Neurology Asia 2023; 28(3) : 639 – 648

Spectrum of neurological involvement in mucormycosis following COVID 19: A single tertiary centre study

[1]Somdattaa Ray, [1]Vikram V Kamath, [2]Arjun Raju, [3]Tulasi Nayak, [3]Aditya Moorthy, [4]Preeti GK, [3]Rohit Gaikwad, [5]Deepak Haldipur, [6]Vishwas Vijaydev, [3]Prithvi S Bachalli, [7]Madhusudan HV, [7]Praveen KS, [7]Arun MA, [7]Prahalad ST, [5]Dhanraj Gangolli

[1]Department of Neurology, [2]Department of Radiology, [3]Department of Oromaxillofacial Surgery, [4]Department of Ophthalmology, [5]Department of Otorhinolaryngology, [6]Department of Plastic Surgery, [7]Department of Neurosurgery, Trustwell Hospitals, Bangalore, India

Abstract

Background: This study aims to describe the clinical and imaging spectrum of neurological involvement in rhino-orbital cerebral mucormycosis (ROCM) following COVID. In this observational study, all patients with confirmed COVID associated mucormycosis were recruited. Consecutive patients with neurological signs and symptoms or patients with evidence of neurological involvement based on imaging were evaluated. MRI of brain and paranasal sinuses were done in 3T MRI scanner and evaluated by a radiologist. *Results:* A total of 182 patients were recruited into the study out of which 72 (39.56%) patients had neurological involvement. The mean age of the patients was 50.31±11.06 (Range: 33-83) years. A male preponderance was noted with 56 (74.67%) patients being male. The commonest symptom reported was unilateral vision impairment and periorbital swelling. Patients were noted to have both fulminant and indolent course of illness. Clinical evidence of neurological and orbital involvement was observed in 33 and 55 patients, respectively. Meningeal involvement (50%) was the commonest imaging finding noted in our study. Other common findings noted were skull-based osteomyelitis (44.44%), cavernous sinus thrombosis (29.17%), intracranial abscess (27.78%), cerebritis (22.22%), infarcts (33.33%), neuritis and intracranial haemorrhage (2.78%).
Conclusion: This study reports one of the largest single centre cohorts with neurological findings in COVID associated mucormycosis. COVID associated mucormycosis can present with plethora of neurological manifestations in imaging, such as infarct, intracranial and extracranial abscess, neuritis and nerve abscess, sinus thrombosis that may or may not be accompanied by focal neurological deficit corresponding to the anatomical involvement.

Keywords- fungal abscess, stroke, cerebral mycosis, fungal neuritis, cerebritis.

INTRODUCTION

Rhino-orbital cerebral mucormycosis (ROCM) is a life-threatening infection caused by fungi of the order Mucorales. The infection begins by inhalation of fungal spores leading to colonization and infection of paranasal sinus and nasal mucosa with subsequent spread to contiguous structures such as orbit, cavernous sinus and brain parenchyma.[1,2] Among patients with intracranial mucormycosis (ICM), Rhizopus species is the most frequently isolated organism.[3] ROCM is diagnosed by direct microscopic examination of the fresh tissue that reveals broad, non-septate hyphae branching at right angles.[4]

The estimated prevalence of ROCM in India is 0.14 per 1,000, seventy times higher than that in other countries.[5] The deadly COVID pandemic heralded the onset of yet another epidemic in India - COVID associated mucormycosis (CAM).[6] The unprecedented surge of mucormycosis cases was seen in immediate proximity of the second wave of COVID infection in India.[7] The cause is multi-fold. A triad of COVID infection, pre-existing diabetes mellitus and steroids predisposed patients to the development of CAM.[6] Severe COVID acute respiratory infection is likely to inflict significant

Address correspondence to: Somdattaa Ray, M36, 2221 Wesbrook Mall, Purdy Pavillion, University of British Columbia, Vancouver V6T 2B5, Canada. Tel: +17782276970, email: somray227@gmail.com

Date of Submission: 29 November 2022; Date of Acceptance: 28 June 2023

https://doi.org/10.54029/2023kfj

alveolar damage as well as alter innate immunity by affecting clusters of differentiation of T cell counts.[8] This immunosuppression is further exponentiated by the immunomodulatory drugs used to combat the cytokine storm associated with COVID. High ferritin levels seen in COVID infection is a substrate for growth of mucormycosis. New onset diabetes mellitus (DM) associated with COVID infection as a result of islet cell damage[9] as well as poorly controlled DM that worsened with steroid administration resulted in lower pH of serum and increased availability of unbound iron.[10] These were strong substrates for fungal growth that led to CAM. The cytokine storm further inflicted damage by causing insulin resistance.[11] Prolonged mechanical ventilation has also been associated with fungal co-infection.[12]

Presence of DM confers a significant risk to the development of intracranial extension of ROCM.[3] ICM is a dreaded complication and is associated with a mortality rate of 62-90%.[3] Studies describing the clinical and imaging manifestation of neurological involvement in ROCM are limited and mostly include case reports and case series prior to COVID pandemic.[3,13] In this paper, we discuss the neuroaxis affliction in CAM. We also aim to describe the clinical presentation and imaging correlates with respect to neurological involvement in CAM.

