp. and *Aspergillus flavus* (Fig. 3). The patient received intravenous liposomal amphotericin B, followed by posaconazole. The patient became symptom free after the completion of treatment and in the next follow-up after 1 month, he was feeling good.

### Case 2

A 52-year-old diabetic female patient was admitted to our hospital with complaints of swelling over the right cheek region which was associated with jaw ache during chewing for the past 10 days. She recovered from the COVID-19 infection 1 month back. During the course of the disease, she was not maintaining her oxygen saturation and steroid therapy was used for 2 weeks. After recovery from COVID-19 pneumonia, she developed the above-mentioned symptoms and came to our hospital emergency.

At that time of admission, her pulse was 84 bpm, temperature was 96°F, and BP was 110/78 mm of Hg in the right arm. Local examination of the face showed swelling over the right cheek which was around 6 × 4 cm. On bedside evaluation, her random blood sugar level – 137 mg/dl, TLC – 8360/cumm, neutrophil – 67%, lymphocyte – 21%, monocyte – 3%,

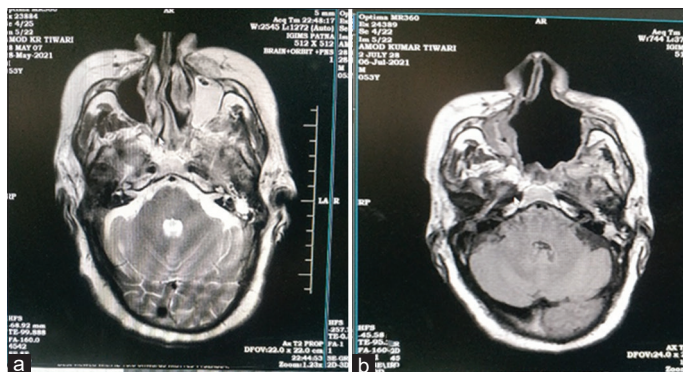


Figure 1: (a) Pre-operative MRI (T1 image) showing left maxillary sinus filled with fluid and soft tissue associated with pre-maxillary subcutaneous fat stranding and retroconal fat stranding; (b) post-operative MRI showing removal of left maxillary sinus and orbit (case 1)

eosinophil – 1.9%, basophil – 0%, and Hb – 10 g/d. Liver and kidney function tests were normal. In radiological evaluation, contrast-enhanced CT scan of the brain, orbit, and PNS showed invasive fungal sinusitis of the right PNS (Fig. 4). It was good to see that there was no orbital invasion which was present.

After all pre-operative evaluation, extensive surgical debridement of the PNS was done by the surgical team. Necrotic tissue was removed and sent to the microbiology and histopathological examination. KOH mount of the direct specimen showed broad aseptated/septated hyaline hyphae with wide/acute angle branching. The specimen was inoculated on an SDA plate and incubated at 25°C and 37°C. On the 3<sup>rd</sup> day, two types of growth on the culture plate were seen. The growth was subjected to LPCB mount preparation. LPCB mount of culture growth showed *Rhizopus* spp. and *Aspergillus flavus*. Intravenous liposomal amphotericin B was given to her followed by oral posaconazole. During treatment, she complained of mild headache which was subsided on taking paracetamol tablet. She recovered very well.

### Case 3

A 63-year-old male patient was admitted with complaints of blood mixed nasal discharge from the left nostril for the past 3 days. He recovered from COVID-19 pneumonia 15 days back which was treated with steroid therapy along with oxygen support.

On examination, his axillary temperature was 98°F and BP was 118/78 mmHg in the right arm. Blood mixed discharge was present over the left nostril. On initial investigation, random blood sugar was 138 mg/dl, TLC – 1040/cumm, neutrophil – 85%, lymphocyte – 7.3%, monocyte – 3%, eosinophil – 1.19%, basophil – 0%, and Hb – 9 g/d. The liver and kidney function tests were normal. CT scan of the brain, orbit, and PNS showed invasive fungal sinusitis of the left PNS. The orbital invasion was not seen (Fig. 5).

