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COVID-19 associated mucormycosis: a life-threatening complication in patients admitted with severe to critical COVID-19 from Pakistan

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To the editor

Mucormycosis is a life-threatening infection that most commonly occurs in patients with uncontrolled diabetes mellitus and/or immunocompromised status [1]. Patients with severe to critical coronavirus disease 2019 (COVID-19) infection have been recently identified as an at-risk population for mucormycosis with reports of COVID-19-associated mucormycosis (CAM) from many countries [2,3]. Here, we describe ten cases of CAM with high mortality from Pakistan.

This observational study was conducted in adult patients with PCR-confirmed severe COVID-19 infection from July 2020 to May 2021 at a 700-bedded tertiary care centre in Karachi, Pakistan. Patients were classified as having severe or critical COVID-19 based on WHO clinical criteria. Mucormycosis was diagnosed based on clinical, radiological, culture, and/or histopathological findings. Individuals with proven disease were classified as having proven mucormycosis if they had clinical or radiological evidence of invasive disease, with histopathological findings of mucormycosis and/or if Mucorales were identified by culture of a sterile specimen. Identification of individuals with probable disease was based on recently updated criteria of the European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG) [4].

A total of 2839 individuals with confirmed COVID-19 were admitted from July 2020 to May 2021 and 280 required mechanical ventilation, of whom, ten were identified as having CAM (four proven, six probable). Details of these patients are listed in Table 1. The median age of CAM patients was 63 years (range 33–86 years) with male to female ratio of 3:2. Seven out of ten patients had underlying diabetes (well-controlled in two and uncontrolled in five patients with glycated haemoglobin (HbA1c) ≥6.5% and two had haematological malignancies and were undergoing chemotherapy. Three required invasive mechanical ventilation for acute respiratory distress syndrome due to COVID-19, eight received systemic steroids and two had received intravenous tocilizumab for severe to critical COVID-19. The median duration of illness with COVID-19 before the diagnosis of mucormycosis was 16 days (range 12–20 days). One case was unique in which the diagnosis was made retrospectively when the patient worsened post-chemotherapy and was readmitted with pulmonary mucormycosis and later tested positive for severe acute respiratory syndrome coronavirus 2. Six out of ten patients had pulmonary mucormycosis and four had rhino-cerebral mucormycosis. Rhizopus spp. was isolated in seven, Mucor spp. in two, and in one patient aseptate hyphae from nasal tissue failed to grow on culture. Five patients had additional organisms on culture: four had Aspergillus spp., two had Pseudomonas aeruginosa and two had Klebsiella pneumoniae. Among patients with pulmonary mucormycosis; two had a haematological malignancy (diffuse large B-cell lymphoma and acute myeloid leukaemia), for which they were receiving chemotherapy, and two had chronic lung disease with one having post-tuberculosis bronchiectasis and one having severe pulmonary hypertension requiring long-term oxygen therapy. Three of the six patients with pulmonary mucormycosis required invasive mechanical ventilation and the remaining three required non-invasive ventilation support. None of the patients with pulmonary involvement survived despite treatment with amphotericin B deoxycholate. Three patients with rhino-cerebral involvement underwent surgical debridement along with enucleation of eye and maxillectomy/or ethmoidectomy. Histopathology of the tissues from all patients with rhino-cerebral involvement revealed acute
| Case | Age | Sex | Risk factors/Underlying conditions | ICU procedures | Corticosteroids before mucormycosis/Days of therapy | Site of infection (mucormycosis)/Days post-COVID diagnosis | Classification | Radiology | Mycological evidence | Co-infection | Outcome | Cause of death |
|------|-----|-----|-----------------------------------|----------------|----------------------------------------------------|-----------------------------------------------------|---------------|------------|---------------------|--------------|----------|-------------------|
| 1    | 62  | M   | Critical COVID-19                | Mechanical ventilation | Yes/10 (methylprednisolone) | Lungs/14 | Probable | CXR: Increase in patchy airspace opacification in bilateral lung zones with new consolidation in right lower lung zone | Positive tracheal aspirate culture | Aspergillus fumigatus, Pseudomonas aeruginosa | Died | ARDS, Multi-organ dysfunction |
| 2    | 77  | M   | DM, HTN, critical COVID-19       | Mechanical ventilation | Yes/10 (dexamethasone, later switched to methylprednisolone) | Lungs/18 | Probable | CXR: Increase in peripheral airspace shadowing in bilateral mid and lower lung zones | Positive tracheal aspirate culture | NA | Died | Septic shock |
| 3    | 50  | F   | DM (HbA1c 11.4), CKD, metabolic acidosis | Haemodialysis | Yes/10 (dexamethasone) | Rhino-orbital cerebral/16 | Proven | MRI Orbits with contrast: Bilateral exophthalmos with thickening of extraocular muscles. Significant facial soft-tissue swelling sub-periosteal abscess glabella | Positive nasal tissue culture Histopathology of extraocular tissue and bony trabeculae of sinuses | Aspergillus niger, Aspergillus nidulans | Died | Septic shock, multi-organ dysfunction, lactic acidosis |
| 4    | 33  | M   | DLBCL, on chemotherapy, critical COVID-19 | Mechanical ventilation | No (last chemotherapy 2 months ago) | Lungs/10 | Proven | CXR: New consolidation in the right upper lobe and infiltrates in the right lower lobe with right paratracheal lymphadenopathy | Positive bronchoalveolar lavage culture | NA | Died | ARDS, Arrhythmias |
| 5    | 86  | F   | DM, HTN, severe pulmonary hypertension, on LTOT, atrial flutter | Non-invasive ventilation | Yes/18 (methylprednisolone) | Lungs/20 | Probable | CT Chest: Diffuse areas of ground-glass haze with multifocal consolidations involving bilateral lung fields associated with interlobular septal thickening. Few consolidations with cavitary changes | Positive tracheal aspirate culture | Carbapenem-resistant Klebsiella pneumoniae | Died | ARDS, Arrhythmias |
| 6    | 35  | M   | AML on induction chemo (Day 23), febrile neutropenia, critical COVID-19, DIC, AKI | Non-invasive ventilation | Yes/14 (dexamethasone) | Lung/12 | Probable | CXR: Patchy bilateral airspace opacification in bilateral mid and lower lung zone, became better-defined and dense, suggesting progression | Positive tracheal aspirate culture | NA | Presumed to have died (LAMA in critical condition) |
| 7    | 53  | F   | DM (HbA1c 10.5), HTN, IHD, COVID-19 with CVST | NA | Yes/duration and type unknown | Rhino-cerebral/146 | Proven | CT head: Sinusitis involving bilateral sphenoid air cells with secondary peristeitis of the sphenoid bone. MRI with skull base osteomyelitis | Nasal tissue smear showed ascepte hypheae but failed to grow on culture | Ceftriaxone-resistant Klebsiella pneumoniae and Aspergillus fumigatus | NA | Lost to follow up |
| 8    | 67  | M   | DM (HbA1c 11.9), IHD, non-severe COVID-19 | NA | No | Rhino-orbital cerebral/12 | Proven | MRI brain: Abnormal T2 hyperintense signals in the right infratemporal region involving the pterygoid muscles with right-sided facial extension and intracranial extension in right temporal lobe | Positive nasal tissue culture Histopathology of enucleated eye Histopathology of right nasal turbinates | NA | Under-treatment |
| 9    | 69  | M   | DM (HbA1c 7.8), HTN, IHD, COPD, post-TB bronchiectasis, S/P left lung pneumonectomy | Non-invasive ventilation | Yes/18 days (methylprednisolone) | Lung/20 | Probable | CXR: New development of patchy opacity in the right mid-lung zone | Positive tracheal aspirate culture | Aspergillus fumigatus, Pseudomonas aeruginosa | Died | ARDS, Septic shock | (continued on next page)
and chronic inflammation along with broad aseptate hyphae invading blood vessels and bony trabeculae.

