



Original Article

Surgical management of post-COVID invasive rhino-orbito-cerebral mucormycosis and its outcomes: Role of neurosurgeons in a tertiary care center

Anand Kumar Das¹, Suraj Kant Mani, Saraj Kumar Singh

Department of Neurosurgery, All India Institute of Medical Sciences, Patna, Bihar, India.

E-mail: Anand Kumar Das - dranand0822@gmail.com; Suraj Kant Mani - manikant818@gmail.com; *Saraj Kumar Singh - dr.sarajkumarsingh@gmail.com



***Corresponding author:**

Saraj Kumar Singh,
Department of Neurosurgery,
All India Institute of Medical
Sciences, Patna, Bihar, India.

dr.sarajkumarsingh@gmail.com

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ABSTRACT

Background: Mucormycosis, which was previously considered to be rare, has emerged with a new challenge in patients infected with or recovering from COVID-19. Immunocompromised patients are particularly prone to developing this disease. The most common form of presentation is rhino-orbito-cerebral mucormycosis (ROCM). We present various neurosurgical approaches to an entire spectrum of its clinical manifestations.

Methods: This is a retrospective study of patients who were admitted to the neurosurgery department with ROCM and a history of COVID-19 infection between November 1, 2020, and September 1, 2021. All cases of ROCM underwent contrast-enhanced computed tomography/magnetic resonance imaging of the brain, paranasal sinuses, and orbit. A tissue biopsy was sent for histopathological analysis. All confirmed cases received liposomal amphotericin B and surgical treatment was immediately undertaken.

Results: Out of 200 patients with ROCM, 40 patients presented with neurological manifestations. Seven out of 40 patients had focal lesions in the brain and skull bone that needed neurosurgical intervention along with sinus debridement and antifungal treatment. These seven patients presented with different clinical manifestations: large-vessel stroke (one), medium-vessel stroke (one), frontal lobe abscess (one), frontal bone osteomyelitis (two), isolated central nervous system involvement (one), and mucor mimicking trigeminal schwannoma (one). The surgical intervention included decompressive craniectomy, frontal craniotomy, subtemporal craniotomy, and a minimally invasive supraorbital keyhole approach.

Conclusion: In high-risk patients, a high level of clinical suspicion combined with appropriate investigations should be performed as soon as possible. Symptoms and early warning signs should not be overlooked, as treatment delays can be fatal. A minimally invasive surgical approach is possible in view of decreasing the morbidity of large craniotomy.

Keywords: Abscess, COVID-19, Mucormycosis, Osteomyelitis, Stroke

INTRODUCTION

Mucormycosis is an invasive fungal infection caused by Zygomycete fungi of the family Mucoraceae.^[16] In the present scenario, this invasive fungal infection, which was previously considered to be rare, has emerged with a new challenge in patients infected with or recovering from COVID-19.^[1] Mucormycosis can occur by inhalation of spores, ingestion of infected food products, or invasion of damaged surfaces.^[19] Immunocompromised patients are particularly

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prone to developing this disease, such as those suffering from uncontrolled diabetes mellitus (DM), organ transplant recipients, malignancy, and prolonged neutropenia. Rhino-orbito-cerebral mucormycosis (ROCM) is the most frequent form of presentation, with a variety of symptoms such as periorbital/facial pain, periorbital swelling, facial numbness, cavernous sinus thrombosis, and diminution of vision to complete ophthalmoplegia.^[11] Nasal turbinates are the first to get inoculated. In an immunocompetent host, the phagocytosis and ciliary system can effectively avoid the invasion by the spores. However, in an immunocompromised host with inefficient phagocytosis, the spores can mature into hyphae and infiltrate the vessels. This angioinvasion is the hallmark feature of mucor, leading to thrombosis and subsequent tissue necrosis.^[17,24] The worldwide incidence of mucormycosis varies from 0.005 to 1.7/million inhabitants, with India having the highest burden at nearly 80 times the prevalence (0.14/1000) of developed countries.^[2,17] This fungal infection has emerged as an epidemic within the COVID-19 pandemic. The association of mucormycosis with COVID-19 patients has been seen and etiopathogenesis proposed for its development includes DM, use of steroids, long-term hospital stay, immunological dysfunction caused by a virus, and extended use of antibiotics.^[1,2,8,11,16,17,19,24]

ROCM management must be a multidisciplinary effort involving an otorhinolaryngologist at the center, as well as an ophthalmologist, neurologist/neurosurgeon, anesthesiologists, plastic surgeons, and rehabilitation professionals.^[8] As intracranial progression of mucor can occur rapidly and is linked to high mortality among patients,^[26] this article aims to share the experience of ROCM management from a neurosurgical perspective and emphasize the role of neurosurgeons.

