Mucormycosis of the Central Nervous System in the Background of the COVID-19 Pandemic in the Absence of Antifungal Medication – An Audit of 2 Very Difficult Months in a Tertiary Care Centre in Southern India

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Abstract
Mucor of the intracranial compartment is a rare and devastating infection commonly seen in debilitated patients. The infection commonly enters through the orbit or through the paranasal sinuses through diploic vessels or through skull base osteomyelitis secondary to sinusitis. The onset of the COVID-19 pandemic coupled with the widespread use of steroids reduced effective immunity of various normally immunocompetent individuals. This saw a veritable avalanche of mucor infections in COVID affected and post COVID-19 infected patients. The presentations were different from the commonly seen routes of entry and presented in different and unique ways. The severity was worsened due to the lack of availability of amphotericin B required for the treatment of the infection. Many of the patients succumbed to their ordeal despite repeated surgical debridement and abscess evacuations. We present a representation of unusual mucor infections of the brain seen during the second COVID-19 wave in India, where an unprecedented number of infections were seen overwhelming the health facilities of all major centres in India.

Keywords: Mucormycosis, COVID-19, Pandemic, Antifungal Medication

Introduction
The second wave of COVID-19 infection in India was acutely felt across the nation. Both urban and rural centres were affected with hospitals overflowing and deaths exceeding the worst estimates possible. Patients passed away waiting for ventilators and ICU beds while those in critical care centres wasted away without improvement. Aggressive use of steroids to limit and reverse the hypersensitivity mediated immune response to the virus was advocated and taken to heart by the harried medical community of India and steroid were even given off the counter for those who wanted it without prescriptions from medical personnel.

As the pandemic peak abated, emergency rooms across the country began to experience a new phenomenon. Patient previously treated successfully for the COVID-19 infection began presenting with symptoms of nasal stuffiness, discharge and eye swelling. Many also presented with seizures and features of raised intracranial tension. Careful examination showed black coloured pus in the sputum and discharge of the patients. The skin and bony architecture of the face also seemed involved. Imaging studies as well as microbiological assessments showed the infection to be Mucormycosis, a rare yet deadly fungal colonisation of the paranasal sinuses and orbit. Over the next 2 months, Emergency teams, ENT and ophthalmological surgeons were overwhelmed by the spate of cases presenting with the deadly fungus.

The problem was severely compounded by the unavailability of Amphotericin B, the supply of which was swamped by the sudden spike in demand caused by the fungus infection. Although India is the largest manufacturer and supplier of the drug, the sudden spike in demand exceeded all expectations and planning.
By the time the drug manufacturers could ramp up production and reintroduce the medication into circulation, uncontrolled mucor ran amok amongst the patients presenting in weird, unusual and unique ways.

We present the novel intracranial presentations of mucor experienced by us in a tertiary care centre in Bengaluru city in south India.

**Mode of spread**

It is well documented that mucor initially colonises the mucosa of the paranasal sinuses as its spores are transmitted by air from the soil. The fungus then overpowers the thin bony septae separating the sinuses from the adjoining orbit thus leading to orbital fungal cellulitis and eventual infection of the globe. If left unchecked they can enter the intracranial compartment as well. There have also been reports of vascular invasion of the fungal elements which lead to a wider and more serious dissemination of the disease, especially into the brain. Lastly a rare and severe modus of spread is perineural spread, where fungal elements travel along the axons of nerves affecting passing structures along the course of the nerve. The presentations of these entities are varied and are often confused with other commoner diseases. The different presentations and modes of spread are shown in figure 1.

**Case Series**

**Part 1: Direct spread**

The propensity of fungal cellulitis of the paranasal sinuses to spread through the diploic and lacunar vessels is well documented. The spread often is through bony divisions that separate the infected sinus or orbital lining from the intracranial cavity. Hence common presentations of such a modus of spread are intracerebral abscesses in the frontal or temporal lobes as shown in figure 2A & 2B. Central skull base osteomyelitis is also seen in the vicinity of the sphenoid sinus around the cavernous venous sinuses. (figure 2C) The even rarer vault osteomyelitis was seen in absence of direct penetrating injury of the bone. The spread was through contiguous spread from the infected orbit as seen in Figure 2D. Another rare presentation was clival Mucormycosis with complete destruction of the bone and a prevertebral abscess of mucor pus extending down all the way to the upper dorsal spine. (figures 2E & F).

