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Original Article

COVID-19 associated rhino-orbital-cerebral mucormycosis: An observational study from Eastern India, with special emphasis on neurological spectrum

Souvik Dubey, Debaleena Mukherjee [1], Peyalee Sarkar [1], Pradip Mukhopadhyay, Debasis Barman, Manimoy Bandopadhyay, Alak Pandit, Amitabha Sengupta, Sudip Das, Soumitra Ghosh, Souvik Adhikari, Partha Sundar Biswas, Pranabananda Pal, Himadri Roy, Nilanjana Patra, Amrita Das, Pallab Sinha, Md. Karimulla Mondal, Smiti Rani Shrivastava, Kumkum Bhattacharya, Madhumita Mukhopadhyay, Kamraan Ahmed, Tushar Kanti Halder, Mainak Saha, Kaoshar Ahmed, Souvik Maity, Abhishek Mandal, Deblina Chatterjee, Srijana Saha, Arpita Chunakar, Alangkar Saha, Biman Kanti Ray*

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A B S T R A C T

Aims:
1: Describe the epidemiology and determine risk factors for COVID-19 associated mucormycosis.
2: Elaborate the clinical spectrum of Rhino-Orbital-Cerebral Mucormycosis (ROCM), pattern of neuroaxis involvement and it's radiological correlates.
Methods: Observational study. Consecutive, confirmed cases of mucormycosis (N = 55) were included. A case of mucormycosis was defined as one who had clinical and radiological features consistent with mucormycosis along with demonstration of the fungus in tissue via KOH mount/culture/histopathological examination (HPE). Data pertaining to epidemiology, risk factors, clinico-radiological features were analysed using percentage of total cases.
Results: Middle aged, diabetic males with recent COVID-19 infection were most affected. New onset upper jaw toothache was a striking observation in several cases. Among neurological manifestations headache, proptosis, vision loss, extraocular movement restriction; cavernous sinus, meningeal and parenchymal involvement were common. Stroke in ROCM followed a definitive pattern with watershed infarction.
Conclusions: New onset upper jaw toothache and loosening of teeth should prompt an immediate search for mucormycosis in backdrop of diabetic patients with recent COVID-19 disease, aiding earlier diagnosis and treatment initiation. Neuroaxis involvement was characterized by a multitude of features pertaining to involvement of optic nerve, extraocular muscles, meninges, brain parenchyma and internal carotid artery.

1. Introduction

The COVID-19 pandemic, along with steroid as a therapeutic armamentarium, in association with diabetes, and irrational use of antibiotics make the land fertile for fungal growth, as evidenced by the recent surge of mucormycosis which mostly entangles the sinuses, orbits and brain [1,2].

The term mucormycosis was coined by American pathologist R. D. Baker. In 1885, German pathologist Paltauf reported the first case of mucormycosis in humans. In 1943, Gregory et al. described the first case of rhino-orbital cerebral mucormycosis associated with diabetes [3–6]. Mucormycosis, depending on organ/s involved, is further sub classified as, rhino-orbital-cerebral mucormycosis (ROCM) which is most commonly observed, followed by cutaneous, pulmonary,disseminated, renal and gastrointestinal [7]. Following

* Corresponding author.
E-mail address: bimankantiray2019@gmail.com (B.K. Ray).
[1] Debaleena Mukherjee and Peyalee Sarkar contributed equally, henceforth considered as joint second author.

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Aspergillus, Mucorales fungi are the next most common pathogens in subjects with haematological malignancy, haematopoietic stem cell transplantation, solid organ transplantation and are increasingly being recognized in individuals with diabetes mellitus [7]. Strikingly, outbreaks have been observed earlier, following natural disasters [8]. The association between COVID-19 and mucormycosis is already established but presence of two important confounders, diabetes and indiscriminate use of steroids, make it difficult in establishing the exact cause and effect relationship. SARS-CoV-2 virus itself has been implicated in disruption of cell mediated immune response leading to invasion, tissue necrosis and thrombosis by mucormycosis [9]. Factors on which mucor growth may depend, like mask reuse, oxygen therapy, overuse of zinc, poor oral hygiene, addictions, environmental factors, specific habits like gardening, occupational exposures at construction sites, exposure to farm animals, pets and probable symbiotic relationship with COVID-19 virus need further detailed studies [10]. Wide array of mucormycosis associated neurological symptoms like headache, proptosis, ptosis, double vision, diminution of vision, facial pain, deviation of angle of mouth, facial numbness, focal weakness, altered sensorium and seizure stem from involvement of specific neuro anatomical substrate/s by this deadly fungus [11–14].

