



Intracranial Mucormycosis—A Minacious Foe

Sharad Pandey¹ Abrar Ahad Wani²

¹Department of Neurosurgery, A.B.V.I.M.S. and Dr Ram Manohar Lohia Hospital, New Delhi, India

²Department of Neurosurgery, S.K.I.M.S. Srinagar, Jammu and Kashmir, India

Indian J Neurosurg 2021;10:92–94.

Currently, India is battling with the novel COVID-19 virus that has affected millions of people across the country with a high infectivity rate and associated fatality. Recently “mucormycosis,” a notifiable disease at present, has risen in alarming proportions among COVID-19-infected patients. This disease was earlier witnessed in South Asian countries like India and China, particularly among patients with decreased immunity like diabetes mellitus, patients undergoing solid organ transplants, those with hematological malignancy, and those undergoing corticosteroid therapy. However, emerging evidence is showing a rising incidence of this life-threatening, opportunistic infection among patients infected with severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2).

India accounted for 71 percent of the total cases of mucormycosis from across the world in March 2021.¹ It is a rare, opportunistic, invasive, and highly fatal fungal infection occurring due to saprophytic environmental fungi—*Rhizopus arrhizus* (family Mucoraceae), the most common worldwide, followed by *Apophysomyces* (predominant in Asia), *Mucor irregularis*, *Cunninghamella*, *Lichtheimia (absidia)*, *Saksenaia*, and *Rhizomucor*.^{2–4} Depending upon the site of involvement, this disease can have different clinical presentations—rhinocerebral, pulmonary, cutaneous, gastrointestinal, and disseminated and miscellaneous rare forms such as endocarditis, osteomyelitis, peritonitis, renal, etc.^{1,5}

Mucormycosis involves the central nervous system (CNS) by direct extension from infected paranasal sinuses or orbit or by hematogenous dissemination from the lungs. Rhino-orbito-cerebral mucormycosis is considered as the most common manifestation of mucormycosis. This disease's hallmark is attributed to tissue necrosis from angioinvasion and subsequent thrombosis and endarteritis, causing notoriously black, necrotic eschars.⁶ Clinically, patient may complain of nasal blockade, crusting, hyposmia or anosmia, headache, blurring or loss of vision, facial pain or numbness, redness of eyes, atypical signs and symptoms like proptosis, ophthalmoplegia or periorbital cellulitis, and various other

Address for correspondence Sharad Pandey, MS, MCh, Department of Neurosurgery, A.B.V.I.M.S. and Dr Ram Manohar Lohia Hospital, New Delhi 110001, India (e-mail: drsharad23@yahoo.com).

neurological signs and symptoms if intracranial extension is present.⁷ The three most frequent imaging findings in intracranial mucormycosis are cavernous sinus thrombosis, brain infarction, and internal carotid artery occlusion. The cavernous sinus is often the first intracranial structure to be involved, leading to cavernous sinus thrombosis and ocular paresis or palsy by impairing the function of oculomotor (CN III), trochlear (CN IV), abducens (CN VI), and trigeminal nerve (V1 and V2 branches) that traverse it bilaterally. Few may present with focal seizures, hemiparesis, or altered consciousness, which signals brain invasion or infarction. Isolated cerebral mucormycosis is a unique clinical entity, which is seldom reported.⁸

To date, only a handful of cases of cerebral mucormycosis have been reported worldwide so far. From advanced search in the databases of PubMed and Google Scholar, till May 2021 only 21 cases of cerebral mucormycosis in people with COVID-19 have been reported (►Table 1)⁹. Out of 21 cases, 17 were from India, and only 4 cases from rest of the world. One such similar case of cerebral mucormycosis presented to our institute in May 2021.