MATERIALS AND METHODS

We performed a retrospective study of patients who were admitted to our neurosurgery department with ROCM and current or past history of COVID-19 infection between November 1, 2020, and September 1, 2021. We included only those patients who required neurosurgical intervention. All participants who took part in the study signed a written and well-informed consent form. The study was carried out in accordance with the Declaration of Helsinki. The demographic profile, clinical presentation, examination and imaging findings, and laboratory findings were retrieved from records. All suspected cases of ROCM had contrast-enhanced computed tomography (CECT) of the paranasal sinus, orbit, and brain. For patients with an intracranial extension on CECT, contrast-enhanced magnetic resonance imaging (CEMRI) of the brain, orbit, and paranasal sinus was obtained. A tissue biopsy was taken from the nasal cavity and sent for histopathological analysis and culture. All patients received

liposomal amphotericin B after confirmation of histopathology and surgical treatment was undertaken immediately. Table 1 shows the case summary of all seven patients.

CASE HISTORY

Case 1 (Large-vessel stroke)

A 66-year-old nonsmoker and nonalcoholic male with a medical history of hypertension and COVID-19 infection presented to hospital emergency with altered mental status. He had a headache, swelling over the right eye and face with the right side nasal blockage, and nasal bleeding for 7 days. He had a high-grade fever for the past 5 days. There was a history of COVID-19-associated pneumonia 1 month back, for which he was admitted to ICU and was treated conservatively with high-flow oxygen, antibiotics, steroids, and low-molecular-weight heparin.

On the initial assessment, the patient was drowsy. The temperature was 102°F, pulse – 64/min with a blood pressure of 150/96 mm Hg. He was tachypneic (30/min) with oxygen saturation of 88%. Random blood sugar was 457 mg/dl. Initial Glasgow Coma Scale (GCS) was 8 (E1 V2 M5) with the left side hemiplegia, upper motor neuron Type 7 nerve palsy, and right-sided ptosis. There were no signs of meningeal irritation. There was blackish discoloration around both eyes, the right side conjunctiva was diffusely chemosis. The right side pupil was dilated (5–6 mm) and not reacting to light and the left was of normal size but sluggishly reacting to light. The patient was sedated and intubated immediately. Mechanical ventilation was initiated along with anti-edema measures (mannitol + hypertonic saline). The patient was started on intravenous fluids and insulin to optimize his hyperglycemic state. Empirical antibiotics and antiepileptics were also started. His white blood cells were significantly elevated with markedly increased neutrophils. His renal function and serum electrolytes were normal.

Contrast MRI brain with angiography showed necrotizing sinusitis of bilateral maxillary and ethmoidal sinus with extensive thickening of bilateral buccinator space, right pterygopalatine fossa, and right premaxillary region. There was an absence of flow voids of the right internal carotid artery (ICA) and right middle cerebral artery (MCA) suggestive of the right ICA and MCA thrombosis (long segment). The contralateral anterior cerebral artery (ACA) was filling the anterior communicating artery and ipsilateral ACA. There was diffusion restriction of the right cerebral hemisphere with significant mass effect and midline shift [Figures 1a-f]. Tissue scraping was taken and sent for mycology and culture. Tissue mycology on potassium hydroxide (KOH) wet mount and lactophenol cotton blue stain showed growth of fungal element – broad, hyaline, and

aseptate hyphae with broad-angle branching suggestive of mucormycosis [Figures 1g and h]. The patient was started on liposomal amphotericin B (10 mg/kg once a day) with strict monitoring of renal functions, hydration, and blood sugar level. Within 3 h of admission, the patient sensorium dropped to GCS-6 (E1V2M3). Urgent surgical decompression (right fronto-temporo-parietal craniectomy) and debridement of the sinus were done. However, within a few hours, the patient developed hypotension. Despite all vasopressor and resuscitation efforts, the patient succumbed to death.

Case 2 (Medium-vessel stroke)

A 65-year-old male presented in emergency with an altered sensorium with the complaints of frontal headache, blackish discoloration, and swelling of the right eye for the past 3 days. He had a history of diabetes and hypothyroidism for which he was taking medication. He tested positive for COVID-19 and took home-based management for 7 days before presenting to us. On initial assessment, the patient was unconscious, tachypneic (40/min) with oxygen saturation of

80% on a high-flow oxygen mask. His temperature was 100°F, pulse – 94/min, and had a blood pressure of 160/100 mmHg. His blood investigation showed a random blood sugar of 386 mg/dl. His Glasgow Coma Score was 6 (E1 V1 M4). There were no signs of meningeal irritation. His right-sided conjunctiva was diffusely chemosis. The right pupil was dilated, sluggishly reacting to light, and left-sided pupil was of normal size reacting to light. The right side ptosis was present.