Studies depicting clinical features of ROCM and patterns of neuroaxis involvement along with it's radiological correlates, fall short of their actual need. These are of utmost importance in aiding early diagnosis, predicting the natural history of ROCM and skewing towards a favourable outcome. Authors here intend to show the entire neurological spectrum of ROCM and it's radiological correlates, from a tertiary care, referral based apex institute of Eastern India.

2. Subjects, materials and methods

The study is an observational study. It was carried out from April 2021 to June 2021 at a tertiary care referral based institute, declared as apex hub for management of mucormycosis in Eastern India (Fig. 1).

All consecutive, confirmed cases of mucormycosis (N = 55) were included in the study {a case of mucormycosis was defined as one who had clinical and radiological features consistent with mucormycosis along with demonstration of the fungus in tissue (broad, aseptate or pauci-septate hyphae with wide-angle branching and evidence of tissue invasion) via KOH mount/culture/histopathological examination (HPE)}. The clinical features considered were new onset toothache/loosening of tooth, headache/retro-orbital pain, facial swelling, erythema, ptosis/proptosis, facial numbness, deviation and focal neurodeficits, developing recently in a background of COVID-19 disease in patients who had multiple risk factors like diabetes along with steroid use. Radiological criteria for diagnosis were dependent on presence of features of invasive fungal disease like bony erosion, extraocular muscle, vascular and parenchymal invasion. COVID associated mucormycosis (CAM) was defined as occurrence of mucormycosis in a subject with current/previous diagnosis of COVID-19 (RT-PCR/Rapid antigen test positive for SARS-CoV-2). Cases were considered as Early CAM when mucormycosis was diagnosed $\leq$7 days and Late CAM when they occurred $\geq$8 days after COVID-19 diagnosis [15].

The subjects were thoroughly evaluated with detailed history taking, ophthalmological, neurological, ear, nose, throat and sinuses examinations along with imaging and electro-physiological studies. Data regarding time gap between onset of mucor related symptoms and first contact with healthcare/treatment initiation were noted.

All subjects on admission underwent 3 T Magnetic Resonance Imaging (MRI) of brain, orbits and paranasal sinuses (PNS), both plain {T1, T2/T2 Fluid Attenuation Inversion Recovery Sequence (FLAIR), T2 Fat Suppression (FS), Gradient Echo Sequence (GRE), Diffusion Weighted Imaging (DWI), Apparent Diffusion Coefficient (ADC)} and contrast studies and Magnetic Resonance Angiography (MRA) of brain vessels except in cases with contraindications. CT PNS was also done. Visual Evoked Potential (VEP) studies were done on the day of admission, Facial Nerve Conduction Studies (NCS) (in subjects with facial nerve involvement) and Forced Duction Test (FDT) (in cases of ophthalmoplegia) were performed on day 2 of admission. Cerebrospinal fluid analysis (CSF) was performed for all who presented with clinical or radiological features of meningeal/parenchymal (except stroke) involvement.

The subjects were evaluated by a multidisciplinary team comprising of neurologists, ophthalmologists, endocrinologists, otorhinolaryngologists, physicians, microbiologists, pathologists, and plastic surgeons as per standard protocol. Intravenous Amphotericin B deoxycholate/Liposomal amphotericin B was administered for minimum of three weeks followed by Posaconazole 300 mg BD on day 1 and 300 mg OD (oral) thereafter. Debridement of local necrotic tissue through endoscopic or open approach, orbital floor clearance and exenteration were done where indicated. Socioeconomic status of the subjects was assessed as per the Modified Kuppuswamy socioeconomic scale updated for the year 2021 [16]. Data were analysed using percentage of total cases.