After all initial workup, extensive surgical debridement of the PNS was done. Necrotic tissue was removed and sent for microbiology and histopathological examination. KOH mount of the direct specimen showed broad aseptated/septated hyaline hyphae with wide/acute angle branching. On culture, *Rhizopus* species along with *Aspergillus flavus* were isolated. On the basis of this report, the medical team started intravenous liposomal

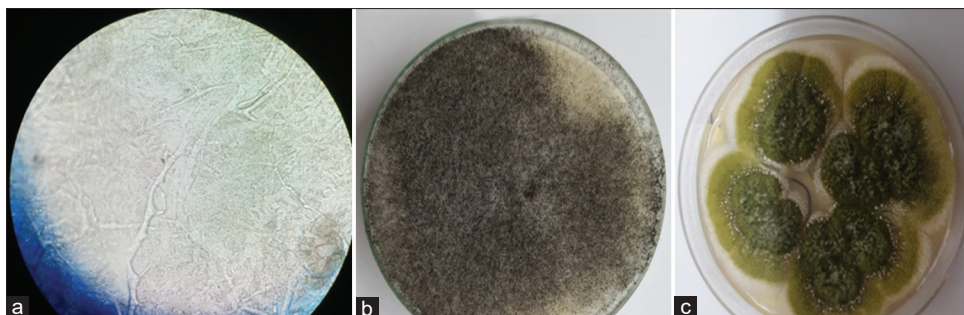
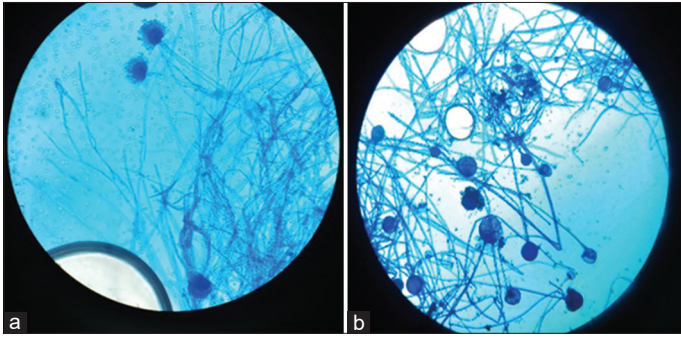
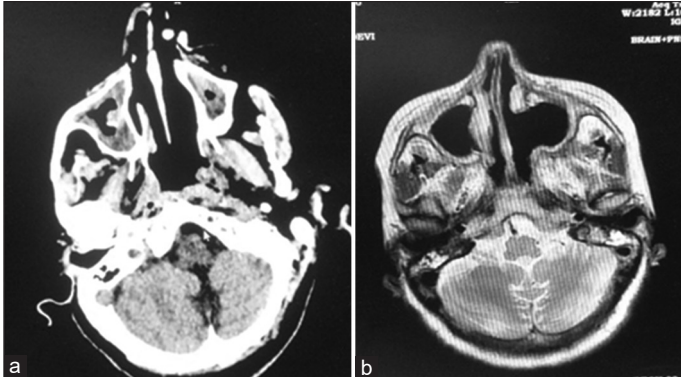


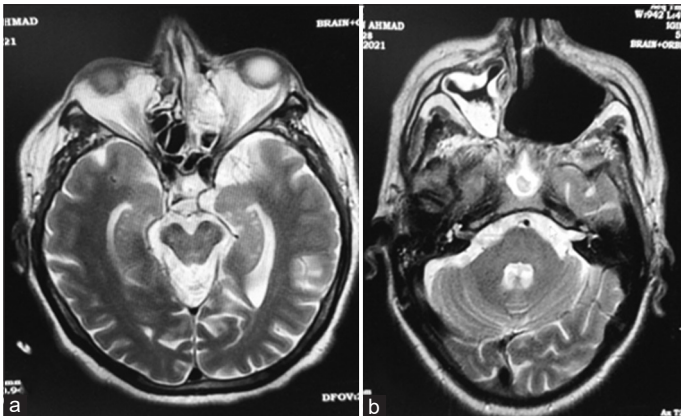
Figure 2: (a) KOH mount showed broad aseptated/septated hyaline hyphae with wide angle branching; (b) *Rhizopus* spp. – Obverse side of culture plate (SDA) – salt pepper-like growth; (c) *Aspergillus flavus* – Obverse side of culture plate (SDA) – yellowish-green velvety colony with white margin (case 1)