METHODS

We conducted an observational study at a tertiary care hospital. All patients with suspected ROCM were evaluated by the Otorhinolaryngology and Oromaxillofacial team. Patients with ophthalmological signs and symptoms were evaluated by the Ophthalmologist. Consecutive CAM patients presenting to outpatient clinics or to the emergency with neurological signs and symptoms or patients whose imaging showed evidence of neurological involvement even without focal neurological deficits were evaluated by Neurology and Neurosurgery team. All patients examined between April 2021 and December 2021 were recruited into the study. The study was approved by the institutional ethics committee.

The diagnosis of ROCM was confirmed from tissue samples of palate, nasal mucosa or sinus obtained by diagnostic nasal endoscopy and /or functional endoscopic sinus surgery. The tissue samples were examined by direct microscopy using KOH mount as well as histopathological examination and culture.

Patients were included into the study if 1) They had history of fever and /or history of COVID infection as confirmed by a positive COVID real time polymerase chain reaction (RT PCR) assay; 2) History suggestive of cranial nerve involvement, limb weakness, altered sensorium; 3) MRI , CT of brain that showed evidence of skull base osteomyelitis (SBO), intracranial extension, orbital and/ or meningeal involvement 4) Tissue diagnosis.

Patients were excluded from the study if (A) There was sinonasal involvement alone or sino orbital involvement without any evidence of acute meningeal or intracranial involvement and (B) Imaging was unavailable for review.

A standard form was used to record data from the case records regarding demographics, clinical history and examination, duration of illness, interval between the COVID infection and onset of symptoms related to ROCM, and course in the hospital.

If prior imaging was unavailable, patients underwent imaging Magnetic resonance imaging (MRI) and/ or CT (computed tomography) of brain and paranasal sinus. MRI of brain and paranasal sinus (plain and contrast) were obtained in a 3 Tesla MRI scanner (Siemens) and all the images were reviewed by a radiologist. The details of cavernous sinus involvement, location of infarct or bleed, internal carotid artery (ICA) thrombosis, intracranial and extracranial abscess, neuritis, SBO and meningeal thickening were recorded. The data was entered into the MS excel sheet and data was analysed using SPSS version 20 and MS Excel. Descriptive statistics were expressed in the form of percentage for categorical variables and mean ± standard deviation as well as range for continuous variables.

RESULTS

A total of 182 patients with CAM were seen in our centre. Among these, 72 (39.56%) patients had neurological impairment based on clinical findings and/or imaging and were included in our study after satisfying all criteria.

In our study, the mean age of the patients was 50.31±11.06 (Range: 33-83) years. A male preponderance was noted with 56 (74.67%) patients being male. The interval between the onset of ROCM symptoms and COVID diagnosis was 15.18 ±11.06 (range 3-60 days). Six patients developed ROCM symptoms while being treated for COVID infection. The mean duration of symptoms before presentation to the hospital is 8.4±9.4 days. Mean HbA1C at admission was

10.37±2.07. Six patients had HbA1C below 8 and two among them had normal HbA1c.

The commonest symptom reported was unilateral vision impairment and periorbital swelling (Table 1). Clinical evidence of neurological and orbital involvement was observed in 33 and 55 patients, respectively. Apart from 13 patients who had indolent progression of symptoms (symptoms for at least 2 weeks before presentation to the hospital), rest of the patients had rapid progression. Four patients had no orbital or neurological involvement on clinical evaluation but imaging showed orbital and intracranial lesions in three patients and basi-frontal lesions without orbital involvement in one patient.

Radiologically, infarctions were most commonly seen in frontal lobe, frontoparietal lobe, centrum semiovale and corona radiata. Infarcts were also seen in thalamus (n=2) (Figure 1A, 1B), gangliocapsular region (n=5), corpus callosum(n=2), pons (n=4), parietal (n=1), parieto occipital (n=1) and cerebellum (n=1). Among patients with acute ischemic stroke, bilateral infarcts were observed in 3 patients. Lacunar infarcts were seen in 11 patients. The lacunar infarcts were predominantly located in frontal, parietal region and deep white matter in corona radiata as well as centrum semiovale. Intracranial bleed was also observed (Figure 1C). Patient V had infarcts in anterior cerebral artery – middle cerebral artery watershed territory. Patient K had area of diffusion restriction in initial imaging that subsequently became well-defined abscesses in follow up scans. Patient J had bilateral strokes in both anterior and posterior circulation, bilateral ICA thrombosis and also had markedly decreased flow in mid basilar artery due to encasement by extra- axial lesion in the pre-pontine cistern extending from basi-sphenoid osteomyelitis.