3. Results

Epidemiology and risk factors: Mean age of subjects was 53 ± 10.28 years, with 33 (60%) being in between forty to sixty years of age, with a male predominance (35, 63.64%). Forty-three subjects (78.18%) were from rural background. Thirty two subjects (58.18%) belonged to lower middle class and the rest were from upper middle class. Assessment of risk factors (Table 1) revealed all subjects (100%) had Diabetes Mellitus (as per American Diabetes Association diagnostic criteria) at the time of diagnosis with Mucormycosis and most strikingly 21 subjects (38.18%) had been diagnosed with diabetes for the first time, during the course of SARS-CoV-2 infection. 46 subjects (83.64%) had RT-PCR positive SARS-CoV-2 infection in the recent past. Remaining 9 subjects (16.36%) had clear symptoms suggestive of SARS-CoV-2 defined illness, however did not have previous RT-PCR reports. As these subjects had been previously vaccinated, Covid IgG antibodies were not done. Time gap between RT-PCR positivity/covid like symptoms to onset of mucormycosis specific symptom/s ranged between 1 and 8 weeks. Early CAM was observed in 6 subjects (13.04%), whereas late CAM in 40 (86.96%). Twenty-six subjects (47.27%) had evidence of SARS-CoV-2 associated pneumonia. Thirty-three subjects (60%) had history of steroid intake during SARS-CoV-2 infection. To note, 22 subjects (40%) did not have definite history or documentation of steroid use. Forty-four (80%) subjects had history of hospital admission. Mean length of previous hospital stays was around 10–11 days. Thirty three subjects (60%) had been treated with oxygen therapy (via nasal cannula/face mask/non rebreathing mask). None of them had required invasive ventilation.

Answers to questions on mask use habits were ill consistent and beyond analysis. Assuming that SARS-CoV-2 and ROCM share a common route of entry, history of anosmia was stressed, and surprisingly 29 subjects (52.73%) infected with mucormycosis had history of anosmia associated with SARS-CoV-2 infection. Keeping the pathophysiology of mucormycosis in mind, questions directed to specific hobbies and oro-nasal hygiene (including addictions) revealed that 14 subjects (24.45%) had history of construction site exposure. A fair number of subjects (14, 24.45%) indulged in farming and 13 (23.64%) had history of significant exposure to