MRI brain with paranasal sinus showed mucosal thickening of the right maxillary, ethmoidal, and frontal sinus. There was a lysis of planum ethmoidale and cribriform plate. Bilateral and symmetrical frontal lobe infarcts with an involvement of genu and anterior body of corpus callosum. The involved area showed diffusion restriction along with the disappearance of gray-white matter interface with significant mass effect suggestive of anterior cerebral artery territory stroke [Figures 2a-d]. The patient was intubated and was kept on ventilator support. He was given intravenous fluids, insulin, and potassium supplementation along with

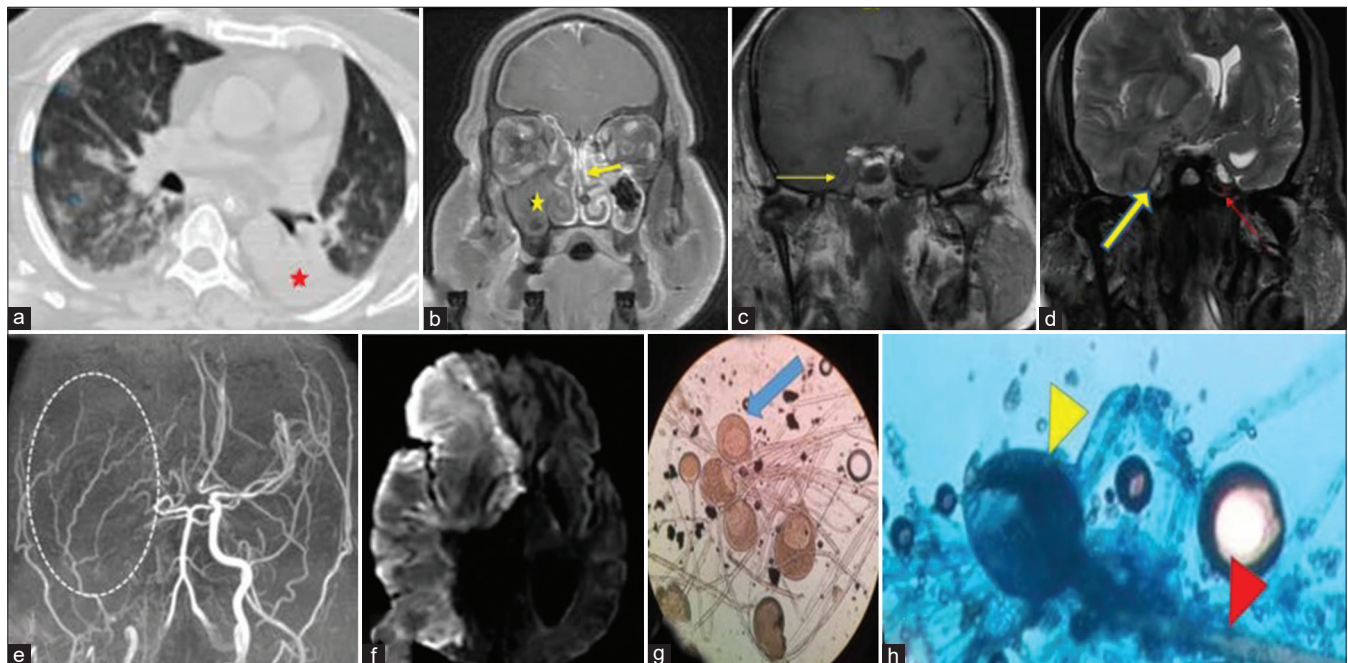


Figure 1: (a) Axial high-resolution computed tomography chest image showing bilateral patchy areas of ground-glass opacities with the left lung lower lobe consolidation (red star) (1 month before presentation), (b) coronal postcontrast T1-weighted fat saturation (T1W-FS) image showing heterogeneous enhancing soft tissue in the left maxillary and ethmoid sinuses (yellow arrow) with nonenhancing right turbinates and maxillary sinuses (yellow star), (c) coronal postcontrast T1W-FS image showing thrombosed right cavernous sinus and absent flow void of the right internal carotid artery (ICA) (yellow arrow), and (d) coronal T2-weighted fat saturation image showing the heterogeneous hyperintense appearing of the right cavernous sinus with ICA (blue arrowhead) and direction of spread (shaft of arrow). Opposite ICA is intact (red arrow), (e) three-dimensional time-of-flight MR angiography, maximum intensity projection, showing nonvisualization of the right internal carotid and middle cerebral arteries (dashed oval), (f) axial diffusion-weighted image showing restricted diffusion in large area of the right cerebral hemisphere, (g) KOH stained magnified image ($\times 40$) showing sporangium containing sporangiospores (thick blue arrow) with sporangiophore and nonseptate hyphae, and (h) lactophenol cotton blue stained magnified image ($\times 40$) showing sporangium (yellow arrowhead) with sporangiophore (red arrowhead).