Intracranial abscesses were seen in frontal lobe (n=8), basifrontal region (n=5), temporal lobe (n=6), basal ganglia (n=1) (Figure 1D, 1E) and pons (n=1) (Figure 1F). Cerebritis was observed in 16 patients (Table 2). The lesions were considered as cerebritis based on the irregular diffusion restriction in diffusion weighted sequences, hypointensities and isointensities within the hyperintense lesion in T2 weighted sequences and peripheral enhancement on contrast sequences. Three patients with cerebritis went on to develop abscess in the same location. One patient each had cerebritis in temporal and basifrontal location that subsequently evolved into abscess while in the third patient, bilateral paramedian frontal cerebritis progressed to form abscess. Patient S had diffuse cerebritis involving bilateral basifrontal lobes extending to genu of corpus callosum with abscess formation. Patient L had extradural abscess along with cerebritis. Concurrent abscess in one basifrontal lobe and cerebritis in another basifrontal lobe was seen in patient J (Figure 1G,1H). Patient M had multiple cerebritis and abscesses involving frontal, temporal, parieto occipital region and pons. Extracranial abscesses were observed in temporal fossa (n=1), cerebellopontine cistern (n=2) and midline in fronto basal region (n=2). Out of 21 patients with intracranial abscess, 19 (90.5%) patients had abscesses in close proximity to the infected tissue. All 5 (100%) patients with extracranial abscess were close to the infected tissue. Out of 16 patients with cerebritis, 14 (87.5%) patients had lesions close to the infected sinuses.

Extra axial abscess extending to Meckel's cave and then along trigeminal nerve with subsequent trigeminal neuritis was observed in 6 patients (Figure 1 H) (Table 2). In two patients, the lesion started as an abscess in the temporal lobe with subsequent spread through trigeminal nerve into cerebellopontine angle cistern (Figure 2A). Bilateral trigeminal neuritis was seen in one patient. The trigeminal neuritis was associated with pontine hyperintensity indicating spread of infection to trigeminal nuclei (Figure 1H).

Among 24 patients with imaging features of acute infarct, nine patients had reported relevant signs and symptoms pertaining to stroke. Optic nerve encasement was observed in 22 patients (Table 3). Ischemic optic neuropathy (Figure 2B, 2C) in conjunction with and without optic nerve encasement was seen in 5 and 4 patients, respectively. Multiple cranial nerve palsies in association with skull base osteomyelitis were noted in one patient and in association with meningeal thickening in two patients.

Patient V presented with features of stroke without any evidence of sinonasal involvement. ICM was confirmed after histological examination of the brain tissue obtained by stereotactic biopsy. Patient R had an indolent course with development of orbital symptoms 3 months after first symptom of sinusitis. His MRI brain showed focal temporal meningeal enhancement. Patient S had stroke secondary to ICA occlusion 5 months after completion of treatment of rhino-orbital mucormycosis (ROM). Patient J had recurrence of infarcts despite being on dual antiplatelets and anticoagulation. Her imaging showed severe SBO and ICA thrombosis. Patient U developed transient ischemic attack on stopping aspirin for one week

Table 1: Demographic and clinical features in post COVID mucormycosis with neurological involvement (n=72)

Sl. no	Features	n (%)
1.	Pre-existing Diabetes mellitus	45 (62.5%)
2.	Newly detected Diabetes mellitus	23 (31.94%)
3.	Steroid administration	69 (95.83%)
4.	Cheek/facial pain	20 (27.78%)
5.	Cheek numbness/ paraesthesia	7 (9.72%)
6.	Face swelling	14 (19.44%)
7.	Jaw pain	2 (2.78%)
8.	Eye pain	20 (20.78%)
9.	Unilateral eye swelling	27 (37.5%)
10.	Bilateral eye swelling	3 (4.17%)
11.	Unilateral vision impairment	29 (40.27%)
12.	Headache	18 (25%)
13.	Hemiparesis	9 (12.5%)
14.	Ptosis	2 (2.78%)
15.	Double vision	1 (1.39%)
16.	Bilateral vision impairment	3 (4.17%)
17.	Speech impairment	2 (2.78%)
18.	Bilateral lower limb weakness	1 (1.39%)
19.	Altered sensorium	5 (6.94%)
20.	Fever	3 (4.17%)
21.	Vomiting	1 (1.39%)
22.	Nasal discharge	2 (2.78%)
23.	Oral cavity pain	1 (1.39%)
24.	Breathing difficulty	1 (1.39%)
25.	Central retinal artery occlusion	14 (19.44%)
26.	Central retinal venous occlusion	1 (1.39%)
27.	Optic nerve involvement	37 (51.39%)
28.	Unilateral infranuclear 7^{th} nerve involvement	8 (11.11%)
29.	Bilateral 7 th nerve involvement	1 (1.39%)
30.	Supranuclear 7^{th} nerve involvement	1 (1.39%)
31.	9^{th} and 10^{th} nerve involvement	3 (1.39%)
32.	12^{th} cranial nerve involvement	2 (2.78%)
33.	Unilateral vision loss	28 (38.89%)
34.	Bilateral Vision loss	2 (2.78%)
35.	Unilateral ophthalmoplegia	27 (37.5%)
36.	Bilateral ophthalmoplegia	2 (2.78%)
37.	Dusky or necrotic palate	19 (26.39%)

