Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Microbiology and Infection 27 (2021) 1704–1707

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Letter to the Editor

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

Nosheen Nasir [1], Joveria Farooqi [2], Syed Faisal Mahmood [1], Kauser Jabeen [2,*]

[1)] Department of Medicine, Aga Khan University, Karachi, Pakistan
[2)] Department of Pathology and Laboratory Medicine, Aga Khan University, Karachi, Pakistan

ARTICLE INFO

Article history:
Received 6 July 2021
Received in revised form
23 July 2021
Accepted 26 July 2021
Available online 8 August 2021

Editor: L. Leibovici

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) $\geq$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

* Corresponding author. Kauser Jabeen, Department of Pathology and Laboratory Medicine, Aga Khan University, Karachi, Pakistan.
E-mail address: kausar.jabeen@aku.edu (K. Jabeen).

https://doi.org/10.1016/j.cmi.2021.07.038

Table 1
Summary of COVID-19-associated mucormycosis cases from Pakistan

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	NA	Presumed to have died (LAMA in critical condition)	
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	*Aspergillus niger*, *Aspergillus nidulans*	Died	Septic shock, multi-organ dysfunction, lactic acidosis
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 shadowing 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 periosteitis of the sphenoid bone. MRI with skull base osteomyelitis	Nasal tissue smear showed aseptate hyphae but failed to grow on culture	Ceftriaxone-resistant *Klebsiella pneumoniae* and *Aspergillus fumigatus*	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 hyper-intense 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 niger*/ *Pseudomonas aeruginosa*	Died	ARDS, Septic shock

(*continued on next page*)

Table 1 (*continued*)

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
10	64	F	DM (HbA1c 8.3), HTN, CLD	NA	Yes/duration and type unknown	Rhino-orbital/12	Proven	CT orbits: overall appearances are likely secondary to left orbital and periorbital cellulitis without abscess formation	Positive nasal tissue culture Histopathology of left eye and left ethmoid sinus tissue	NA	Under-treatment	

Abbreviations: AKI, acute kidney injury; AML, acute myeloid leukaemia; ARDS, acute respiratory distress syndrome; CAM, COVID-19-associated mucormycosis; CKD, chronic kidney disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CT, computed tomography; CVST, cerebral venous sinus thrombosis; CXR, chest X-ray; DIC, disseminated intravascular coagulation; DLBCL, diffuse large B-cell lymphoma; DM, diabetes mellitus; F, female; HbA1c, glycated haemoglobin; HTN, hypertension; ICU, intensive care unit; IHD, ischaemic heart disease; LAMA, left against medical advice; LTOT, long-term oxygen therapy; M, male; MRI, magnetic resonance imaging; TB, tuberculosis.

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 disproportionally 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

There are no conflicts of interest for any of the authors.

Funding source

No external funding was received for this study.

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.

References

[1] Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi (Basel, Switzerland) 2019;5. https://doi.org/10.3390/jof5010026.

[2] Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhalla A, et al. Coronavirus disease (COVID-19) associated mucormycosis (CAM): case report and systematic review of literature. Mycopathologia 2021;186:289–98.

[3] Hoenigl M, Seidel D, Carvalho A, Rudramurthy SM, Arastehfar A, Gangneux JP, et al., ECMM and ISHAM Collaborators. The emergence of COVID-19 associated mucormycosis: analysis of cases from 18 countries. Available at: https://ssrn.com/abstract=3844587; 2021.

[4] Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and update of the consensus definitions of invasive fungal disease from the European organization for Research and treatment of cancer and the Mycoses study Group education and Research consortium. Clin Infect Dis 2019;71:1367–76.

[5] Bellanger AP, Navellou JC, Lepiller Q, Brion A, Brunel AS, Millon L, et al. Mixed mold infection with Aspergillus fumigatus and Rhizopus microsporus in a severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) patient. Infect Dis Now 2021. https://doi.org/10.1016/j.idnow.2021.01.010.