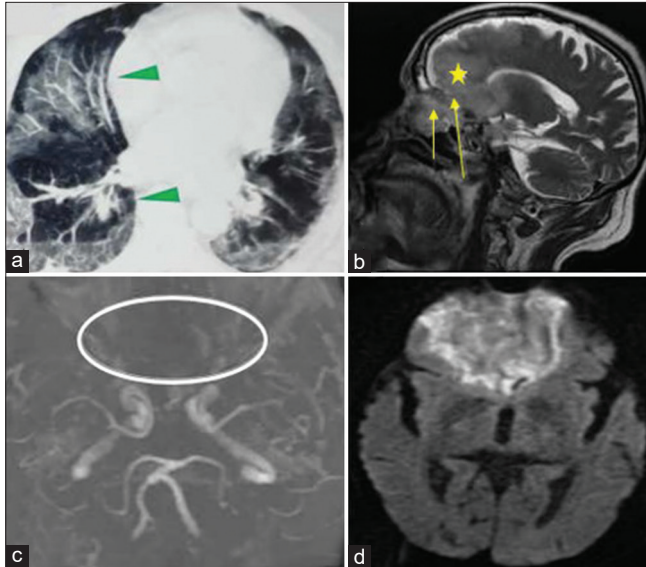


Figure 2: (a) Axial high-resolution computed tomography chest image showing bilateral patchy areas of ground-glass opacities (green arrowheads), (b) sagittal T2W image showing hyperintense region of the frontal lobe (yellow star), note direct contiguity of abnormal high T2 signal between the frontal lobe and similar lesion in the ethmoid sinus (yellow arrow), (c) three-dimensional time-of-flight MR angiography, maximum intensity projection image showing lack of visualization of both anterior cerebral arteries (white oval region points to the normal expected locations), and (d) axial diffusion-weighted image showing restriction in both frontal lobes.

decongestants (mannitol + hypertonic saline). Empirical antibiotics and antiepileptic also started. His renal function and serum electrolytes were normal.

With the above features in a post-COVID patient, a presumptive diagnosis of invasive fungal infection was made. Tissue scrapings from the nose showed growth of fungal elements – suggestive of mucormycosis. The patient was started on liposomal amphotericin B (10 mg/kg). Urgent surgical decompression (craniectomy) and sinus debridement were planned. However, within 3 h of admission, the patient deteriorated to GCS-3 (E1M1V1) with fixed dilated pupils on both sides. His brain stem reflexes were absent. Due to hemodynamic instability, the surgical plan was deferred. The patient immediately started vasopressors but could not sustain and succumbed within 8 h of admission despite all measures.

Case 3 (Frontal bone osteomyelitis)

A 32-year-old male presented with the chief complaints of headache, fever, and tender swelling over the forehead for the past 10 days [Figure 3a]. The patient was conscious. His vitals were within normal range. He recovered from COVID-19 infection 15 days back after taking oral medications at home.

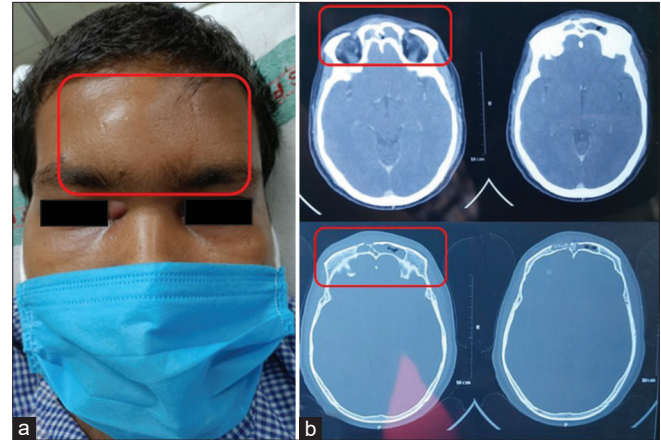


Figure 3: (a) Tender swelling over forehead and (b) noncontrast CT brain showing lysis of frontal bone suggestive of frontal bone osteomyelitis.

No h/o comorbidities such as diabetes and hypertension were present. On examination, patient was conscious without any neurological deficit and deep tendon reflexes were normal. CEMRI paranasal sinus showed mucosal thickening of the frontal sinus and noncontrast computed tomography brain suggested frontal bone osteomyelitis [Figure 3b]. Tissue from nostrils was sent for histopathological examinations which confirmed mucormycosis. Liposomal amphotericin B was started and surgery was planned immediately. Bicornal skin flap was raised and infected frontal bone was debrided. The defect was reconstructed using split calvarial frontal bone. Postoperative CT showed a well-reconstructed frontal bone defect. During the postoperative period, the fever got relieved and the patient was discharged after 10 days of admission.

Case 4 (Frontal bone osteomyelitis)

A 48-year-old male presented with fever and swelling over the forehead for the past 5 days. There was no h/o headache, seizure, or nasal blockage. The patient was conscious and oriented. He had a history of DM for which he was taking insulin. He was also admitted for COVID-19-associated pneumonia 1 month back for which he was given antibiotics, anticoagulant, and steroids. Neurological examination was completely normal. Noncontrast computed tomography brain showed frontal sinusitis with osteomyelitis [Figure 4a]. Tissue scrapings from nostrils were sent for histopathological examination and confirmed mucor infestation. Liposomal amphotericin B was started and surgery was planned to debride frontal bone through a small right eyebrow incision [Figure 4b]. The outer table of frontal sinus and mucosa was debrided. The inner table of the frontal sinus was completely intact. The patient improved clinically in the postoperative period and was discharged on day 10.