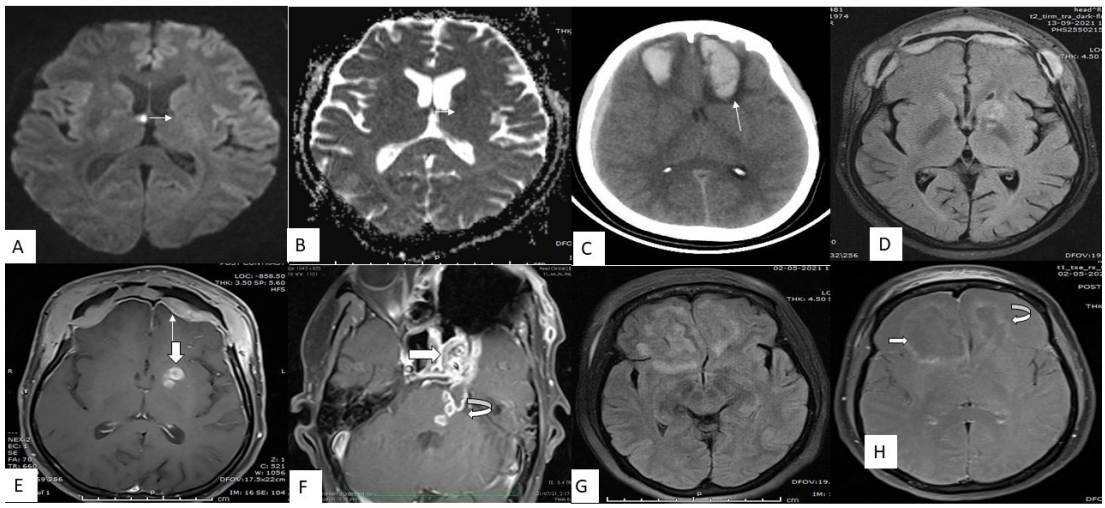

Figure 1A-1H. 1A and 1 B: DWI and ADC images show diffusion restriction and low ADC quotient over right medial thalamus (white arrow), respectively suggestive of right thalamic infarct. 1C: CT brain shows hyperdensity in bilateral frontal region (white arrow) suggestive of intracranial hemorrhage. 1D, 1E: FLAIR axial image shows hyperintensity in left caudate and globus pallidus that shows enhancement in T1 axial Fat Sat post contrast images suggestive of basal ganglia cerebritis (thick arrow). Frontal osteomyelitis (thin narrow) and adjacent meningeal enhancement is also noted. 1F: T1 axial Fat sat post contrast image shows multiple ring enhancing lesions in the left pons (curved arrow) with adjacent enhancement extending into the Meckel's cave (block arrow) suggestive of trigeminal nerve abscess. 1G: FLAIR images show inhomogenous hyperintensity in bilateral frontal region.1H: T1 Fat Sat post contrast image shows faint ring enhancement over right frontal and poorly defined peripheral enhancement over left frontal region suggestive of early abscess (block arrow) and cerebritis (curved arrow) respectively.

for a surgical procedure. He later expired due to hypovolemic shock secondary to profuse bleeding from the exenterated socket perhaps as a result of carotid artery rupture. Patient B had presented to us with sinonasal mucormycosis and multiple cranial neuropathies as a result of extensive SBO. She succumbed to severe hypernatremia secondary to central diabetes insipidus. During hospitalisation, 15 patients died as a result of various disease related complications.

DISCUSSION

There have been studies from India describing the profile of ROCM following COVID-19. These studies primarily highlighted the pattern of rhino- orbital involvement although neurological findings were also reported.[7,11] This study reports one of the largest single centre cohorts with neurological findings in CAM. We primarily focused on eaborating the clinical and imaging gamut of neuroaxis spread. The most common symptom observed in our cohort was unilateral vision impairment followed by unilateral eye pain, eye swelling and facial pain. These findings support the fact that orbital involvement is a forerunner of neuroaxis invasion. Facial pain as a result infraorbital nerve and trigeminal infiltration, serves as another channel for intracranial spread of ROCM.[14] Fever is an uncommon presentation in ICM[14] and that is reiterated in our findings.

In line with previous studies[11], in this study, onset of ROCM is seen 1-3 weeks after COVID infection and also during the course of active COVID infection. We also had patients with ROCM without positive COVID RT PCR but had evidence of recent COVID infection as proven by high titres of COVID antibodies.[11] A male predilection towards development of CAM is reported in our cohort as well as earlier reports. Moreover, males have also been noted to have greater degree of severe illness.[11] The significant predisposition towards males seems to be an extrapolation of male preponderance in COVID pandemic.[7] CNS involvement in CAM has been reported to range from 21-37%[15], while in this study, cerebral involvement was 39.56%.

Most common imaging finding seen in ICM is cavernous sinus thrombosis (CST) followed by ICA occlusion and infarcts.[11,13] In a study of 70 patients with CAM, intracranial extension was detected in 12 patients. Infarcts were observed in 6 patients and intracranial haemorrhage (ICH) was seen in 2 patients.[16] In another imaging study

Table 2: Imaging findings is post COVID Mucormycosis with neurological involvement (n=72)