**Figure 3:** LPCB mount showing (a) biseriolate phialides covering entire vesicle with septated hyphae; (b) sporangium with sporangiophores and rhizoids



**Figure 4:** (a) Pre-operative CT brain and PNS showing bilateral mucosal thickening in both maxillary and sphenoid sinuses; (b) post-operative MRI (T2 image) showing mucosal resection and preservation of both maxillary sinuses (case 2)



**Figure 5:** (a) Pre-operative MRI (T2 image) showing mucosal thickening and fluid collection in cells of ethmoid sinus and mucosal thickening in the left maxillary sinus; (b) post-operative MRI showing single cavity formed after resection of maxillary sinus, ethmoidal sinus, and nasal septum

amphotericin B. After a full course of amphotericin B, the patient becomes symptom free.

## DISCUSSION

Mucormycosis itself is a very rare disease and the combined infection of mucormycosis with aspergillosis is very rare. We have seen that the incidence of mucormycosis infection was surprisingly increased in some states of India after the second wave of the COVID-19 pandemic, where it was declared as

an epidemic initially. The reason for this sudden rise was still not clear but one of the reasons for this association was the injudicious use of steroids for the management of COVID-19 pneumonia. Other possible reasons may be the use of industrial oxygen, contaminated masks, excessive use of vitamins, zinc, iron, and inappropriate use of steam inhalation which lead to local trauma of nasal mucosa, etc. One more important risk factor for the incidence of mucormycosis infection in these patients was uncontrolled blood sugar level. Here, we have reported a case series of combined infections of mucormycosis and aspergillosis in a post-COVID-19 patient with uncontrolled diabetes mellitus which is rare on normal days. Our patients were having uncontrolled blood sugar levels which is an important risk factor for mucormycosis.

Mucormycosis is caused by Mucorales. Among *Rhizomucor* and *Absidia*, *Rhizopus* is the most common genus causing mucormycosis. About 90% of cases of rhinocerebral mucormycosis is caused by *Rhizopus* spp<sup>3</sup>. Uncontrolled blood sugar levels can change the immunological defense response of the body to infections causing decreased granulocytic phagocytic activity with a change in polymorphonuclear leukocyte response. Reports have suggested that the ability of the serum of immunocompromised patients to inhibit *Rhizopus in vitro* is reduced, which makes them suitable hosts for opportunistic fungal infections. Furthermore, acidosis and high blood sugar level provide an excellent environment for the fungus to grow [7].

Aspergillosis is a clinical condition, which manifests in the human body as either invasive aspergillosis, pulmonary aspergilloma, or allergic bronchopulmonary aspergillosis [8]. It is most commonly caused by *A. fumigatus*. Aspergillosis is also an opportunistic pathogen similar to mucormycosis and commonly infects immune compromised persons. Invasive aspergillosis of the rhino-orbital-cerebral (ROC) region may spread to the adjoining regions and appears as yellow or black necrotic ulcers [9]. Delay in diagnosis or intervention will lead to massive tissue destruction and even death of the patient.

After reviewing the literature, we have found a few cases of combined fungal infections in immune compromised patients [10]. Through this case series, we have tried to highlight that a post-COVID-19 patient having uncontrolled blood sugar may have increased susceptibility for mixed fungal infection. Aqsa et al. published a case of combined infection in a patient with multiple myeloma [8]. Another similar case report of coinfection of mucormycosis and *Aspergillus* in a diabetic patient was published by Kumari et al. [11].

The management of such patients consists of aggressive treatment of underlying medical disease and associated comorbidities with correction of hypoxia, acidosis, hyperglycemia, and electrolyte abnormalities [12]. The drug of choice in invasive fungal infection is systemic amphotericin B, preferably liposomal preparation. All three cases of this case series were managed by the expert medical and surgical teams. The surgical team did extensive surgical debridement of the patients and systemic amphotericin B

was given to all three patients. These patients were called for follow-up after 1 month of discharge and found symptoms free by a team of clinicians.

## CONCLUSION

Coinfection of mucormycosis and *Aspergillus* in the same patient is a very rare finding in the normal scenario but if it occurs, can produce a severe life-threatening condition in susceptible patients. Therefore, there is a need for early suspicion along with early diagnosis and aggressive treatment which can reduce the mortality and morbidity in such patients.

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