A rare case report of post-COVID Mucormycosis-Aspergillosis co-infection

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Summary

Background and Purpose. Mucormycosis and Aspergillosis square measure the foremost frequent fungal infections caused by these filamentous fungi. Co-infection is scarce and involves a poor prognosis. The commonest presentation of invasive fungal infection (IFI) is rhinocerebral involvement. It generally affects immunocompromised patients.

Case Report. A 55-years-old post-COVID male patient with uncontrolled diabetes mellitus developed swelling and chemosis in the left eye. In plain computed tomography (CT) orbit, mucosal thickenings were seen in the ethmoid, sphenoid, left frontal, and left maxillary sinuses without any erosions or extensions. Nasal endoscopy showed black-brown overgrowth on the left middle turbinate. Biopsy revealed growth of both Mucor and *Aspergillus*. The patient, treated for diabetic ketoacidosis along with amphotericin-B for anti-fungal management, showed significant improvement, and is now stable.

Conclusions. To the best of our knowledge, it is the first case of co-infection with Mucormycosis (*Rhizopus* spp.) and Aspergillosis (*Aspergillus flavus*) in a post-COVID patient. An early diagnosis is a major advantage in its management. The multidisciplinary approach of such cases is invaluable. The implementation of higher diagnostic methods including polymerase chain reaction (PCR) in the diagnosis at all tertiary care facilities is mandatory.

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Introduction

Mucormycosis (MCM) is a rare opportunistic fungal infection caused by fungi belonging to the Mucorales order and the Mucoraceae family (1). It is a devastating infection with high mortality rates despite recent advances in its diagnosis and treatment. The filamentous fungi of the Mucorales order of the Zygomycetes class are the causative agent (14). The various predisposing factors for MCM are uncontrolled diabetes (particularly in patients with ketoacidosis), malignancies such as lymphomas and leukemias, renal failure, organ transplant, long-term corticosteroid, immunosuppressive therapy, cirrhosis, burns, protein-energy malnutrition, and acquired immune deficiency syndrome (AIDS) (9).

Another fungal infection is the one caused by *Aspergillus* spp., determining a broader constellation of pulmonary diseases, pathologically characterized by inflammation in the airway and acute and chronic invasion, largely depending on host risks. (6) Recent work in this direction has focused on describing the epidemiology and significance of Aspergillosis following severe viral infections, including influenza and coronavirus disease (COVID-19).

The commonest presentation of invasive fungal infection (IFI) is rhino-cerebral involvement (12). MCM and Aspergillosis square measure the foremost frequent fungal infections caused by these filiform fungi (16). Co-infection is scarce and carries a poor prognosis (15,4,13,10). It ordinarily affects immunocompromised patients.

Hereby, we report a rare case of rhino-orbital MCM (caused by *Rhizopus* species) in association with invasive Aspergillosis (caused by *Aspergillus flavus*) in a diabetic patient with poor glycemic control.

Case Report

A 55-years-old male patient was admitted with complaints of headache and generalized weakness for 10 days and swelling

around the left eye (Figure 1) with blurring of vision for 4 days. The patient was reported positive for SARS CoV-2 by RT-PCR 22 days before presentation, for which he was hospitalized with a chest computed tomography (CT) severity score of 17/25 and treated with oxygen, steroids, and ramdesivir therapy. He was reported negative 9 days after onset. However, he gradually developed complaints of headache, swelling of the left eye, and blurring of vision (left eye only), for which he was referred to our healthcare facility. The patient was a known case of type-II diabetes but was not undergoing any medical treatment.

On presentation, he had elevated blood pressure of 140/92mm of Hg which gradually returned to normal limits without any antihypertensive medication. On physical examination, the patient had bilateral crackles and wheeze on lungs auscultation. Periorbital edema with tenderness was present, along with conjunctival chemosis and mechanical ptosis. The other organs were apparently fine. Neurology, Ophthalmology, and ENT referrals were advised. In plain CT orbit, mucosal thickenings were seen in the ethmoid, sphenoid, left frontal, and left maxillary sinuses without any erosions or extensions. On the left nasal endoscopy, blackish-brown overgrowth with yellow-white patches was seen on the left middle turbinate (Figure 2) which was biopsied and sent for fungal culture and identification. The right nasal endoscopy proved to be normal.