Case 5 (Left frontal lobe abscess)

A 48-year-old male presented with the chief complaints of fever and nasal blockage for 5 days and altered sensorium for the past 2 days. The patient was a known diabetic for the past 3 years. One week back, only he was discharged after getting treatment for COVID infection. He was on oral antibiotics, anticoagulants, and a tapering dose of steroids. On examination, his GCS was 13 (E4 V4 M5) with no limb weakness. No ptosis was present. Ophthalmoplegia could not be assessed due to the confused status of the patient. Deep tendon reflexes were exaggerated. MRI brain and paranasal sinus were advised which revealed mucosal thickening of the left maxillary, ethmoid, and frontal sinus with the left frontal abscess (6 × 5.2 × 3.3 cm) [Figures 5a-d]. A tissue biopsy from the nostril was sent for histopathological

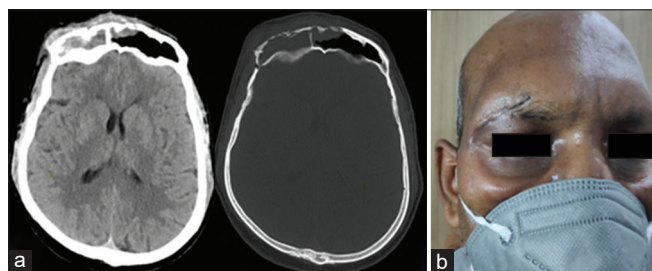


Figure 4: (a) Noncontrast CT brain showing frontal sinusitis with osteomyelitic changes and (b) postoperative image showing right supraorbital eyebrow skin incision.

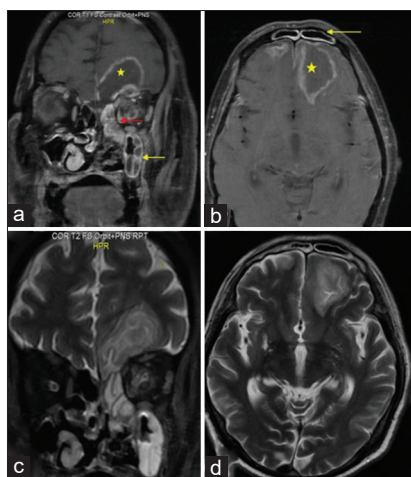


Figure 5: (a) Coronal postcontrast T1-weighted fat saturation (T1W-FS) image of brain and paranasal sinus showing heterogeneous enhancing soft tissue in the left maxillary (yellow arrow) and ethmoid sinus (red arrow) with contiguous extension to rim-enhancing lesion in the left frontal lobe (yellow star), (b) axial postcontrast T1W-FS image showing mucosal enhancement of frontal sinus (yellow arrow) and the left frontal abscess (yellow star), (c) coronal T2-weighted image showing hyperintense maxillary and ethmoid sinus with hyperintense lesion in the left frontal lobe, and (d) axial T2W MRI brain showing hyperintense left frontal lesion.

examination and confirmed the diagnosis of mucormycosis. Liposomal amphotericin B was started and surgery was planned immediately. The left supraorbital craniotomy was done through the left eyebrow skin incision and the abscess was drained completely. The patient improved in the postoperative period and the postoperative image confirmed no residual abscess cavity with pneumocephalus which got absorbed by day 4 without any clinical manifestations. The patient got discharged on postoperative day 10 and was on regular follow-up with no fresh complaints.

Case 6 (Isolated CNS involvement)

A 52-year-old male, known diabetic (uncontrolled on insulin), presented with the complaints of headache and fever for the past 10 days. There was no history of vomiting, seizure, decreased vision, or nasal blockage. He was on antihypertensive medications for the past 5 years. The patient was discharged 1 month back after 15 days of hospital stay for COVID-19-associated pneumonia. He received antibiotics, anticoagulants, and steroids and was on a noninvasive high-flow oxygen mask. On presentation, he was conscious with GCS – 15/15. There were no neck rigidity, limb weakness, ptosis, or ophthalmoplegia. CEMRI brain and paranasal sinus suggested multiple abscesses over the right frontoparietal region with mucosal thickening of the right maxillary and ethmoid sinus. These lesions showed diffuse restriction [Figure 6]. Keeping in mind, the possibility of mucor abscess and tissue scrapings from the right nostril were sent for histopathological examination. Liposomal amphotericin B was started after mucor was confirmed on histopathology. The patient improved clinically after receiving a single dose of amphotericin B. Liposomal amphotericin B was given at a dosage of 10 mg/kg once a day for 2 weeks with strict monitoring of renal functions, hydration, and blood sugar level. Follow-up MRI was done after 2 weeks which

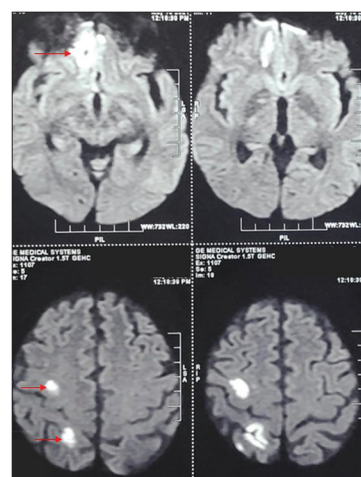


Figure 6: Diffusion-weighted image sequence of MRI brain showing diffuse restriction of multiple mucor abscess (red arrows).

showed complete resolution of the abscess. The patient was discharged on oral isavuconazole for the next 2 weeks.

