

Mini Review

COVID-19, Mucormycosis and Stroke: Triple Whammy

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Submitted: 14 February 2022

Accepted: 26 February 2022

Published: 28 February 2022

ISSN: 2334-2307

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Abstract

There had been an increase in number of cases of mucormycosis in coronavirus disease 2019 (COVID-19) pandemic. Acute ischemic stroke (AIS), an uncommon complication of invasive fungal infection, is seen more often with COVID-19 associated mucormycosis (CAM) due to multiple reasons. Most of the AIS are large artery infarcts occurring ipsilateral to the side of rhino-orbito-cerebral involvement in middle cerebral artery or watershed territories. Intracranial carotid artery involvement in the cavernous sinus is the most common vascular abnormality which may be a progressive vascular disease. Patients can develop ischemic strokes despite being on antiplatelets and/or anticoagulation. Systemic antifungal agents and surgical debridement seems best therapeutic strategy. Morbidity can be reduced by early diagnosis and interventions through a multidisciplinary team.

Keywords

- COVID-19
- COVID-19 associated mucormycosis
- Mucormycosis associated stroke

REVIEW

Mucormycosis is a rare fungal infection caused by angio-invasive mould which is ubiquitous in soil and decaying plants. It belongs to the order Mucorales and the common genera causing this human infection are *Rhizopus*, *Lichtheimia*, *Apophysomyces*, *Mucor*, *Rhizomucor* and *Cunninghamella* [1]. The infection typically occurs in patients with uncontrolled diabetes mellitus (DM), hematological malignancies, hemopoietic or solid organ transplant and iron overload state [2]. The most common site of infection is nasal cavity, paranasal sinuses, and orbit with intracranial extension in varying severity which is called rhino-orbito-cerebral mucormycosis (ROCM). Other sites include lungs, skin, kidney, gastro-intestinal tract and a disseminated form [3]. The incidence of mucormycosis is increasing globally; more so in Asia. India has the highest burden of mucormycosis with 140 cases per million [2].

ROCM leads to neurological involvement in the form of contiguous spread from adjacent structures, cavernous sinus thrombosis, vascular involvement leading to strokes or haemorrhages, and rarely, by causing meningitis and fungal abscess [1]. Vascular involvement leads to acute ischemic stroke (AIS), aneurysm formation and sub-arachnoid haemorrhage (SAH), intracerebral haemorrhage (ICH) and/or carotico-cavernous fistula formation. There are isolated case reports or series of cerebrovascular involvement in mucormycosis [4-7]. In a review, Little et al have described a total of 37 reported cases from literature over a period of 60 years [4].

In the ongoing corona virus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there have been multiple reports of increased incidence of mucormycosis, especially from India [8-11]. Though the exact incidence of COVID-19 associated

mucormycosis (CAM) is not known, in a hospital-based study, we noted a more than 5-fold rise in hospital admissions due to mucormycosis during the COVID-19 pandemic compared to previous two years [8]. Since India had the second highest number of cases of COVID-19, has second highest largest population of DM which is one of the most important risk factors for mucormycosis and the highest incidence of mucormycosis in the world, it was not surprising that India saw a sudden surge of cases of CAM leading to a mucormycosis epidemic on an already ongoing COVID-19 pandemic [12]. The risk factors for invasive fungal infections in COVID-19 include: 1) pre-existing illnesses like DM and other diseases mentioned above, 2) COVID-19 infection which leads to immune dysregulation; new onset DM due to use of steroids as treatment of COVID-19 as well as pancreatic islet cell injury due to SARS-CoV-2 virus; and elevated ferritin level leading to intracellular iron overload which is important factor for growth of mucormycosis; 3) treatment of COVID-19 that includes use of steroids and tocilizumab which are risk-factors for fungal infections and 4) other unproven factors like environmental factors, alterations in host immunity, change in fungal behaviour etc [8].