A 30-year-old male being managed for severe COVID-19 infection was newly diagnosed with diabetes mellitus. His high blood sugar could be due to either steroids, effect of COVID-19 virus on the pancreatic islets, or preexisting altered blood glucose state which got precipitated by the SARS-CoV-2 infection. He developed features of raised intracranial pressure (ICP) and was referred to our institute, Sher-i-Kashmir Institute of Medical Sciences (SKIMS), with headache, nasal stuffiness and discharge, progressive diminution of vision, and proptosis with ophthalmoplegia. MRI showed pan sinusitis with intracranial (left frontal lobe with bilateral cavernous sinus) and left apex involvement. Left carotid artery was narrowed in lumen possibly due to arteritis (►Fig. 1). He was put on amphotericin B, and he underwent debridement of necrotic fungal tissue by ENT surgeon, followed by bifrontal craniotomy and excision of

DOI <https://doi.org/10.1055/s-0041-1732800>
ISSN 2277-954X

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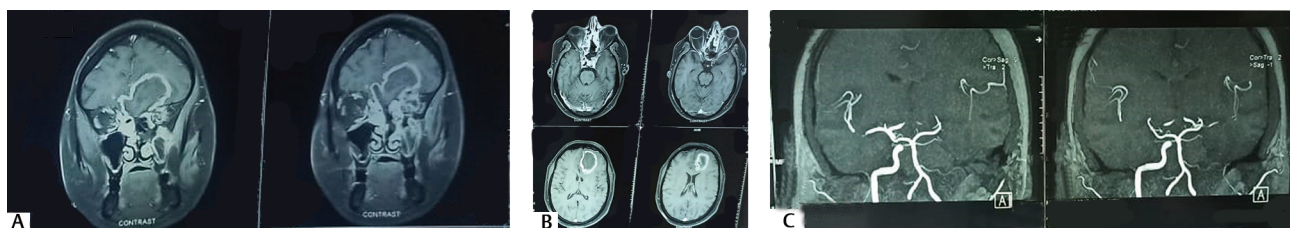


Fig. 1 (A) MRI brain showing peripherally enhancing lesion involving left frontal lobe, (B) pan sinusitis with intracranial (left frontal lobe with bilateral cavernous sinus) and left apex involvement, and (C) left carotid artery nonopacification of lumen possibly due to arteritis.

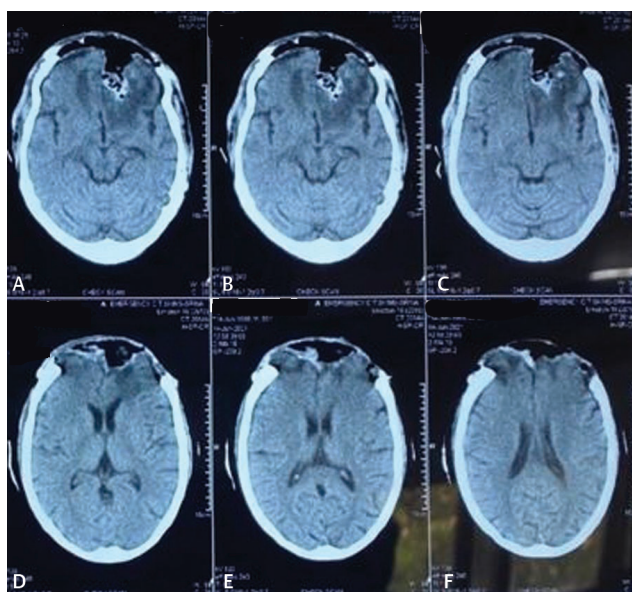


Fig. 2 (A–F) Postoperative CT brain showing post op changes with complete excision of left frontal lesion.

lesion by neurosurgical team. His biopsy confirmed presence of mucormycosis. Postoperative CT showed complete excision of frontal lesion with postoperative changes (► **Fig. 2**). Postoperative period was uneventful with Glasgow coma scale (GCS) score of 15/15, although vision did not improve till the writing of this editorial.