Case 7 (ROCM mimicking trigeminal schwannoma)

A 48-year-old nondiabetic, nonhypertensive, and nonsmoker male presented to us with the only complaint of blurring of vision in the right gaze. There was no history of headache, vomiting, seizure, fever, or nasal blockage. There was no history of COVID-19 infection or any symptoms suggestive of it. On examination, GCS was 15/15 with no limb weakness. Ptosis was absent. The right side sixth nerve paresis was present with restricted lateral movement of the right eyeball. All other movements of the eyeball were normal. Deep tendon reflexes were normal. CEMRI brain was done which suggested a heterogeneously but avidly enhancing mass lesion occupying the right-sided Meckel's cave and extending into the right pterygopalatine fossa, features suggestive of trigeminal schwannoma. No osteolytic features were present [Figure 7a]. Surgery was planned. The right pterional craniotomy was done and gross-total excision of the mass was done. It was a firm mass, occupying space anterior to Meckel's cave with planes separable from surrounding structures and extending into the right pterygopalatine fossa. The patient did well in the postoperative course. His right side sixth nerve paresis improved completely with no added neurological deficit. Postoperative noncontrast computed tomography brain demonstrated gross-total excision of the mass with no residual lesion. Histopathology of specimen sent for biopsy showed invasive fungal infection suggestive of mucormycosis [Figure 7b]. Liposomal amphotericin-B was started and continued for 2 weeks. The patient was then discharged and kept in regular follow-up.

RESULTS

In our institution, we witnessed more than 200 patients of ROCM during the first and second waves of the COVID-19 pandemic. Out of these 200, 160 patients presented with

blackish discharge from the nasal cavity, paranasal sinus mucosal thickening, and pale/blackish discoloration of the nasal mucosa and hard palate. These patients underwent sinus debridement with antifungal medications in the otolaryngology department. Forty patients presented with one or more neurological symptoms such as headache, facial pain, numbness, loss of vision, ptosis, and ophthalmoplegia suggestive of cavernous sinus thrombosis. Twenty-five out of 40 patients received antifungal and anticoagulant (injection Enoxaparin) along with sinus debridement from a combined effort of the medicine and otolaryngology department. Eight patients denied surgical debridement and were lost to follow-up. Seven patients had focal lesions in the brain and skull bone that needed neurosurgical intervention along with sinus debridement and antifungal treatment.

DISCUSSION

ROCM is an infrequent fatal invasive fungal infection that usually manifests in immunocompromised individuals.^[22] Moreover, in the recent era of the COVID-19 pandemic, we have seen a surge in the number of mucormycosis cases. Debridement of necrotic tissue is the most important surgical procedure for mucormycosis. In these patients, drug delivery to the site of infection is poor due to extensive vascular thrombosis. As a result, medical treatment with antifungals alone is ineffective; surgical debridement is a must. The disease burden can be reduced by surgical removal of necrotic tissue until relatively healthy tissue is visible and a fungus-free surgical margin is confirmed by frozen section biopsy.^[15,21]

Here, we have briefed these seven cases to discuss the role of neurosurgeons and various approaches that can be offered to limit the comorbidity associated with surgery in the best possible way, as these patients have poor healing due to immunocompromised status. India bears a huge burden of DM among adults aged 20–79 years and it is the most common predisposing factor for mucormycosis.^[10] Along

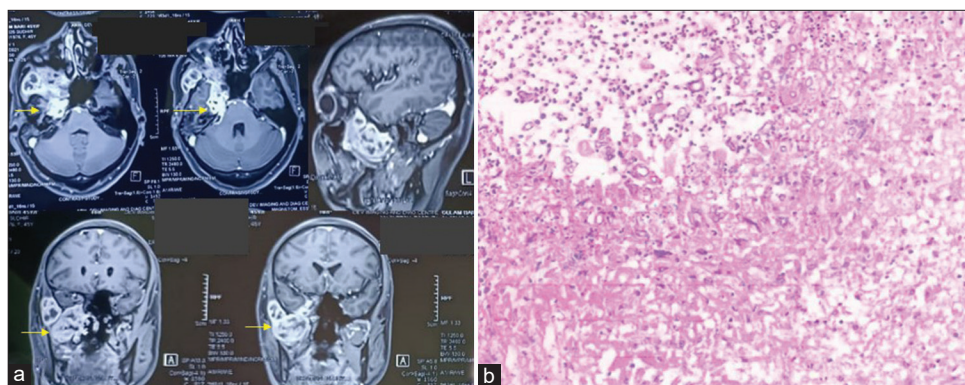


Figure 7: (a) Postcontrast T1W MRI brain showing heterogeneous enhancing mass in Meckel's cave extending to the right pterygopalatine fossa (yellow arrows) and (b) histopathological magnified image (×10) of excised specimen confirmed as mucormycosis.

Table 1 : Case summary.