During the ongoing epidemic of CAM, cases of cerebrovascular involvement in general and acute ischemic stroke (AIS) in particular are reported [8,13-16]. In 2 separate studies, we reported incidence of ischemic strokes in 14.8% [8] and 11.8% [13] patients suffering from CAM. Development of AIS after mucormycosis is a rare phenomenon and there are only isolated case reports as stated earlier. There are several reasons for such high numbers of cases of AIS after CAM. Since there was an increase in the absolute numbers of CAM, the numbers of CAM associated cerebrovascular events also appear to have increased. Secondly, COVID-19 is likely to be severe in those with comorbidities like diabetes mellitus [3] which is also a risk factor for mucormycosis

as well as ischemic stroke. Thirdly, the risk of AIS is higher with COVID-19 where hypercoagulable state can occur. In CAM, both the angio-invasive fungus and the prothrombotic state due to COVID-19 virus could have led to the high incidence of strokes. Improved awareness about this entity could have led to earlier recognition of the disease.

We encountered 49 patients with cerebrovascular involvement with CAM. In this study [13], the mean age of patients was 52.9 years and 71% were males. They developed symptoms of mucormycosis at a median of 18 days after the onset of COVID-19 and cerebrovascular event after a median of 8 days from the onset of mucormycosis symptoms. In 98% patients, the fungal syndrome was in form of ROCM. Commonest cerebrovascular event was AIS in 91.8%, ICH and SAH occurred in 6.1% and 2% respectively. In the study, 63.3% patients had pre-existing DM and 18.4% were detected to have new onset DM after COVID-19. The most common neurological manifestations of AIS were motor weakness, altered mental status, aphasia, and hemianopia. Mean NIHSS was 10.74. Location of the stroke was unilateral anterior circulation (62.2%); bilateral anterior circulation (17.8%); posterior circulation (11.1%) and combined anterior and posterior circulation (8.9%). Vascular imaging could demonstrate intracranial occlusion in 62.1%; extracranial occlusion in 3.4% and normal vessels in 34.5%. Mortality was 51% during hospital stay.

In ROCM, the fungal spores initially invade nasal mucosa and then spread to paranasal sinuses, orbits and finally via the superior orbital fissure to the cavernous sinus [1]. It invades the internal carotid artery in the cavernous sinus leading to carotid vasculitis which causes carotid artery thrombosis and/or occlusion and rarely, aneurysm formation. Basilar artery can be involved if mucormycosis spreads to skull base. The vasculopathy is progressive and can progress even after apparent 'cure' of the fungal infection, as seen in our study [13]. Hematogenous spread from the lungs or disseminated mucormycosis can lead to multiple territorial infarcts.

Ischemic strokes occurring in ROCM are usually large artery infarcts, in middle cerebral artery (MCA) territory or watershed area either on same side of ROCM or on both sides. Since the vasculopathy is a progressive phenomenon, imaging early in the course of illness may show no or minor vascular involvement.

Antiplatelets and/or anticoagulation agents are often used as a part of treatment of COVID-19. In our study, 40% patients were receiving these agents when the stroke occurred [13]. So, these drugs do not appear to provide protection from mucormycosis associated ischemic strokes. Being a rare disease, there are no guidelines on treatment of these types of strokes. The thrombus in the occluded artery is often infective and histopathology of the clot may show fungal elements [17]. In literature there are few reports of use of mechanical thrombectomy or endovascular stenting in treatment of mucormycosis associated strokes [17,18]. Appropriate antifungal drugs and surgical debridement of the infection seems the treatment strategy for these types of strokes.

ICH and SAH are even rare with mucormycosis and are due to venous congestion due to cortical vein involvement, mycotic aneurysm or arterial dissection [13].

Due to the high numbers of cerebrovascular events seen in this study, we recommend that the treating physicians keep a rather low threshold for diagnosis of this complication. As AIS can occur anytime during the course of illness, it is worthwhile to do appropriate frequent imaging of brain and vasculature during management of CAM. Ideally, weekly imaging should be obtained while treating a patient with CAM [17].

Once felt to be a fatal disease, the mortality can be reduced up to 50% by increasing awareness amongst treating physicians, early treatment, multidisciplinary team involvement and abiding with good treatment protocols [19]. However, the disease leads to prolonged hospital-stay, higher cost of treatment for the patients and morbidity.

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Cite this article

Kulkarni R, Pujari S (2022) COVID-19, Mucormycosis and Stroke: Triple Whammy. *J Neurol Disord Stroke* 9(1): 1190.