**Part 2: Vascular spread**

Angioinvasion of the cerebral vasculature from the branches in the paranasal sinuses lead to intravascular complications. These include occlusion of vessels leading to strokes, Dissemination of the fungal elements through the bloodstream leading to multiple abscesses far away from each other (pyemic abscesses figure 3A), and even vessel wall destruction leading to mycotic aneurysms (figure 3B&C) Even rarer, is the space occupying lesion presentation as seen in figure 3D, where a vascular nidus grows into a large mass compressing the surrounding brain leading to deficits and features of raised intracranial tension.

**Part 3: Perineural spread**

The most puzzling and perhaps interesting of the 3 modes of spread is the perineural infiltration of the fungus along the axolemma and oligodendrocytes to distal structures in the brain. We saw infections leading to optic neuritis with a mass lesion in the distal optic nerve mimicking a glioma (figure 4A), fungal trigeminal neuralgia (figure 4B) and spread along the trigeminal nerve into the gasserian ganglion causing severe neuralgic pain (figure 4C), as well as olfactory nerve infection with space occupying lesions secondary to inflammation seen. (figure 4D)
Figure 2: (A) & (B) shows a T1 contrast MRI axial & sagittal slice of the brain showing a ring enhancing lesion with central necrosis in the left temporal lobe suggestive of an abscess. (C) shows a T1 contrast axial MRI of the brain with enhancing infiltrates on the right cavernous sinus and orbital apex extending posteriorly into the posterior fossa. (D) shows a T2 weighted MRI image of the brain showing significant oedema of the skin, subcutaneous tissue and bone of the temporal bone leading to complete destruction and erosion of the bone with the pus extending into the temporal and subtemporal fossa. (E) is sagittal MRI T2 slice of the brain showing destruction and inflammation of the clivus with pus extending below into the prevertebral space as demonstrated clearly in (F).
Case Audit

Of the total of 127 Mucormycosis patients admitted in the 2 month period specified, 104 were diagnosed with rhino-orbital Mucormycosis, of which 97 were operated. Functional endoscopic sinus surgeries (FESS) and orbital surgeries including eventration were carried out by Otorhinolaryngologists and ophthalmologists. A total of 23 patients were referred to neurosurgery for various complaints. Most were managed conservatively especially after the focus of infection was managed surgically as mentioned before. A total of 6 patients were operated for cerebral Mucormycosis. Surgeries ranged from decompressive hemicraniectomies for mucor related strokes, to abscess evacuation, to skull base procedures to decompress the middle or posterior cranial fossa base. The distribution of surgeries is shown in figure 5.

**Figure 3:** (A) shows multiple ring enhancing lesions in a axial T1 FLAIR sequence which also demonstrates the oedema of the respective lesions. Other lesions were also seen in the brainstem and cerebellum. (B) a contrast T1 axial slice shows a lesion on the anterior border of the cerebellum and brainstem. An angio- gram done in (C) shows a large saccular mycotic aneurysm of the left Superior Cerebellar Artery. (D) shows a large fungoma or fungal space occupying lesion which is seen far away from infected bone or sinus. The spread is thus haematological in nature.

**Figure 4:** (A) shows an axial DWI image showing thickening and diffusion restriction along the right optic nerve. The portion of the nerve near the chiasm is especially thickened almost resembling a neoplastic growth. (B) shows a T2 weighted axial MRI slice, which shows a thickened and inflamed left trigeminal nerve causing severe neuralgia to the patient. (C) shows inflammation of the entire trigeminal nerve from the orbit along the cavernous sinus upto the gasserian ganglion and beyond onto the brainstem. (D) shows a space occupying lesion seen in close proximity to the right olfactory nerve in a setting of severe orbital mucor inflammation. The olfactory bulbs appear inflamed in this coronal T2 MRI brain slice.

**Figure 5:** Explaining the distribution of post covid-9 Mucormycosis in St. John’s medical College Hospital, Bangalore.
Mucor progressed rapidly following the covid-19 second spike as shown in figure 6. Maximum cases were seen in May and June mirroring the virus outbreak. The mortality of cerebral Mucormycosis was not high when amphotericin B was available. For a period of 1 month, the drug was in short supply leading to virulent recurrent infections and progression of the disease. Many mortalities were seen in this period mainly due to this problem.