Patient had random blood sugar of 306 mg/dL on presentation. Haemoglobin was 13.5g/dL (13-17), TLC 8.461x10^3/µL with marginal neutrophilia and lymphopenia in differential count ($N_{82}L_{11}E_3M_4$). Liver functions were raised with direct bilirubin 0.62mg/dL (<0.2), serum proteins 5.45gm/dL (6.0-7.8), and serum globulin 1.88gm/dL (2.0-3.5). Serum electrolytes were on the lower side, with sodium 133mmol/L (135-145) and potassium 2.6mmol/L (3.5-5.1). CRP and ESR-1hr (Wintrobe) were elevated with 20.7mg/L (0-6) and 15mm/1hr (up to 10), respectively, although D-dimer was 0.46µg/L (<0.50).

Tissue biopsy from the left middle turbinate for fungal and bacterial culture and sensitivity was sent to the Microbiology laboratory. On potassium hydroxide mount, non-septate branched hyphae (Figure 3) while on lacto-phenol-cotton-blue (LPCB) staining *Rhizopus* spp. were seen (Figure 4). Slide culture of Mucor can be appreciated in Figure 5. The fungal culture on plain Sabouraud Dextrose Agar (SDA) (Figure 6) showed *Aspergillus flavus* on microscopy on LPCB staining (Figure 7). Therefore, the patient was started on broad-spectrum intravenous antibiotics (amoxy-clavulanate and levofloxacin) and antifungals (amphotericin-B 300mg in intravenous fluids), monitoring renal function and input-output fluids. The patient was also given subcutaneous insulin, potassium chloride syrup, and intra-venous magnesium sulphate for diabetic ketoacidosis, and monitoring of fasting and post-prandial blood sugar levels was done. Blood sugar levels were monitored throughout admission.

Following the treatment, the patient has shown significant improvement.

Discussion

Rhizopus spp. and *Aspergillus* are two opportunistic fungi and IFIs have clinical and para-clinical similarities. Severe infections are disseminated involving multiple organs and are regularly fatal in immunocompromised patients (1,16,15,13). This co-infection is frequently described in patients with hematologic malignancies and severe neutropenia (1,15). People with diabetes often develop fungal infections. *Aspergillus* and *Mucorales* hastily invade tissues and unfold both locally and systemically in these patients (13,8). Both of these fungi are filamentous. They are ubiquitous in the environment, found in decaying natural substrates with vegetables and animal excreta.

Different species of *Aspergillus* and *Mucorales* exist. The most commonly found species are *Aspergillus fumigatus* and *Rhizopus*

Figure 1. Periorbital oedema of the left (L) eye in comparison to the normal right eye (R).

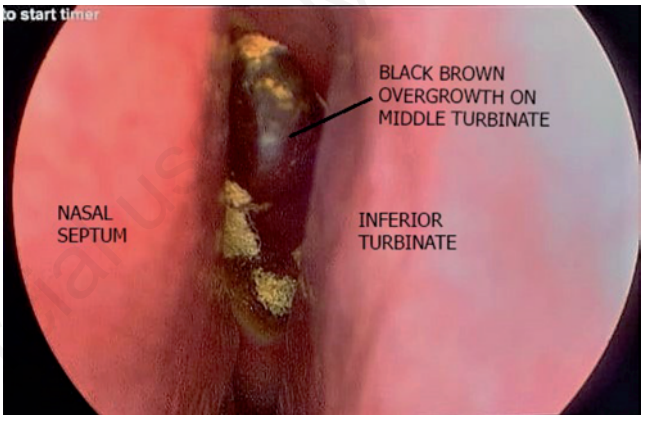

Figure 2. Endoscopic view of left nasal middle turbinate showing black-brown overgrowth with yellowish powdery patches.