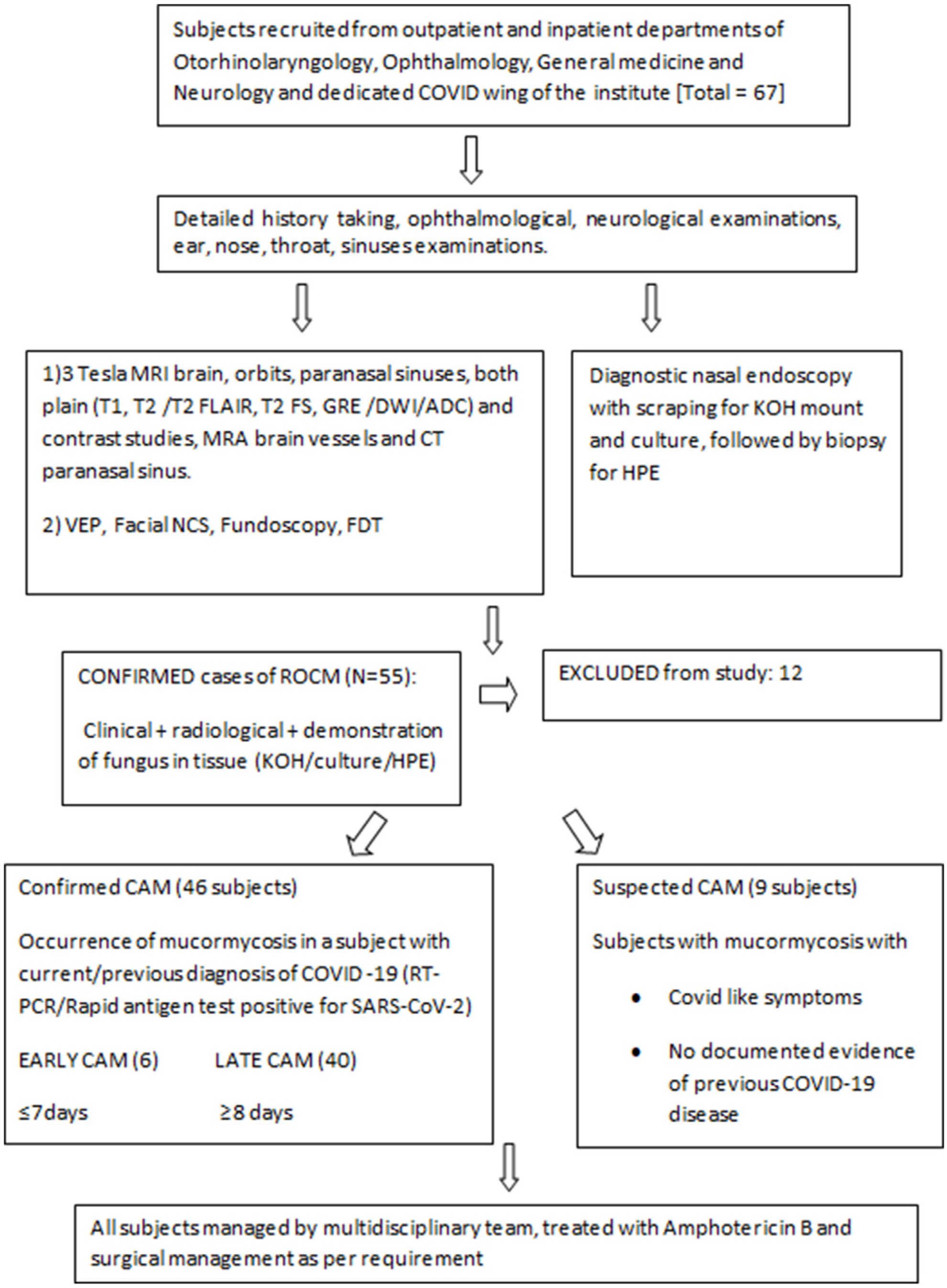

Fig. 1. Steps of methodology.

Table 1
Risk Factors for developing Mucormycosis.

Risk factors	Number of cases (%) (n = 55)
Diabetes Mellitus	55 (100)
RT- PCR COVID positive	46 (83.64)
COVID Pneumonia	26 (47.27)
Steroid therapy	33 (60)
Anosmia	29 (52.73)

animals in form of pets or animal husbandry. Among addictions, smoking, betel and tobacco chewing/sniffing habits were found commonly (25 male subjects, 71% of males) in our study group.

A gap of nearly 2 months between onset of mucor related symptoms to its final diagnosis and treatment initiation perhaps reflects the initial lack of awareness about ROCM among health care workers, especially in the background of COVID-19 illness.

Non neurological burden: The non-neurological disease burden can be broadly classified into symptoms and signs related with sinus invasion and that from orbital involvement. Careful interpretation and dissection of imaging correlated well with clinical features. Unilateral nasal blockade and discharge (often blackish) was present in more than 90% of ROCM. Significant observations included occurrence of upper jaw tooth pain and loosening of teeth in 17 subjects (30.91%) (Table 2) and blackish discoloration over palate and palatal necrosis in nearly 50%.

Table 2
Symptoms of subjects presenting with ROCM.

Clinical symptoms	Number of cases (%) (n = 55)
Headache	45 (81.82)
Ptosis/Proptosis	43 (78.18)
Retro-orbital pain	34 (61.82)
Facial numbness	31 (56.36)
Diminution of vision	27 (49.09)
Tooth ache/loosening	17 (30.91)
Diplopia	13 (23.64)
Facial deviation	11 [20]
Disorientation	9 (16.36)
Focal weakness	6 (10.91)
Nasal regurgitation/Nasal intonation	5 (9.09)
Dysarthria	4 (7.27)
Seizure	1 (1.81)

Unilateral cheek swelling, pain, eye lid swelling, lid ulcerations, blackish discolorations, conjunctival edema were common findings (present in 90%, 77%, 80%, 70%, 56%, 40% respectively). Radiologically nasal cavity (55, 100%), maxillary sinus (52, 94.55%) and ethmoid sinus (52, 94.55%) were most commonly affected.