All patients received amphotericin B deoxycholate (1.5 mg/kg/day) for treatment. Three of the four patients with rhino-orbital cerebral mucormycosis underwent surgical debridement and enucleation of the eye. Five patients died as the result of CAM and two patients left the hospital against medical advice in critical condition and were presumed to have died. Two patients are under treatment and one is lost to follow up. The median duration from the time of diagnosis of mucormycosis to the last follow up was 4.5 days (interquartile range (IQR) 2–13 days) due to five deaths; and the median duration from diagnosis of COVID-19 to the last follow up was 18 days (IQR 18–29 days).

We found that mucormycosis can complicate severe COVID-19, particularly in patients with underlying uncontrolled diabetes and those who receive systemic steroids. Moreover, the case fatality rate was high in this cohort. Mucormycosis is a rare but lethal infection with high mortality rate, especially in developing countries. CAM remains an under-recognized entity given the difficulty in diagnosing this infection in resource-constrained settings [3].

Since the earliest cases of CAM that were published from India and UK, the incidence of CAM has been gradually increasing [3]. In the setting of severe COVID-19 where patients are treated with high-dose systemic steroids, patients who already have diabetes may develop steroid-induced hyperglycaemia, putting them at risk for mucormycosis. The majority of CAM cases have been reported from India [3]. This is consistent with an increased overall incidence from this region and is expected to be similar to Pakistan owing to the similarity in the environment, the prevalence of diabetes mellitus, and other risk factors. Although pulmonary mucormycosis predominated in our case series; rhino-cerebral mucormycosis has been the most common site of infection reported in COVID-19 patients [3]. Furthermore, we had two individuals with mixed mould infection, which has been previously reported in only one case report from France [5].

Mortality in our cohort was higher than global data reporting CAM from 18 countries (70% versus 49%) [3]. However, the disproportionately higher number of pulmonary mucormycosis (which carries a poorer prognosis), may explain this difference. High mortality with pulmonary mucormycosis is concerning because of the difficulty in diagnosis and limited awareness, especially in resource-limited settings.

The study is the first detailed description of CAM cases from Pakistan and recommends keeping a high index of suspicion in patients with suggestive clinical findings who have received steroids for severe COVID-19.

**Transparency declaration**

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**Author contributions**

NN, JF and KJ contributed to conceptualization; NN and KJ contributed to validation and wrote the original draft; and JF and KJ curated the data. All authors worked on the methodology and on reviewing, editing and approving the article.
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