ABSTRACT Invasive mucormycosis, a dreaded and debilitating fungal infection, referred to as ‘black fungus’ is being increasingly seen as a sequela of SARS-COV2 pneumonia. This is a highly invasive infection that arises on the background of an immunocompromised state and can cause extensive necrosis and bony destruction of the paranasal sinuses, orbit and surrounding tissues. In addition to antifungal drugs, treatment often involves aggressive surgical debridement including exenteration of the orbit. We describe four cases of mucormycosis that presented soon after treatment for SARS-COV2 pneumonia and their radiological findings and discuss risk factors, treatment and preventive measures.

KEYWORDS Mucormycosis, Black fungus, maxillectomy, paranasal sinusitis

Introduction
We present a case series of invasive mucormycosis in patients with a history of COVID-19 infection. We discuss the prevalence of fungal co-infection in COVID-19, as well as the diagnostic and management challenges.

Case presentation
Case 1
A 51-year-old female, diabetic on oral anti-hypoglycemic agents, presented with a history of mild covid pneumonia one month back, was hospitalized for 15 days and treated with methylprednisolone and remdesivir. She was discharged with the same corticosteroid and nintedanib. Two days after discharge, she started developing headaches, jaw pain, periorbital swelling, reddish nasal discharge and right cheek swelling. On examination, her right cheek was swollen and tender, with inflammation seen in the right half of the gingiva and palate. There was bleeding to touch, with no blackish discolouration or discharge. Her vital parameters were normal. Investigations showed random blood sugar (RBS) 230 mg/dl (normal < 140mg/dl) and HbA1C of 9.4% (normal < 6.4%). MRI paranasal sinus (PNS) and correlative CT scan were done. Fig 1a (CT PNS bone window axial cut) shows right-sided invasive fungal sinusitis with the erosion of the wall of the right maxillary sinus, right superior alveolus, ipsilateral palatal process and extension to the left superior alveolar and palatine process. Fig 1b (MRI PNS Coronal T2 view fat-suppressed) shows oedema in the right premaxillary and pterygopalatine fossa region. Fig 1c (MRI PNS Axial T1 fat-suppressed post-contrast) shows absent mucosal enhancement along the anterior wall of the right maxillary sinus with abnormal enhancement in the right perimaxillary and pterygopalatine fossa region. She was taken up for functional endoscopic sinus surgery (FESS), debridement and extended maxillectomy. Because of difficulty in feeding, a percutaneous endoscopic gastrostomy (PEG) tube was inserted. Tissue culture grew Rhizopus species. Post-operatively, she was started on intravenous liposomal amphotericin B at 5mg/kg/day and continued to do well, with adequate wound healing.

Case 2
A 66-year-old female, known hypertensive, presented after being treated for COVID pneumonia in the previous month with remdesivir and corticosteroid, then discharged with corticosteroid. She gradually progressed, painful right eye swelling for ten days, from the day after discharge, associated with decreased vision. There was a right-side nasal block and blood-stained nasal discharge. Her vital parameters were normal. RBS was 130 mg/dl and HbA1C 9.2%, and other investigations were
normal. The right eye examination showed proptosis, periorbital swelling, absent eye movement, and pupil dilated and unresponsive to light. Nasal endoscopy showed black eschar along the wall and septum of the right nostril and the right side of both soft and hard palate. MRI PNS and correlative CT showed signs of mucormycosis. In Fig 2a (MRI PNS Axial T2), the green arrow shows mucosal thickening in right anterior ethmoid air cells, and the red arrow shows right intra-orbital fat stranding causing proptosis. Fig 2b (MRI PNS T1 Post-contrast coronal view) shows the ‘black turbinate’ sign, a patchy area of non-enhancement in the right inferior turbinate, compared to the left inferior turbinate. Fig 2c (MRI PNS T1 fat-suppressed post-contrast axial view) shows non-enhancing areas in the right cavernous sinus – a sign of possible thrombosis. She underwent emergency right total maxillectomy, orbital exenteration, septectomy and nasal bone removal, along with PEG tube insertion. Tissue examination showed broad, aseptate, hyaline, wide-angle branching fungal hyphae, suggestive of mucorales. Post-operatively, she was started on Tab Posaconazole 300mg due to the non-availability of Amphotericin-B for the initial two days. Her remaining hospital stay was uneventful.

Case 3

A 46-year-old male patient with no known comorbidities presented with severe left eye pain, swelling and left frontal headache for 3 days. He had been hospitalized for about 25 days in the previous month with COVID-19 pneumonia and treated with corticosteroids and antibiotics. At discharge, he had left-sided migraine, treated with dexamethasone. He presented with RBS of 177 mg/dl and HbA1C of 7.8%, and other tests were normal. On examination, he had breathlessness on exertion and talking, but vital parameters were normal. Left eye examination revealed eyelid oedema, conjunctival congestion and pre-septal abscesses, but vision and eye movements were intact. CT Orbit and MRI PNS have done elsewhere were suggestive of rhino mucormycosis with pansinusitis. He underwent emergency left side medial maxillectomy, ethmoidectomy and sphenoidotomy and FESS. Tissue culture grew absidia species. He was started on intravenous lyophilized amphotericin-B at 1mg/kg, as the liposomal formulation was unavailable. Renal parameters and platelet counts were monitored daily. Liposomal amphotericin-B was available from post-operative day 4 and started at 5mg/kg/day iv. The remaining course in the hospital was uneventful.

