Mucormycosis in a patient with COVID-19 with uncontrolled diabetes

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SUMMARY
A wide range of bacterial and fungal coinfections may be associated with COVID-19. We report a case of rhino-orbital mucormycosis in a patient with COVID-19. A 67-year-old man, known case of diabetes, hypertension and ischaemic heart disease, was being treated for COVID-19 pneumonia when he developed right cheek eschar and ophthalmoplegia. Imaging studies revealed pansinusitis of bilateral maxillary and sphenoid sinuses with thickening and enhancement of right-sided soft tissue, lacrimal gland, mastication muscles, temporal lobe infiltrate and cerebellum infarct. Emergency right face debridement, right eye exenteration and bilateral functional endoscopic sinus surgery were done. Histopathological examination confirmed mucormycosis diagnosis. He was given amphotericin B and broad-spectrum antibiotics. It is important to have high index of suspicion for fungal coinfections in patients with COVID-19 with pre-existing medical conditions. There is a need to emphasise judicious and evidence-based use of immunomodulators in patients with COVID-19 to avoid triggering and flaring up of fungal infections.

BACKGROUND
Mucormycosis is an aggressive, deadly angio-invasive fungal disease caused by fungi of the order Mucorales.1 It has been reported in several studies from Pakistan in various patient groups; and using a prevalence of 0.14/1000 population with mortality of 38%, as computed in India, there are around 25,830 estimated cases in Pakistan.2–4 Immunocompromised individuals are susceptible to mucormycosis, and its feared complications of orbital and cerebral involvement are more likely in patients with diabetic ketoacidosis.5 Pakistan has a high prevalence rate of diabetes mellitus (DM) at 9.8%, which is a well-known risk factor of mucormycosis.2 COVID-19 may be associated with a wide range of bacterial and fungal coinfections. In this COVID-19 pandemic, only limited cases of rhino-orbital mucormycosis have been reported.6–7 We report a case of a patient with COVID-19 who developed rhino-orbital mucormycosis during his treatment.

CASE PRESENTATION
A 67-year-old man, known case of DM, hypertension (HTN) and ischaemic heart disease, was referred to our hospital with a black lesion on his right cheek and right eye swelling. He was being managed in another hospital for non-severe, reverse transcription-PCR-positive COVID-19 pneumonia and uncontrolled DM. On day 3 of his treatment, he had developed right eye swelling and black lesion on his right cheek. He was getting remdesivir, meropenem, linezolid and fluconazole, and was referred to our hospital for further management.

On arrival to the emergency department, he was vitally stable with right eye ophthalmoplegia and had black eschar on the right cheek and hard palate (figure 1). The rest of the systemic examination was unremarkable. Baseline workup, along with blood culture, throat and nose samples for fungal smear and culture, was sent. CT of the chest for COVID-19 screening and CT of the facial region with contrast were ordered. Ear, nose, and throat and infection diseases teams were taken on board and the patient was started on meropenem, vancomycin and amphotericin B. MRI of the head was advised after neurology and ophthalmology input.

INVESTIGATIONS
Baseline workup showed normal creatinine, hypokalaemia (K=2.5), elevated total lymphocyte count (14) with neutrophils of 87.4 and elevated C reactive protein of 153. Urine detail report was positive for mild proteinuria, glucosuria with ketones 3+ and haematuria. He had a glycated haemoglobin of 11.9 with positive galactomannan and negative beta D-glucan. Blood and urine cultures did not grow any microorganisms. Nasal and throat fungus smear/potassium hydroxide preparation revealed few broad coenocytic (A-septate) hyphae, moderate budding yeast cells with pseudohyphae and culture-grown Rhizopus spp.

CT of the chest with COVID-19 screening protocol revealed multifocal patchy areas of ground-glass haziness involving right lung field and left lower lobe suggestive of COVID-19 infection.

CT of the facial region with contrast showed abnormal soft tissue thickening in the region of the right side of the face with thickening and enhancement of right lacrimal gland, mild pre-septal swelling, thickening and enhancement of temporalis, lateral pterygoid and muscles of mastication on the right side. These findings were likely representing infected/inflammatory process (figure 2). There was pansinusitis with air fluid levels in bilateral maxillary sinuses and sphenoid sinuses. Pneumatised petrous temporal bone apex was visualised with fluid within it. There were ill-defined hypodensities in bilateral cerebellar hemispheres and right temporal lobe. These findings indicated possibility of an infarction.

MRI of the head revealed abnormal T2 hyper-intense signals in the right infratemporal region involving the pterygoid muscles and extending into the right side of the face and the pre-septal region.

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Superiorly they were extending intracranially and were infiltrating into the right temporal lobe. These were likely secondary to infective process. There were abnormal T2 hyperintense signals showing diffusion restriction in the right cerebellum and the pons representing an acute infarct. Subtle acute lacunar infarcts at the posterior aspect of the bilateral lateral ventricles were also visualised.