Burden of neuroaxis involvement: Among diverse spectrum of neurological symptoms observed (Table 2), headache (45 subjects,81.82%) and proptosis/ptosis (43 subjects, 78.18%) were most common, followed by retro-orbital pain (34 subjects, 61.82%), facial numbness (31 subjects, 56.36%) and diminution of vision (27 subjects, 49.09%), (% in bracket indicates % of unilateral involvement barring headache). Headache followed by proptosis/ptosis and rapid diminution of vision was a common sequence of symptoms reported by majority of cases. Proptosis/ptosis, retro-orbital pain, facial numbness and diminution of vision were bilateral in 10%, 8%, 5% and 3% of the subjects, respectively. Facial deviation was reported in 11 cases (20%). Dysarthria and double vision (diplopia) were observed in 4 (7.27%) and 13 subjects (23.64%) respectively. Nasal regurgitation of food (liquids more than solids) and nasal intonation of speech were noticed in 5 subjects (9.09%). Nine cases (16.36%), developed disorientation during course of the illness. Focal deficit in form of limb weakness was observed in only 6 cases (10.91%). However, seizure was seen in only 1 subject. Our observations reflect, clinical signs due to neuroaxis involvement may not always correlate with clinical symptoms. Among diverse clinical signs (Table 3), extraocular movement abnormalities were most common (32 subjects, 58.18%), of which isolated lateral rectus involvement was seen in 3 subjects (5.45%). Bilateral extraocular movement restriction was observed in 4 cases (7.27%). Unilateral complete ophthalmoplegia was seen in almost half of the subjects (27, 49.09%). Optic nerve involvement was observed in 29 cases (52.73%) which was unilateral in 25 cases (45.45%) and bilateral in 4 (7.27%). Clinical objective signs of unilateral trigeminal nerve involvement (sensory more than motor) were noticed in 26 cases (47.27%). Only two subjects had signs of bilateral trigeminal nerve involvement. Facial nerve involvement in mucormycosis was seen in 22 subjects (40%) of which 3 subjects (5.45%) had upper motor neuron (UMN) type and 19 cases (34.55%) had lower motor neuron (LMN) type involvement. Brain parenchymal involvement though multifactorial (direct fungal invasion, stroke due to mucormycosis) was not uncommon, seen in 19 subjects (34.55%).Meningeal involvement was also seen in 25% (14 cases). Importantly, though CRP, D-Dimer and ferritin levels of all the subjects during the time of SARS-CoV-2 infection were not available, blood reports after diagnosis of mucormycosis, showed CRP more than 5 times elevated, D Dimer more than 3 times elevated and ferritin level more than 3 times elevated in 85%, 75% and 70% of subjects respectively.

Table 3
Clinical signs of subjects with ROCM.

Clinical signs	Number of cases (%) (n = 55)
Extraocular movement restriction	32 (58.18)
Optic nerve involvement	29 (52.73)
Facial numbness	26 (47.27)
Facial nerve involvement	22 [40]

Radiological correlates: Imaging of sinuses revealed nasal cavity (55 subjects, 100%), maxillary sinus (52, 94.5%) and ethmoidal sinus (52, 94.5%) involvement as most common. CT scan and MR imaging of Orbit showed 33 subjects (60%) with orbital wall invasion (breach in lamina papyracea/medial wall of orbit) and 29 subjects (52.73%) had extraocular muscles involvement either in combination or in isolation. Among extraocular muscles, involvement of medial rectus was most commonly observed in 27 subjects (49.09%) followed by inferior rectus involvement in 26 cases (47.27%). Orbital soft tissue involvement was observed in 30 subjects (54.55%). Orbital apex was invaded by mucormycosis in 23 (41.81%) cases and 10% had bilateral involvement. Cavernous sinus involvement was seen in 15 subjects (27.27%) and was bilateral in 8%. It is noteworthy that 25 subjects (45.45%) had unilateral facial muscles involvement and was bilateral in 12% of cases. Pterygoid muscles were involved in 31 subjects (56.36%). Intensity changes were obvious in pterygopalatine fossa and infratemporal fossa unilaterally in 39 subjects (70.91%) and bilaterally in 18%. Intensity changes over parotid gland unilaterally were observed in about 8% of subjects. Stigma of acute to subacute stroke was found in 11 subjects (20%). Hemorrhagic transformation was seen in two cases of stroke. Stroke correlated well with the side where internal carotid was involved/more involved (in case of bilateral ICA involvement), and most common observation was presence of watershed infarction (superficial and deep territory) with 4 patients having ACA/MCA and MCA/PCA territory watershed infarction. Among the stroke patients, Internal carotid artery (ICA) at the level of cavernous sinus was encased by mucormycosis in 10 cases (18.18%), while MR angiography showed normal calibre of ICA on the affected side in 1 subject (1.82%).Bilateral ICA involvement was observed in 2 subjects (3.64%). Additionally, 4 subjects (7.27%) demonstrated ICA involvement without any evidence of infarction. Meningeal enhancement was found in 14 subjects which constituted 25.45% of cases. Enhancement over anterior temporal lobe was most common (five subjects), followed by over frontal lobe. Radiological evidence of direct brain parenchymal invasion by mucormycosis was seen in 8 subjects (14.55%). Frontal lobe involvement (gyrus recti) was most common (five subjects) with two subjects having temporal lobar invasion (Fig. 2). Careful and meticulous interpretation revealed:

1) Clinically silent disease with radiological evidence suggestive of clinico-radiological dissociation in 25% of subjects.
2) Unilateral clinical symptoms and signs with features of bilateral radiological involvement in 33% of cases

4. Discussion

Epidemiology and risk factors: Our observations revealed, middle aged (forty to sixty years) males, and rural, middle class population, were most affected. All subjects were found to be diabetic at the time of diagnosis of mucormycosis. It was noteworthy that a fair proportion of subjects were diagnosed to have new onset diabetes during or following the course of COVID-19 illness. Whether this is responsible for immune dysregulation, making subjects susceptible to mucormycosis needs future probing [17].

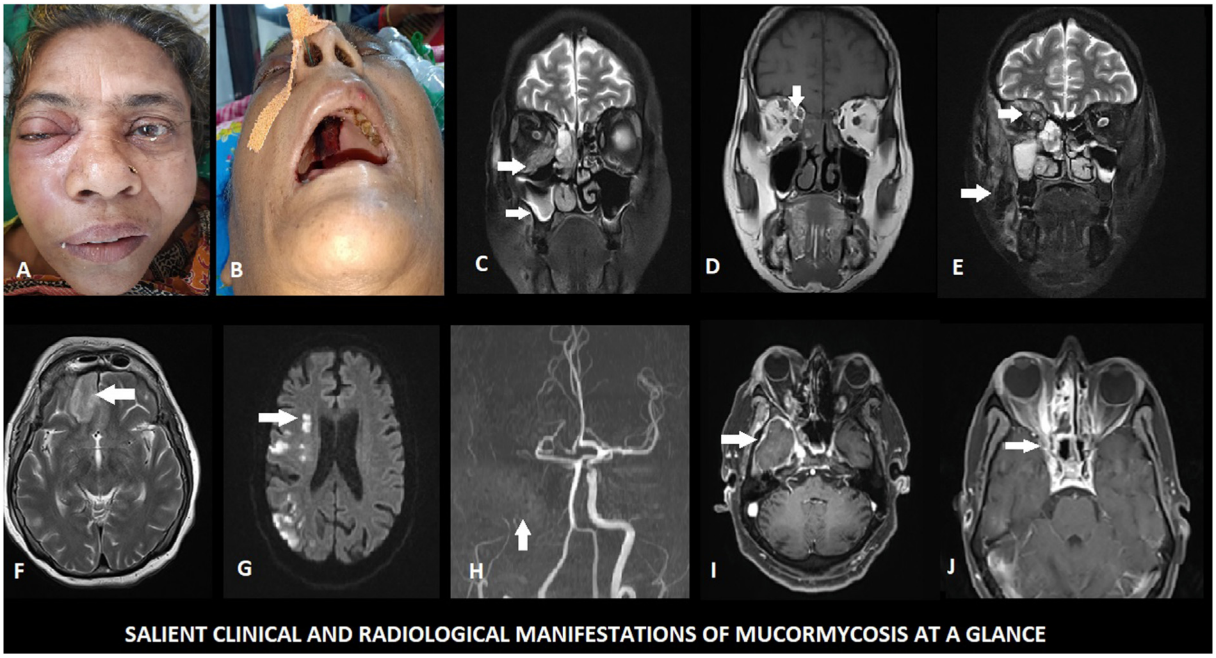

Fig. 2. Salient clinical and radiological manifestations of mucormycosis at a glance.
A: Right eye proptosis with malar edema, erythema and flattening of right nasolabial fold.
B. Blackish discoloration, ulceration and perforation of hard palate.
C. MRI brain, T2, coronal image showing right orbital soft tissue and extraocular muscle infiltration and sinusitis.
D. MRI brain, T1 fat suppression, coronal showing edematous and bulky extraocular muscles.
E. MRI brain, T2 fat suppression, coronal showing sinusitis, orbital soft tissue, extraocular muscle, optic nerve and facial muscle infiltration.
F. MRI brain, T2 axial showing hyperintensity in right basi-frontal region suggestive of cerebritis.
G. MRI brain, axial, DWI showing hemodynamic stroke involving superficial and deep watershed zones.
H. MR angiography brain vessels showing no flow in right Internal carotid artery petrous and cavernous segments onwards, in the same patient.
I. MRI brain, axial, contrast image showing meningeal enhancement in right temporal region.
J. MRI brain,axial, contrast showing enhancement in right orbital apex and cavernous sinus.