Literature review revealed that almost all patients had diabetes mellitus as comorbidity and few had undergone cancer chemotherapy. In a retrospective study by Sen et al. six consecutive patients with COVID-19 developed rhino-orbito-cerebral mucormycosis (5 out of 6 had intracranial involvement and all six survived).¹⁰ Sarkar et al reported a cluster of 10 cases of clinically diagnosed orbital mucormycosis with concurrent COVID-19 illness, out of which only one patient had cerebral involvement.¹¹ This patient was managed conservatively but expired over the course of the treatment. Moorthy et al reported mucormycosis in 16 patients, aspergillosis in one patient, and mixed infection in one patient.¹² Out of them, nine patients had intracranial extension. All patients received liposomal amphotericin B at

Table 1 Cases of cerebral mucormycosis reported worldwide in COVID-19 patients⁹

S. No.	Study done by	Place (of report)	Number of cases of mucormycosis	COVID-19 status	Comorbidities	Confirmed/suspected Mucor	CNS involvement of mucormycosis
Cases reported worldwide:							
1	Dallalazadeh et al ¹⁵	United States	02	Confirm	Y	Confirm	Y
2	Alekseyev et al ¹³	United States	01	Confirm	Y	Confirm	Y
3	Veisi et al ¹⁴	Iran	02	Confirm	Y-01 N-01	Confirm	Y-01 N-01
4	Sargin et al ¹⁶	Turkey	01	Confirm	Y	Confirm	Y
Cases reported in India:							
5	Revannavar et al ¹⁷	Mangalore	1	Confirm	Y	Confirm	Y
6	Sen et al ¹⁰	Mumbai	6	Confirm	Y	Confirm:5 Suspect:1	Y:5 N:1
7	Sarkar et al ¹¹	Puducherry	10	Confirm	Y	Confirm:6 Suspect: 4	Y:1 N:9
8	Moorthy et al ¹²	Bengaluru	17	Confirm	Y-15, N-02	Confirm	Y-08 N-09
9	Sharma et al ⁷	Jaipur	23	Confirm	Y-21 N-02	Confirm	Y-02 N-21
10	Present case	Srinagar	01	Confirm	Y	Confirm	Y

Abbreviations: COVID-19, coronavirus disease 2019; CNS, central nervous system; N, no; Y, yes.

doses of 3 to 5 mg/kg. Eleven patients survived, six died, and one was lost to follow-up. Out of six deceased patients, four experienced loss of vision at the time of presentation and five had intracranial extension. Sharma et al found 23 cases of mucormycosis of the paranasal sinuses over a 4-month study period; all patients underwent surgical debridement.⁷ Intracranial involvement was observed in only in two cases and they were managed conservatively. Out of total reported 21 cases of cerebral mucormycosis, 17 were from India, and four cases were from rest of the world, Alekseyev et al reported a case of rhinocerebral mucormycosis with history of poorly controlled diabetes mellitus.¹³ Imaging revealed the disease's extension into the sinuses and intracranial abscess in the infratemporal fossa with cavernous sinus enhancement. Along with intravenous amphotericin B, patient underwent staged debridement and excision of lesion. Patient responded well and was discharged in stable condition. Veisi et al reported two cases of confirmed COVID-19 patients who received corticosteroid therapy; one case developed rhino-orbito-cerebral mucormycosis, and another one developed rhino-orbital mucormycosis after the initiation of corticosteroid.¹⁴ Patient with intracranial extension, despite regular daily surgical debridement of the paranasal sinuses and medical therapy, could not survive (→ **Table 1**).

In our case, patient with rhino-orbito-cerebral mucormycosis was managed by a team of physician, ENT surgeon and neurosurgeon, and the patient responded well and is still admitted with us for intravenous therapy of amphotericin B.

Successful treatment of mucormycosis requires a multi-disciplinary team approach. Surgical debridement of infected tissue, prompt institution of effective antifungal treatment, and correction of the underlying metabolic and immune derangement is the key to success.⁶ Neurosurgical intervention is required when there is a need to relieve increased ICP, to divert the cerebrospinal fluid (CSF) passage in case of obstructive hydrocephalus, and to excise the lesions which fail to regress even after aggressive medical treatment. Neurosurgery also plays an important role in cases of hemispheric stroke, causing increase in ICP and impending herniation. In such cases, decompressive hemicraniectomy may be performed. In cases of advance cerebral infection, the only option is to give aggressive appropriate antifungal drug, but in such cases, the success rate is very low.

To conclude, a high index of suspicion in uncontrolled diabetics and patients who had received steroids is the need of hour, as timely surgical debridement of involved sino-orbital tissue and antifungal treatment tremendously reduces intracranial spread and mortality.

Conflict of Interest

None declared.

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