Findings on MRI	n (%)
Acute ischemic infarcts	24 (33.33%)
Cerebritis	16 (22.22%)
Intra cranial abscess	21 (29.16%)
Extra cranial abscess	5 (6.94%)
Extra cranial lesion	4 (5.56%)
Cavernous sinus thrombosis	21 (29.17%)
Internal carotid artery stenosis	3 (4.16%)
Internal carotid artery thrombosis	13 (18.05%)
Superior ophthalmic vein thrombosis	6 (8.3%)
Cerebral venous sinus thrombosis	1 (1.38%)
Skull based osteomyelitis	32 (44.44%)
Meningeal enhancement	36 (50%)
Extra axial lesion (excluding abscess)	14 (19.44%)
Intracranial hemorrhage	2 (2.78%)
Subarachnoid hemorrhage	1 (1.38%)
Soft tissue extension into basifrontal region from the ethmoid cells	4 (5.56%)
Ischemic optic neuropathy	9 (12.5%)
Cranial nerve abscess/ neuritis	10 (13.89%)
Optic neuritis	3 (4.16%)
Optic chiasma abscess	1 (1.38%)
Unilateral trigeminal neuritis	6 (8.33%)
Bilateral trigeminal neuritis	1 (1.38%)
Trigeminal nerve abscess	4 (5.56%)

of 25 cases of CAM, patients were diagnosed to have infarcts, pachymeningeal enhancement, extension into the cavernous sinus, and perineural spread along the trigeminal nerve.[17] Meningeal thickening is the commonest imaging finding in our study, followed by SBO, CST, acute infarcts and intracranial abscess. Meningeal thickening in ROCM is nodular as a result of gelatinous exudates composed of inflammatory cells and fibrin. Arachnoiditis followed by hydrocephalus had been reported in earlier studies.[18] In our study, both smooth and nodular meningeal thickening are noted. None of our patients have hydrocephalus. SBO was initially reported in chronic mucormycosis.[19] Recent studies including our study have described SBO in acute mucormycosis. Apart from involvement of pterygoid, sphenoid and clivus, SBO was also seen to extend upto arch of C1 vertebrae in our patients, implying the early and malignant nature of SBO in PCM (Figure 2D).

Table 3: Orbital involvement in the entire Post COVID mucormycosis cohort (n=182)

Imaging finding	n (%)
Orbital cellulitis with intraconal abscess	8 (4.4%)
Unilateral Orbital cellulitis	76 (41.76%)
Bilateral orbital cellulitis	5 (2.75%)
Optic nerve encasement	22 (12.09%)

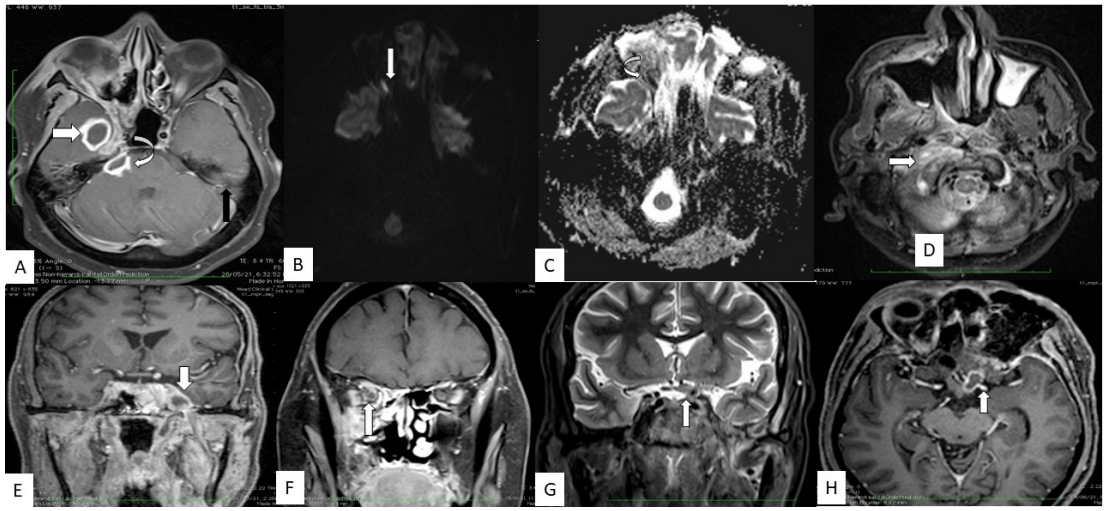

Figure 2A-2H. 2A: T1 axial Fat sat post contrast image shows ring enhancement over the right prepontine region (curved arrow) and ring enhancement in right temporal lobe (block arrow) suggestive of extra axial abscess in pre pontine cistern and temporal abscess. 2B and 2C: DWI and ADC images show increased diffusion restriction and low ADC over the right optic nerve (block and curved arrow) suggestive of right optic nerve infarction. 2D: Axial T2 weighted STIR image shows hyperintensities in right half of anterior arch of C1 vertebra (block arrow) consistent with osteomyelitis. Associated adjacent prevertebral soft tissue thickening seen. 2E: Coronal T1 Fat Sat post contrast image shows peripherally enhancing abscess in left para cavernous region (block arrow). 2F: T1 coronal Fat Sat post contrast image shows perineural enhancement along the right optic (block arrow) nerve suggestive of optic perineuritis. 2G: Coronal STIR image shows thickening of pre chiasmatic segment of left optic nerve (block arrow) – consistent with extension of infection along the nerve. 2H: Axial T1 Fat Sat post contrast image shows peripherally enhancing abscess along prechiasmatic segment of left optic nerve (block arrow).