Figure 6: Explaining the temporal relationship between the covid-19 second spike in India and the upsurge of Mucormycosis cases.

Of the patients operated for neurosurgical mucor, the commonest presentation was skull base osteomyelitis secondary to the infection in the paranasal sinuses and orbit. Infection of the skull base of the middle cranial fossa and rarely the posterior fossa was seen. Osteomyelitis was also seen in the frontal bone secondary to frontal sinusitis and orbital cellulitis. Abscesses were also seen as an extension of the infection. Commonest locations were temporal lobe followed by frontal lobe abscesses. These mostly were seen as an extension of the osteomyelitis. Pyemic abscesses secondary to hematogenic dissemination were also seen but only rarely. Perineural abscesses which spread along the nerve sheath were also seen as described above onto the substance of the brainstem and cerebellum. These however were small and managed medically. Angioinvasion of the mucor lead to strokes and mycotic infarcts. These were seen in 1 patient with complete middle cerebral artery occlusion and was managed through an emergency decompressive craniectomy. Unusual presentations were seen in a large number of patients and have been described in detail above. They contribute to the novelty of this report. Most unusual presentations were managed conservatively with antifungals and anticonvulsants. All recovered well with minimal deficits. The distribution of neurosurgical presentations of mucor is summarised in figure 7.

Figure 7: Showing the different clinic-pathological presentations of cerebral Mucormycosis seen in our hospital.

Discussion
COVID-19 and mucormycosis share risk factors, such as presence of DM, which can independently contribute to mortality, but have conflicting management principles. While immune suppression with steroids may be required in moderate to severe COVID-19, the use of steroids and the worsening glycaemic control provide an opportunity for mucor to become invasive. Mucor produces keto-reductase as a virulence factor enabling them to grow in the acidic and glucose-rich environment generated in ketoacidotic states.
Additionally, Müller et al have postulated that the human pancreas could be a possible target for the SARS-CoV-2 virus and that the β-cell infection may result in insulin resistance. This metabolic dysregulation, in previously non-diabetic or well-controlled diabetic COVID-19 patients, might predispose them to develop mucormycosis. Moorthy et al recently reported the association of COVID-19 infection with uncontrolled DM and usage of corticosteroids. Similarly, Sen et al reported a series of 6 diabetic patients with concurrent mucormycosis and COVID-19 infection. Their all patients had uncontrolled blood sugar values and were treated with steroids during active COVID-19 infection. Current literature suggests that usage of systemic steroids in patients, who otherwise may have controlled diabetes, or may not be diabetics at all, can precipitate mucormycosis. Mekkonen et al reported a case of invasive fungal rhinosinusitis with orbital involvement in a patient with COVID-19 with uncontrolled DM and HbA1c of 14%. Mehta and Pandey reported a case of a patient with COVID-19 infection, treated with steroids and tocilizumab, who during the course of the treatment, developed rhino-orbital mucormycosis. Waizel-Haïat et al reported a case of rhino-orbital mucormycosis associated with ketoacidosis secondary to recent onset DM and COVID-19 infection. Despite aggressive management the patient developed multi-organ failure and died.

In conclusion, ROCM is a known occurrence in COVID-19 affected patients. Over a third of patients can have unfavorable final outcome. Uncontrolled DM at presentation, involvement of the orbital apex and CNS by the infection, and the usage of steroids determined an unfavorable outcome. Involvement of the CNS was seen to be the only factor determining mortality. In a similar geographic setup, as compared to previous non-COVID related cases, the coexistence of COVID-19 in this series, did not seem to worsen the final outcome in terms of mortality. It is prudent that physicians and Neurosurgeons, alike, involved in the care of patients with COVID-19 be aware of the outcomes of ROCM in COVID-19 patients.

Conclusion

The sheer numbers faced during the onslaught of the Mucormycosis wave which followed the second spike of covid-19 cases made diagnosis, surgery and prognostication difficult especially during the period where demand for antifungals outstripped supply. But a combined team approach to the disease with good patient doctor counselling helped tide over the majority of the period successfully. What it did provide was a treasure trove of experience and data which can aid future generations in their fight against pandemics in the future. This is our humble attempt to chronicle the events and the diversity of presentations of this period for posterity.

References


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