DIFFERENTIAL DIAGNOSES
On initial presentation, our list of differential diagnoses included mucormycosis, orbital cellulitis, cavernous sinus thrombosis and orbital tumour. The acute history, physical examination findings, ongoing COVID-19 infection, history of long-standing diabetes,

and growth on fungal smear and cultures helped us in establishing a working diagnosis of mucormycosis.

TREATMENT
Emergency right face debridement, right eye exenteration and bilateral functional endoscopic sinus surgery were performed, and the patient was shifted to intensive care unit (ICU) (figure 4). DM and HTN medications were optimised and feeding nasogastric (NG) tube was placed after swallowing assessment. The patient was on vancomycin for 5 days, and remained on intravenous amphotericin B and intravenous meropenem during his hospital stay.

Histopathology examination of the biopsy specimen showed right cheek skin and right eyeball invaded by numerous aseptate fungal hyphae and multiple nasal tissue pieces exhibiting numerous aseptate fungal hyphae which further supported our working diagnosis.

OUTCOME AND FOLLOW-UP
Postoperatively, head CT scan showed interval removal of the right orbital structures with soft tissue removal of the right cheek with interval packing of the defects (figure 5). Interval maturation in the infarcts in the right cerebellum, right hemipons and right temporal lobe was visualised. There was redemonstration
of the high-density material in the bilateral sphenoid and left maxillary and bilateral ethmoid sinuses.

Once the patient’s condition was stable, he was discharged on antifungal (intravenous amphotericin B), broad-spectrum antibiotic (intravenous meropenem), antihypertensive (valsartan, amlodipine), antidiabetics (sitagliptin and insulin glargine) and feeding NG tube with instructions for daily dressings of wound and follow-up in the outpatient clinic after 1 week. At follow-up clinic visit, the patient had remained afebrile with a healthy, healing wound and no postoperative complications were reported.

DISCUSSION
Coinfections with COVID-19 are increasingly being recognised in view of its impact on the prognosis of the disease. A recent review reported 62 of 806 (8%) secondary bacterial or fungal infections and a widespread use of broad-spectrum antibiotics (1450 of 2010, 72%) often with no underlying evidence of infection. Complex interplay of multiple factors, including comorbidities, use of immunosuppressive therapy, risk of hospital-acquired infections and alteration of immune system by COVID-19, may be responsible for coinfections.

There are specific pathophysiological features of COVID-19 that may predispose an individual to secondary fungal infections. First, there is immune dysregulation with reduced numbers of T lymphocytes, CD4+ T cells, CD8+ T cells, and markedly higher levels of interleukin (IL)-2 receptor, IL-6, IL-10 and tumour necrosis factor-alpha. Second, there is propensity of the SARS-CoV-2 to cause extensive pulmonary disease and subsequent alveolo-interstitial pathology may enhance the risk of invasive fungal infections, specifically those with a primary pulmonary entry such as mucormycosis, pneumocystis and invasive pulmonary aspergillosis.10

A retrospective interventional study from India reported five cases of rhino-orbital mucormycosis in uncontrolled, diabetic, COVID-19-positive patients treated with systemic corticosteroid.11 An observational study from Pakistan identified 15.6% fungal infection rate in patients with confirmed COVID-19 who required ICU admission.12

A national multicentre prospective cohort study conducted in UK reported an incidence of invasive fungal infections of 26.7% with higher mortality in invasive compared with non-invasive fungal infections (53% vs 31%, respectively). Corticosteroid therapy and a history of chronic pulmonary disease were associated with a higher risk of invasive fungal disease.13

The patient we reported had long-standing, uncontrolled diabetes and the signs of rhino-orbital infection were noticed only 3 days after admission for COVID-19 infection. These factors may have contributed towards the patient developing mucormycosis coinfection.

Therefore, it is important to have a high index of suspicion and low threshold for fungal coinfection in patients with COVID-19 with pre-existing medical conditions. Furthermore, suspected cases should undergo immediate imaging and specific diagnostic studies with collaborated effort from multidisciplinary teams, including infectious diseases, otorhinolaryngology, ophthalmology, neurosurgery, critical care, microbiology and pathology departments. Prompt recognition and management is necessary in cases of invasive rhino-orbital mucormycosis, as a delay of only 6 days in recognition can double the 30-day mortality from 35% to 66%.11 There is a need to emphasise on the judicious and evidence-based use of immunomodulators to avoid triggering and flaring up of the fungal infections.

Contributors MS was involved in conception of the study and collected patient data (history and investigations) from various sources and interpreted them for the generation of this manuscript. He took part in writing the introduction and case presentation and participated in literature review. He also provided important intellectual input during critical review of the manuscript. MHM was involved in the case presentation and discussion segment of the manuscript. He was also involved in data collection and interpretation, performed literature review and gave intellectual input during critical review of the manuscript. SW was involved in writing the discussion and conclusion segments and was involved in formatting of the final manuscript. He supervised the data collection and coordinated the critical revision process. All authors reviewed and approved the final draft of the manuscript for submission.

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