Generally, the first intracranial structure to be involved is cavernous sinus.[13,14] Mucormycosis invades cavernous sinus through direct extension from sphenoid sinus, spreads from ethmoid sinus and orbits through valveless emissary and orbital veins respectively or spreads along neural foramina.[2,13] Para-cavernous extension of disease (Figure 2E) and superior ophthalmic vein thrombosis is noted among our patients, that was also described earlier.[20] Cavernous sinus disease confers a risk towards development of ICA occlusion with subsequent stroke.

Mechanisms of ICA thrombosis include inflammation resulting from retrograde spread of mucormycosis from ophthalmic arteries and direct invasion from the adjacent sphenoid sinus and cavernous sinus.[21] The fungi multiply within the internal elastic lamina, separating it away from the media. With endothelial invasion, carotiditis develops that leads to thrombosis, stenosis with subsequent infarction or development of aneurysmal dilatation or dissection with subsequent ICH.[22,23] Both ICA stenosis and thrombosis are noted in this study. Fungal invasion of skull base puts basilar artery at risk for thrombosis, posterior circulation stroke[24] and subarachnoid haemorrhage (SAH).[25] Although, no patient in our study had basilar artery occlusion, recurrent infarcts were observed in the posterior circulation in our patient who had basilar artery encasement secondary to basisphenoid osteomyelitis. Sudden onset bleeding from the eye socket of one of our patients was presumably secondary to rupture of a mycotic aneurysm of ICA. SAH and ICH (Figure 1C) were rarely observed in our cohort and in earlier studies and case reports.[22,23,26,27]

ICA occlusion was reported in 3.4- 27.7% of patients in earlier studies of CAM.[11,22] In our study, ICA occlusion is seen in 16 (22.22%) patients. Prothrombotic state induced by COVID, predilection towards angioinvasion by mucormycosis and uncontrolled DM might predispose towards neurovascular involvement in CAM.[22] The study by Kulkarni and colleagues revealed interesting insights on stroke following CAM. The study reported involvement of both anterior and posterior circulation, bilateral infarcts and simultaneous strokes in multiple territories.[22] Similar findings were noted in our study. However, their study reported that all their patients had large territory infarcts. On the contrary, most of our patients had lacunar infarcts. The possible explanation for the discrepancy could be the

difference in patient population. ROCM with clinical strokes were recruited by Kulkarni and colleagues, while our cohort included ROCM with clinical and imaging evidence of neurological involvement even before they developed neurological signs. This would also explain the disparity with respect to lower number of patients with clinical signs corresponding to imaging findings.

In concordance with earlier studies[28], cerebritis and abscesses are most frequently observed to originate in unilateral basifrontal lobe that later extends into bilateral frontal lobes through genu of corpus callosum among our patients. Spread to the basifrontal lobe is facilitated by the fungal infection of the ethmoidal sinus and cribriform defect into the skull base [29]. Temporal lobe is the second most common site for development of cerebritis in our study that is more likely seen in association with adjacent extracranial disease such as Meckel cave lesion and trigeminal neuritis. Similar observations were reported earlier.[28,30] Cerebritis is rare in parieto- occipital region and basal ganglia. Basal ganglia cerebritis has been more commonly reported among intravenous drug users (IDU).[3] Isolated ICM without sinonasal involvement has been observed following open head trauma and among IDU.[31] In this cohort, one patient with features of stroke had isolated ICM without sino-orbital involvement that was proven following stereotactic brain biopsy.

In this study, imaging has shown trigeminal nerve and optic nerve inflammation and abscess as a result of direct infiltration with fungal elements. Unilateral trigeminal neuritis extending upto Meckel's cave has been previously reported in CAM.[28] In our study, bilateral mandibular neuritis is noted in one patient. Intracranial invasion of ROCM through trigeminal nerve is evident as pontine lesions at the region of exit of trigeminal nerves[32] that begins as an area of focal diffusion restriction.

Ischemic optic neuropathy is observed in our patients that are associated with or independent of optic nerve encasement. It occurs as a result of central retinal artery occlusion due to angioinvasion or due to fungal invasion of optic nerve.[33] In addition to trigeminal neuritis and abscess, our patients also have perineural spread along the optic nerve subsequently leading to optic perineuritis (Figure 2F) and optic chiasma abscess (Figure 2G, 2H). Optic neuritis presented in the form of optic nerve hyperintensities in the prechiasmal segment of optic nerve. Unilateral and bilateral infranuclear facial nerve palsy (IFP) are found in our study, similar to earlier reports.[34] IFP is associated with multiple cranial nerve involvement as a complication of SBO in one patient. All but one patient with IFP has meningeal thickening that could be one of the possible mechanisms of IFP. Vestibulocochlear nerve and hypoglossal neuritis have also been reported in CAM.[35]

Fungal hyphal invasion of the parenchymal infarct has been considered as a preterminal event.[31] Although, we were unable to follow up every patient with infarctions, we have observed that patients with hyphal invasion of infarct as evident by blooming in SWI sequences[14], had good outcome when they were treated with full course of amphotericin. Patient with bilateral orbital involvement and cerebritis also showed significant improvement with surgical debulking and completion of amphotericin course. ROCM is well known to have a fulminant course of illness with mortality within few days of onset of first symptom as seen in many of our patients. However, the rapidly progressive course in ROCM is not universal. Few patients had symptoms up to four weeks limited to eye pain and face swelling before they developed vision impairment and were initiated on appropriate treatment. Progression of the disease can be rapid or indolent.[13,14] Until the factors dictating the course of ROCM in these patients are deciphered, every suspected ROCM patient needs to be evaluated and managed with aggression. In our cohort, delayed neurological complication were observed in few patients 4-6 months after successful completion of treatment for ROM. This mandates the need for long term follow up imaging of patients with ROM.