Case no.	Age/sex	Clinical symptoms	Examination findings	History	Comorbidity	Imaging findings	Surgical procedure	Outcome
1	66/Male	Headache, altered mental status, swelling over right eye and face, right side nasal blockage and nasal bleeding, fever	GCS-8 (E1 V2 M5) with the left side hemiplegia, UMN type 7 th nerve palsy. Rt ptosis. DTR exaggerated and left side extensor plantar.	COVID recovered (steroid intake +)	DM (HbA1c-12.4%), HTN	CEMRI, necrotizing sinusitis of bilateral maxillary and ethmoidal sinus. MR angio-Rt ICA and MCA thrombosis	Right fronto-temporo-parietal craniectomy done	Died within 4 h postsurgery
2	65/Male	Headache, blackish discoloration, and swelling of the right eye	GCS-6 (E1 V1 M4), Rt ptosis. DTR exaggerated and bilateral extensor plantar.	COVID recovered (steroid intake +)	DM (HbA1c-10.4%), hypothyroidism	CEMRI-Mucosal thickening of the right maxillary, ethmoidal, and frontal sinus. Bilateral and symmetrical frontal lobe infarct. MR angio-bilateral ACA thrombosis.	Surgery deferred due to hemodynamic instability.	Died within 8 h of admission
3	32/Male	Headache, fever, and tender swelling over forehead	GCS-15 (E4 V5 M6) without any limb weakness. No ptosis/ ophthalmoplegia. DTR normal.	COVID recovered (steroid intake +)	No	Mucosal thickening of frontal sinus with lysis of frontal bone S/o frontal bone osteomyelitis	Bicoronal skin flap was raised and infected frontal bone was debrided. Defect was reconstructed using split calvarial frontal bone.	Alive
4	48/Male	Fever and swelling over forehead	GCS-15 (E4 V5 M6) without any limb weakness. No ptosis/ ophthalmoplegia. DTR normal.	COVID recovered (steroid intake +)	DM	Frontal sinusitis with frontal bone osteomyelitis	Outer table of frontal sinus was debrided through right eyebrow skin incision	Alive
5	48/Male	Fever, altered sensorium, nasal blockage	GCS-13 (E4 V4 M5) without any limb weakness. No ptosis/ ophthalmoplegia. DTR exaggerated.	COVID recovered (steroid intake +)	DM	Mucosal thickening of left maxillary, ethmoidal, and frontal sinus. The left frontal lobe abscess.	Left supraorbital craniotomy done through left eyebrow skin incision and abscess was drained completely	Alive
6	52/Male	Headache and fever	GCS-15 (E4 V5 M6) without any limb weakness. No ptosis/ ophthalmoplegia. DTR normal.	COVID recovered (steroid intake +)	DM, HTN	Mucosal thickening of the right maxillary and ethmoidal sinus. Multiple abscess in the right frontal and parietal lobe	Liposomal amphotericin-B only	Alive
7	48/Male	Blurring of vision on the right side gaze	GCS-15 (E4 V5 M6) without any limb weakness. No ptosis. Right 6 th nerve paresis. DTR normal.	No COVID infection	No identifiable predisposing factor	Heterogeneously enhancing mass lesion occupying right side Meckel's cave and extending into the right pterygopalatine fossa.	Right pterional craniotomy with gross-total excision of mass was done	Alive

with DM, the emergence of COVID-19 infection acted like a storm for the spread of this invasive fungus. Hyperglycemia, acidosis, and elevated free serum iron cause overexpression of GRP-78 receptor on endothelial cells of blood vessels and facilitate angioinvasion by interaction with CoH3 protein on fungal hyphae.^[6,10,14,25] COVID-19 virus further enhances this diabetogenic state by acting on angiotensin-converting enzyme 2 receptors in islet cells of the pancreas.^[10] Mucor produces an enzyme, ketoreductase which functions in a hyperglycemic state and enables them to grow and spread in an acidic environment.^[5] Immunological dysfunction in COVID-19 affected patients mainly in the form of reduced CD4/CD8 T-cell population and increases the predilection of opportunistic fungal infections. The use of steroids in COVID patients dysregulates glucose levels and suppresses phagocytic response and chemotaxis.^[11,14] In addition to hyperglycemia, iron metabolism is altered and a hyperferritinemic milieu is created in COVID-19 infection. This leads to excess intracellular iron accumulation, producing reactive oxygen species and leading to tissue damage.^[10,14]

Angioinvasion with hematogenous spread is a characteristic feature of mucormycosis. Fungal hyphae proliferate along the internal elastic lamina, causing hyperplasia of intima and thrombosis, ultimately resulting in occlusion of vessels. COVID-19 infection exhibits a similar feature of thrombotic microangiopathy (due to upregulation of the prothrombotic CX3CL1 marker), which may have a synergic effect with mucormycosis, responsible for the fulminant spread of infection.^[3,10,13,14,16] In this series, the aggressive invasion of the ICA (Case-1) and anterior cerebral artery (Case-2) from paranasal sinuses has resulted in decreased blood flow (ischemic stroke) causing hemispheric and ACA territory infarct. Aspergillosis, another fungal infection, has also angioinvasive characteristics with similar imaging features and predisposing factors. Therefore, only histopathology can differentiate between the two. In *Aspergillus*, hyphae show regular branching at acute angles, whereas *Mucor* shows irregular branching at 90° or greater. Tuberculosis is another cause of infection-induced cerebral infarctions. In these cases, the infarcts are primarily central (basal ganglia and thalami) due to the involvement of lenticulostriate and thalamostriate arteries.^[15]