Majority were proven cases of CAM while the remaining had history suggestive of COVID like illness in the recent past. COVID pneumonia was observed in a large majority. Although 60% of subjects had definite history of receiving steroids, it was not confirmed in 40% [18,19]. Though majority had history of hospital admission and more than half were treated with oxygen, they were not universal in our study group. Prolonged hospital stay (more than three weeks) and mechanical ventilation during COVID-19 disease failed to establish any relationship with CAM in our study population. More than half of the subjects, who had anosmia associated with SARS-CoV-2, later developed ROCM, which might suggest some intriguing relationship with the route of entry (nasal) of mucormycosis spores. Assessment of occupational risk factors unveiled that construction site jobs, work in animal husbandry and farming may impose increased threats, however to declare strength of association, it demands future well designed studies. Single most important and noteworthy observation, was that multiple risk factors when present simultaneously made individuals more susceptible to ROCM rather than any single risk factor alone [17,19].

Non neurological burden: ROCM started unilaterally in almost all cases. Unilateral nasal blockade, blackish discharge, maxillary sinus and ethmoid sinus involvement were very common, similar to other studies. Unilateral cheek swelling, pain, eye lid swelling, conjunctival edema, chemosis, proptosis, lid and cheek ulceration and blackish discoloration, necrosis were very frequent findings, again similar to other studies [17,20].

Three most noteworthy non neurological observations were:

1) New onset tooth ache/loosening primarily involving the upper jaw was frequently observed and was often the sole presenting manifestation.
2) Blackish discoloration over palate and palatal necrosis were seen in nearly half of the subjects, who ultimately had a poor prognosis despite aggressive therapy.
3) Almost one fourth of subjects without significant nasal and PNS related symptoms with negative endoscopic findings had radiological stigma of disease in mentioned areas, and one third with clinically unilateral disease had radiological stigma of bilateral involvement, emphasizing value of appropriate imaging in ROCM [21].

Pattern of neuroaxis involvement in ROCM, symptoms, signs and it's radiological correlates:

1) **Proptosis/ptosis**: In critical analysis, proptosis was far more common in ROCM in our study which is quite similar with other studies. Asymmetrical proptosis is the result of localized increase in intraorbital contents due to expanding lesions of the orbit and in lesions arising from neighboring structures encroaching the orbit [22]. In ROCM, proptosis might stem from increase in intraorbital content, intraorbital invasion, extraocular muscle infiltration, or sequelae of intracranial lesion. Ptosis in ROCM might thus be due to myogenic, neurogenic or mechanical cause [23]. Radiological assessment substantiated the clinical findings well, with,

myogenic weakness (due to extraocular muscles infiltration) and mechanical compression being the common causes of proptosis/ptosis, followed by neurogenic weakness (due to third nerve involvement at the level of superior orbital apex or cavernous sinus).