Our study is not bereft of limitations. Due to retrospective nature of study, not every patient was clinically followed up at regular intervals. Severe scarcity of amphotericin at the time when ROCM rose to epic proportions, led to treatment of some patients with only Posaconazole while rest received amphotericin. In view of inhomogeneous treatment data, we were unable to study the effect of surgical debridement and antifungal treatment in patients with neurological involvement.

In conclusion, ROCM after COVID infection can present with plethora of neurological findings in imaging, such as infarct, intra axial and extra axial abscess, neuritis and nerve abscess, sinus thrombosis that may or may not be accompanied by focal neurological deficit corresponding to the anatomical involvement. Neurological symptoms were noted in our patients long after completion of treatment in ROM, underscoring the need for long

term follow up even after completion of treatment. Both fulminant and indolent progression of the disease were observed in our cohort. This study expands the clinical and imaging spectrum of neurological involvement in ROCM following COVID.

ACKNOWLEDGEMENT

We would like to thank Soumya for her help in retrieval of records and Supriya Ray for editing.

DISCLOSURE

Financial support: None

Conflict of interest: None

REFERENCES

1. Dave TV, Nair AG, Hegde R, *et al*. Clinical presentations, management and outcomes of rhino-orbital-cerebral mucormycosis (ROCM) following COVID-19: a multi-centric study. *Ophthalmic Plast Reconstr Surg* 2021; 37(5):488. DOI: 10.1097/IOP.0000000000002030
2. Gamaletsou MN, Sipsas NV, Roilides E, Walsh TJ. Rhino-orbital-cerebral mucormycosis. *Curr Infect Dis Rep* 2012; 14(4):423-34. doi: 10.1007/s11908-012-0272-6.
3. Roden MM, Zaoutis TE, Buchanan WL, *et al*. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis* 2005; 41(5):634-53. doi: 10.1086/432579. Epub 2005 Jul 29.
4. Schelenz S, Barnes RA, Barton RC, *et al*. British Society for Medical Mycology best practice recommendations for the diagnosis of serious fungal diseases. *Lancet Infect Dis* 2015; 15(4):461-74. doi: 10.1016/S1473-3099(15)70006-X.
5. Prakash H, Chakrabarti A. Epidemiology of mucormycosis in India. *Microorganisms* 2021; 9(3):523. DOI: 10.3390/microorganisms9030523
6. Moorthy A, Gaikwad R, Krishna S, *et al*. SARS-CoV-2, uncontrolled diabetes and corticosteroids—an unholy trinity in invasive fungal infections of the maxillofacial region? A retrospective, multi-centric analysis. *J Maxillofac Oral Surg* 2021; 20(3):418-25. DOI: 10.1007/s12663-021-01532-1
7. Moorthy A, Nayak T, Bachalli PS, *et al*. COVID-associated rhinocerebral mucormycosis: a retrospective analysis of presentation and outcomes. *Eur Arch Otorhinolaryngol* 2022; 18:1-9. DOI: 10.1007/s00405-022-07544-y
8. Yang W, Cao Q, Qin L, *et al*. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China. *J Infect* 2020; 80(4):388-93. doi: 10.1016/j.jinf.2020.02.016.
9. Müller JA, Groß R, Conzelmann C, *et al*. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. *Nat Metab* 2021;3(2):149-65. doi: 10.1016/j.cmet.2021.05.013
10. Artis WM, Fountain JA, Delcher HK,Jones HE. A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis transferrin and iron availability. *Diabetes* 1982; 31(12):1109-14. doi: 10.2337/diacare.31.12.1109.
11. Sen M, Honavar SG, Bansal R, *et al*. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India–Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC), Report 1. *Indian J Ophthalmol* 2021; 69(7):1670. doi: 10.4103/ijo.IJO_1565_21
12. Yang X, Yu Y, Xu J, *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; 8(5):475-81. DOI: 10.1016/S2213-2600(20)30079-5
13. Chikley A, Ben-Ami R, Kontoyiannis DP. Mucormycosis of the central nervous system. *J Fungi* (Basel) 2019; 5(3):59. doi: 10.3390/jof5030059
14. Yohai RA, Bullock JD, Aziz AA, Markert RJ. Survival factors in rhino-orbital-cerebral mucormycosis. *Surv Ophthalmol* 1994; 39(1):3-22. doi: 10.1016/s0039-6257(05)80041-4.
15. Hoenigl M, Seidel D, Carvalho A, *et al*. The emergence of COVID-19 associated mucormycosis: a review of cases from 18 countries. *Lancet Microbe* 2022;3(7):e543-e552. doi: 10.1016/S2666-5247(21)00237-8.
16. Ramaswami A, Sahu AK, Kumar A, *et al*. COVID-19-associated mucormycosis presenting to the Emergency Department—an observational study of 70 patients. *QJM* 2021; 114(7):464-70. doi: 10.1093/qjmed/hcab190.
17. Joshi AR, Muthe MM, Patankar SH, Athawale A, Achhapalia Y. CT and MRI findings of invasive mucormycosis in the setting of COVID-19: experience from a single center in India. *AJR Am J Roentgenol* 2021; 217(6):1431-2. doi: 10.2214/AJR.21.26205
18. Parsi K, Itgampalli RK, Vittal R, Kumar A. Perineural spread of rhino-orbitocerebral mucormycosis caused by Apophysomyces elegans. *Ann Indian Acad Neurol* 2013; 16(3):414. doi: 10.4103/0972-2327.116921.
19. Chan LL, Singh S, Jones D, Diaz Jr EM, Ginsberg LE. Imaging of mucormycosis skull base osteomyelitis. *AJNR Am J Neuroradiol* 2000; 21(5):828-31. PMID: 10815656
20. Kaushik KS, Ananthasivan R, Acharya UV, *et al*. Spectrum of intracranial complications of rhino-orbito-cerebral mucormycosis—resurgence in the era of COVID-19 pandemic: a pictorial essay. *Emerg Radiol* 2021 ;28(6):1097-106. doi: 10.1007/s10140-021-01987-2
21. Patil A, Mohanty HS, Kumar S, Nandikoor S, Meganathan P. Angioinvasive rhinocerebral mucormycosis with complete unilateral thrombosis of internal carotid artery—case report and review of literature. *BJR| Case Rep* 2016: 20150448. doi: 10.1259/bjrcr.20150448
22. Kulkarni R, Pujari SS, Gupta D, *et al*. Cerebrovascular