Case 4

A 65-year-old male, known diabetic, was diagnosed with Covid-19 pneumonia 45 days back and treated with antibiotics and parenteral steroids. He now presented with swelling and numbness of the right side of the face, gradually worsening for 1 month associated with toothache and loosening of teeth. RBS was 163 mg/dl and HbA1C 9.2%. CT scan and MRI PNS were done. Fig 3a (CT PNS soft tissue window coronal view) shows right maxillary sinus mucosal thickening with fat stranding in retroantral, pterygopalatine and right orbit. Fig 3b (MRI PNS T1 fat-suppressed post-contrast axial view) shows abnormal enhancement in the right premaxillary and pterygopalatine fossa region. He underwent right-sided total maxillectomy, ethmoidectomy, sphenoidotomy, inferior and middle turbinectomy, and debridement of infratemporal fossa and vidian canal, along with PEG tube insertion. Tissue culture grew Rhizopus species.

Discussion

Mucormycosis, known by the more ubiquitous term black fungus, is a life-threatening, angioinvasive infection caused by fungi in Mucorales, which has a predilection for skin, nasal sinuses and lungs. Its prevalence in India is estimated to be around 70 times higher than globally. [1] Disseminated mucormycosis has a rapidly progressive course, characterized by direct invasion and necrosis of nasal and sinus mucosa followed by invasion into the orbit, brain, lung and other organs. The most commonly isolated genera include Rhizopus, Mucor, Rhizomucor and Absidia. Cunninghamella is a rare but more virulent strain. Overall mortality is 40-80% and is dependent on various factors and underlying comorbidities, with higher mortality seen in disseminated mucormycosis. [2-5]

The present case series highlights the rapid onset and destructive nature of this disease—all four patients presented following SARS-COV2 pneumonia treated with corticosteroids and had high blood sugars at admission. Duration of symptoms ranged from 2 days to 1 month before presentation. Symptoms were unilateral and included eye pain, swelling and numbness. The common radiological findings were inflammation of the paranasal sinuses with the destruction of surrounding bones and extension into the orbit.

Mucormycosis associated with COVID-19 infection in India was first reported in Surat, Gujarat, in May 2021, and since
then, it has rapidly increased in number. The hyperinflammatory response seen in coronavirus infections along with an immunosuppressed state resulting from the use of steroids and immunosuppressive agents has been hypothesized to create a favourable environment for fungal coinfections. [6] Other risk factors for mucormycosis include hyperglycaemia, injudicious use of steroids, inappropriate antibiotics, immunodeficiency states such as HIV and post hematopoietic stem cell transplant, iron overload, chelating agents, prolonged ICU stay, malnutrition, infected linens and use of unsterile water in humidifiers. [3,7,8]

Clinical features vary from mild cutaneous illness to fulminant, disseminated infections. [8] Clinical features include fever (44%), headache, cheekbone pain, nasal blockage (38%), black or bloody nasal discharge, diplopia, decreased vision (30%), periorbital pain and oedema (34%). In addition, hard/soft palate examination shows blackish pigmentation, which is a hallmark for mucormycosis.

Cutaneous mucormycosis is the most common type and carries the most negligible mortality (4-10%), characterized by indurated plaques, nodules and ulcers. Pulmonary mucormycosis is the second most common and causes dyspnoea. As seen in these case series, Rhino orbital mucormycosis is most commonly noted in people with diabetes.[2] Disseminated mucormycosis has the highest mortality.[9]

Initial investigations include complete blood count, which may decrease absolute lymphocyte count, renal function test, blood sugars and serum ferritin. High serum ferritin may pose a risk factor for Mucorales infection since fungi thrive in an iron-rich environment.[7] Radiological investigation of choice is magnetic resonance imaging (MRI) with contrast, which shows loss of contrast enhancement. Computed tomography (CT) is less sensitive than MRI and is used for tissue sam-
There are no conflicts of interest to declare by any of the authors. This work did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Prevention of mucormycosis includes measures such as using clean linen[15] and sterile water in humidifiers.[16] Simple bedside tests like ocular motility, conjunctival reflexes, sinus tenderness, ocular swelling, and palatal examination can help detect mucormycosis in hospitalized patients.[6]

**Conclusion**

The above case series highlights the morbidity and difficult management decisions associated with invasive mucormycosis. SARS-COV2 patients on systemic corticosteroids should be monitored for early warning signs of this disease. In addition, restricted use of steroids and tighter glycemic control with improved hygiene practices can help prevent.

**Funding**

This work did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Conflict of Interest**

There are no conflicts of interest to declare by any of the authors of this study.

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