The nasal cavity gets first affected following the inhalation of spores and results in discoloration and necrosis of the turbinates. The infection further extends to the paranasal sinuses and orbit causing cellulitis, ophthalmoplegia, and loss of vision and can also spread to the cavernous sinus with intracranial involvement.^[13] Intracranial involvement may manifest as cerebral abscess and most commonly it affects the frontal lobe. This contiguous spread could be due to associated hypoxia of the tissues in COVID-19 infection, which accentuates the partial infarction due to

fungal invasion. It deepens the extent of tissue necrosis and could be a nidus for abscess formation.^[4,6] The source of infection could be bacterially originating from the oral cavity, sinus, or orbit. Another possible source is fungus itself manifesting as a mycotic brain abscess either through primary infection or as an extension of rhino-cerebral-mucormycosis, which is infrequent.^[4] Case 5 presented with a frontal lobe abscess and was ipsilateral to the involved sinus. However, the culture was negative for fungal elements probably because amphotericin-B was started preoperatively. Case 6 showed isolated CNS involvement with multiple mucor abscesses over brain parenchyma, which is extremely rare, and the patient responded very well to amphotericin-B. No distant focus other than sinus was detected for possible hematogenous spread.

The intracranial spread occurs through vessels of the orbital apex (ophthalmic artery) or cribriform plate (ethmoidal artery) without causing any bone or dura involvement.^[15,21] Skull osteomyelitis is very uncommon and even if present, it occurs at the end of the disease.^[4] However, in our study, Cases 3 and 4 presented with frontal bone osteomyelitis in the early course without any intradural disease progression and were well reconstructed after debridement without any recurrences to date.

Another course of invasion includes a perineural extension which is a very rare complication reported in post-COVID ROCM patients.^[20] Following spore inhalation, the infection spreads to the pterygopalatine fossa through the sphenopalatine foramen. The pterygopalatine fossa then acts as the disease's epicenter, providing a route for infection to spread to different sites along the nerves and vessels that run through it. The maxillary nerve serves as a conduit for infection spread. Infections of the palate can occur through the greater and lesser palatine nerves and infections of the cheek and orbital soft tissues through the infraorbital nerve.^[13] Infection can also travel from the maxillary nerve to the cavernous sinus through the foramen rotundum. After reaching the cavernous sinus, the infection can ascend to Meckel's cave, where it can subsequently travel through the cisternal part of the trigeminal nerve to the brain.^[7,9,12] This is evident in MR imaging of Case 7 which is supported by the histopathologic diagnosis of mucor.

When mucor infection presents with intracranial extension, the mortality rate escalates to be in the range of 50–80%. The survival rate depends on several factors such as early diagnosis, immediate control of hyperglycemia, removal of precipitating factors such as steroids, surgical debridement of the necrotic tissue, and antifungal therapy.^[23] Antibiotics and antifungal medications should be started as soon as clinical suspicion is detected. If an intracranial extension is present, first-line medical treatment consists of i.v. liposomal amphotericin-B at a dose of 10 mg/kg body weight. It must be

continued until a favorable clinical response and resolution of the radiological feature of active infection is obtained, which may take a few weeks, after which oral posaconazole (300 mg twice a day for 1 day followed by 300 mg daily) or isavuconazole (200 mg thrice daily for 2 days followed by 200 mg daily) can be started.^[25] The liposomal form is preferred because it is less nephrotoxic and thus allows for higher doses to be given for a longer period. Second-line treatment includes intravenous posaconazole, which can be tried as salvage therapy in patients with impaired renal function or if amphotericin-based treatment fails. Amphotericin-induced renal toxicity should be closely monitored.^[3,18]

In a developing country like India, where diabetes is more prevalent, COVID-19-infected diabetic patients should be closely monitored for the danger signs and symptoms of ROCM. Patients should be kept informed of the warning symptoms such as headache, facial numbness and tingling, and blurred vision, which should result in early detection of the disease.^[11] Patients are typically immunocompromised and in poor overall health. Furthermore, the fulminant nature of the disease and the aggressiveness with which it is managed, patients frequently have considerable morbidity and a poor quality of life after surgery.^[11] Therefore, the authors accentuate an array of clinical manifestations of ROCM in India so that prompt diagnosis could be made and surgical approach could be individualized to decrease the burden of morbidities.

CONCLUSION

In high-risk patients, a high level of clinical suspicion combined with appropriate investigations should be performed as soon as possible. Symptoms and early warning signs of intracranial involvement should not be overlooked, as treatment delays can be fatal. A minimally invasive surgical approach is possible in view of decreasing the morbidity of large craniotomy.

Authors' contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by all authors. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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