involvement in mucormycosis in COVID-19 pandemic. *J Stroke Cerebrovasc Dis* 2022; 31(2):106231. doi: 10.1016/j.jstrokecerebrovasdis.2021.106231
23. Little JS, Cheng MP, Hsu L,Corrales CE, Marty FM. Invasive fungal carotiditis: A rare manifestation of cranial invasive fungal disease: Case series and systematic review of the literature. *Open Forum Infect Dis* 2019; 6(10):ofz392. doi: 10.1093/ofid/ofz392
24. Fu KA, Nguyen PL, Sanossian N. Basilar artery territory stroke secondary to invasive fungal sphenoid sinusitis: a case report and review of the literature. *Case Rep Neurol* 2015;7(1):51-8. doi: 10.1159/000380761.
25. Singh G, Vishnu VY. Neurological manifestations of rhino-oculo-cerebral mucormycosis in the COVID-19 era. *Nat Rev Neurol* 2021;17(11):657-8. doi: 10.1038/s41582-021-00560-2
26. Takahashi S, Horiguchi T, Mikami S,Kitamura Y, Kawase T. Subcortical intracerebral hemorrhage caused by mucormycosis in a patient with a history of bone-marrow transplantation. *J Stroke Cerebrovasc Dis* 2009; 18(5):405-6. doi: 10.1016/j.jstrokecerebrovasdis.2008.12.006
27. Sasannejad P, Ghabeli-Juibary A, Aminzadeh S, Olfati N. Cerebellar infarction and aneurysmal subarachnoid hemorrhage: An unusual presentation and rare complications of rhinocerebral mucormycosis. *Iran J Neurol* 2015; 14(4):222.
28. Singh H, Dua S, Goel A, *et al*. Rhino-orbital-cerebral mucormycosis in times of COVID-19: A neurosurgical experience. *Surg Neurol Int* 2021;12. doi: 10.25259/SNI_772_2021
29. Hosseini SMS, Borghei P. Rhinocerebral mucormycosis: pathways of spread. *Eur Arch Oto-Rhino-Laryngol Head Neck* 2005; 262(11):932-8. doi: 10.1007/s00405-005-0919-0.
30. Mehta R, Nagarkar NM, Jindal A, *et al*. Multidisciplinary management of COVID-associated mucormycosis syndemic in India. *Indian J Surg* 2022; 84(5):934-42. doi: 10.1007/s12262-021-03134-0
31. Malik AN, Bi WL, McCray B, Abedalthagafi M, Vaitkevicius H, Dunn IF. Isolated cerebral mucormycosis of the basal ganglia. *Clin Neurol Neurosurg* 2014; 124:102-5. DOI: 10.1016/j.clineuro.2014.06.022
32. Elzein F, Kalam K, Mohammed N, *et al*. Treatment of cerebral mucormycosis with drug therapy alone: A case report. *Med Mycol Case Rep* 2019; 23:4-7.
33. Bhatia H, Kaur R, Bedi R. MR imaging of cavernous sinus thrombosis. *Eur J Radiol Open* 2020; 7:100226. doi: 10.1016/j.mmcr.2018.10.005
34. Pal P, Singh B, Singla S, R. Kaur R. Mucormycosis in COVID-19 pandemic and its neurovascular spread. *Eur Arch Otorhinolaryngol* 2022; 279(6):2965-72. doi: 10.1007/s00405-021-07106-8
35. Gupta N, Dembla S. Cranial nerve involvement in mucormycosis in post-COVID patients: a case series. *Egyptian J Radiol Nuclear Med* 2022; 53(1):1-0. https://doi.org/10.1186/s43055-022-00700-8