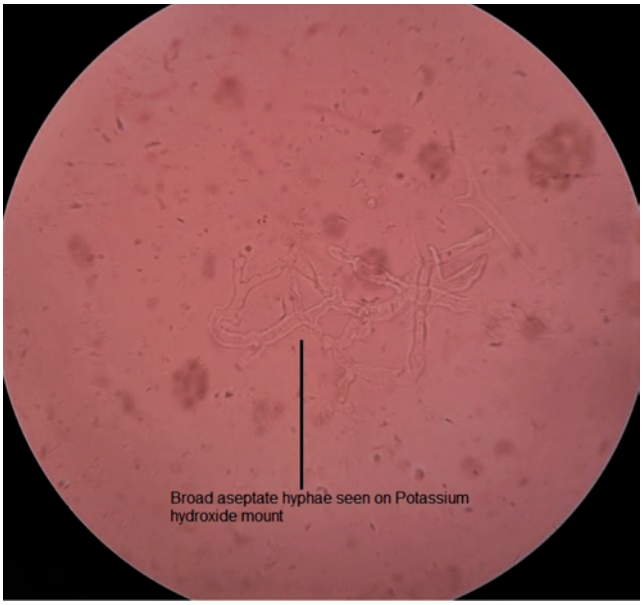

Figure 3. Branched aseptate hyphae are seen on potassium hydroxide mount.

spp., respectively (16). Contamination is primarily through the inhalation of spores. Acquisition via the cutaneous or percutaneous path also occurs with trauma disrupting skin, burns, direct injection, or catheters. *Aspergillus* spp. invades tissues, and inflammatory mediators arrive at the sites of infection, thereby causing damage (5). Effective immunological reaction in diabetic subjects with poor control is compromised. These patients have low granulocytic and phagocytic activity with an impaired polymorphonuclear leukocyte cell response. Immunocompromised patients inhibit *Rhizopus* poorly *in vitro*. Additionally, acidosis and hyperglycemia facilitate the fungus growth (13). Rhino-cerebral localization is typical in cases of diabetic patients, pulmonary localization in those with hematologic malignancies, and skin involvement in trauma patients (7). Presenting features in rhino-cerebral and oro-facial Mucormycosis resemble common causes of sinusitis.

Diabetes often masks the symptoms in such patients. Direct mycological and histological examinations are the gold standard for diagnosis. Delay in diagnosis or lack of appropriate treatment

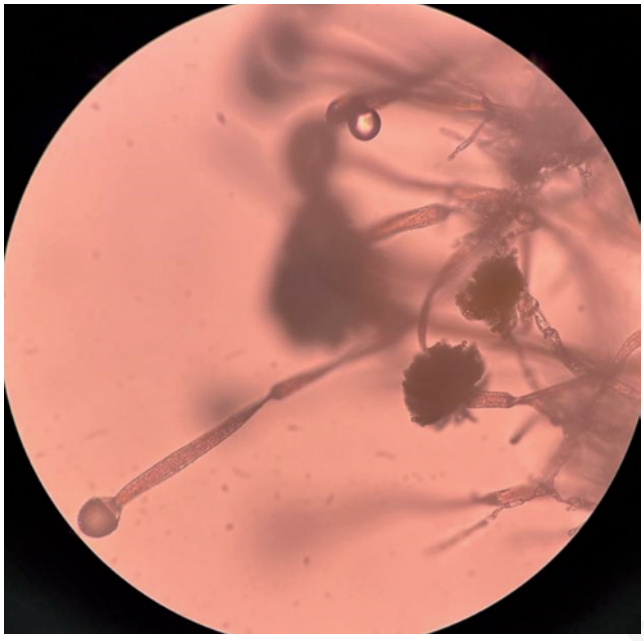

Figure 4. Rhizopus spp. on lacto-phenol-cotton-blue (LPCB) plain Sabouraud Dextrose Agar.

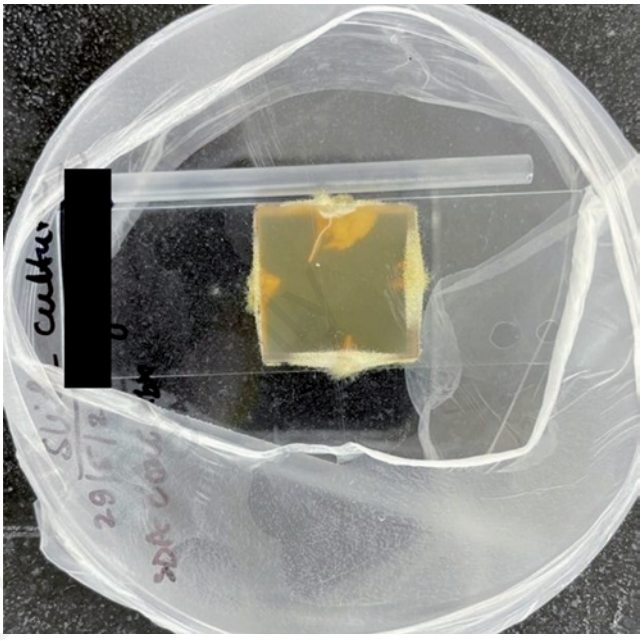

Figure 6. Slide culture of Mucor on Sabouraud Dextrose Agar (SDA) without antibiotic.

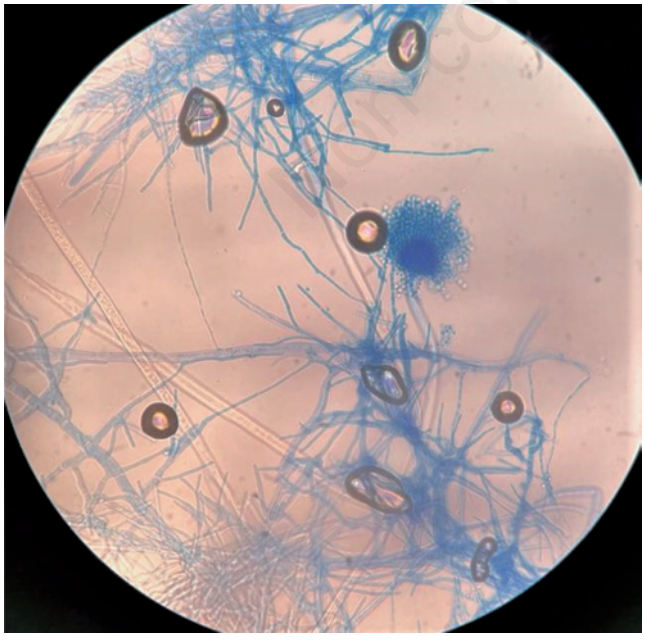

Figure 5. Aspergillus flavus as seen on lacto-phenol-cotton-blue (LPCB) staining from growth on Sabouraud Dextrose Agar (SDA) medium.

Figure 7. Growth on Sabouraud Dextrose Agar (SDA) without antibiotic.

may lead to massive tissue destruction and possible extension of the infection into the cranial base, vault, and orbit (10). Managing principles are: complete management of underlying medical disease, correction of hypoxia, acidosis, hyperglycemia, and electrolyte derangement (13). Amphotericin-B is active against most causative agents of Mucormycosis and Aspergillosis (14,3). In this case, the patient was treated with IV lyophilized amphotericin-B. Follow-up and secondary prophylaxis may also be necessary in some cases.

COVID-19 has recently been associated with a significant incidence of secondary infections, both bacterial and fungal probably due to immune dysregulation. The possibility of invasive secondary fungal infections in patients with COVID-19 infection, especially in those with pre-existing risk factors, should be kept in mind to enable early diagnosis and treatment with the subsequent reduction of morbidity and mortality (11).

Conclusions

With the invariable crisis and chaos caused during the COVID-19 pandemic, there was an urgency to provide oxygen and initiate the patient on steroid therapy at the earliest. Altered patient response to such exposures has resulted in the rise in cases of post-COVID fungal infections. Early diagnosis is a major advantage to the treating physicians for in-time management. This particular case, probably the first rare case of post-COVID co-infection of Mucormycosis (*Rhizopus spp*.) and Aspergillosis (*Aspergillus flavus*), might be an outcome of the contributory effect of immunocompromised state, high risk due to type-II diabetes, and induced steroid therapy for COVID management. A refined selection of post-COVID cases in higher numbers and cautious collection, as well as processing of patient specimens, will certainly provide higher chances of a definitive diagnosis and an early initiation of specific and efficient treatment. The multidisciplinary approach with the involvement of different specialists is invaluable. The implementation of higher diagnostic methods, including molecular methods, such as PCR, to speed up the diagnostics at all tertiary care facilities for the welfare of the increasingly reported cases, is recommended.

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