2) **Headache**: Unilateral headache, on the side of the lesion was more frequent than holocranial headache. Pain sensitive structures in brain are meninges, large pial arteries, venous sinuses, and trigemino-cervical complexes (TCC). Extra cranial pain sensitive structures are scalp and sinuses. Mucormycosis can involve all the substrates leading to headache [24]. Radiological evaluation revealed sinuses involvement as most common followed by superior orbital apex and cavernous sinus involvement. Meningeal involvement (characteristically focal) was also fairly common, present in about one fourth of subjects.
3) **Retro-orbital pain**: Retro-orbital pain unilateral to the side of involvement was present in more than half of the subjects. Causes range from local space occupying lesion, invasive lesion, granulomatous lesion, vascular cause (angioinvasion/vaculitis), and optic nerve demyelination. In our study, all cases were due to fungal invasion in retro-orbital space, entering via disruption of lamina papyracea. Radiological evaluation also revealed orbital soft tissue involvement in more than half the subjects. Bilateral retro-orbital pain was relatively rare [25].
4) **Diminution of Vision**: Diminution of vision apart from problems pertaining to media stem from optic nerve involvement. In this study, a little less than half of the subjects had unilateral and only 7% had bilateral optic nerve involvement. It was either due to direct fungal invasion/infiltration, as evidenced by optic nerve or optic nerve sheath (2 subjects) intensity changes, or compression of optic nerve by damaged soft tissue in orbital cone/retro-orbital space (majority). Some subjects had involvement of optic nerve at the level of superior orbital apex, evidenced by imaging. However all subjects, who had intensity changes over superior orbital apex didn't complain of diminution of vision, suggesting clinically asymptomatic optic nerve involvement was also not uncommon in ROCM. In two subjects, diminution of vision was found to be due to central retinal arterial occlusion, indirectly suggestive of angioinvasion by mucormycosis. Vision loss was striking in two cases of clinical and radiological panophthalmitis [26–28].
5) **Facial numbness**: Unilateral trigeminal V2 distribution sensory loss was a consistent clinical finding, present in nearly half of the subjects. Bilateral sign was rare. Motor examinations targeting muscles supplied by trigeminal nerve were impaired in one fifth of subjects. Probable anatomical substrates where trigeminal nerve may be invaded by mucormycosis: cavernous sinus, brain stem, subarachnoid space and terminal small facial branches involvement. Strikingly, corneal reflex was normal in majority of cases with evidence of facial numbness.Radiological evidence of trigeminal nerve involvement at the level of cavernous sinus didn't explain preservation of corneal reflex. Moreover numbers of subjects with numbness were more than subjects with radiological cavernous sinus involvement thus necessitating a search for a different anatomical location, which revealed facial terminal small branches (V2 distribution) involved in majority, as evidenced by intensity changes of facial muscles in imaging. Probable angioinvasion of small vessels supplying terminal branches of trigeminal nerve leading to infarction and subsequent sensory loss was another potential explanation. Sparing of upper half of corneal reflex afferent pathway mediated by V1, lead to intact corneal reflex in majority. Brainstem and subarachnoid space involvement were not substantiated by imaging and CSF examinations in any of our cases [29].
6) **Facial deviation**: Unilateral facial deviation was not uncommon in ROCM in our study. Facial deviation stems from facial nerve involvement, either LMN or UMN type with LMN outnumbering UMN type in this study. All UMN type palsies were associated with cerebrovascular accident (CVA), more precisely due to watershed infarction. After critical analysis, LMN type facial nerve palsies, were believed to be due to most peripheral involvement by invasive mucormycosis either at the level of parotid gland (as evidenced by parotid gland intensity changes in imaging in substantial number of cases) or due to vasa nervosum angioinvasion by mucor causing infarction of facial nerve at the level of parotid or when it emerges through the parotid gland (as evidenced by extensive involvement of soft tissue of cheek in imaging), also corroborated by differential involvement of muscles in facial NCS. Cheek swelling and pain were common confounders during evaluation of facial nerve palsies. All cases of dysarthria in our study group were associated with facial nerve palsy [30–32].
7) **Diplopia, external ophthalmoplegia, pupillary reflex, internal ophthalmoplegia and it's radiological correlates**: Most fascinating observations are,
   a) Diplopia was relatively uncommon despite frequent external ophthalmoplegia. This could be attributed to either complete external ophthalmoplegia or simultaneous/preceding ptosis, leading to poor perception of double vision.
   b) Unilateral complete ophthalmoplegia was observed in almost half of the subjects. Analysis of possible route through which mucor spread, revealed sequential involvement of nasal cavity, PNS, pterygopalatine fossa, breach in lamina papyracea (cancellous bone), invasion into retro-orbital space, soft tissue, extraocular muscles, optic nerve then further extension to invade superior orbital apex [33], cavernous sinus and then extension to involve opposite site. This might be the probable reason, why unilateral ophthalmoplegia was more common in this study [34].
   c) Bilateral ophthalmoplegia were not uncommon due to rapidly progressive course of the disease [35].
   d) Medial rectus and inferior rectus involvement with other extraocular muscles were most commonly found. The possible route map of mucor spread, as depicted previously, being self-explanatory as mucor finds its way into retro-orbital space through breach of lamina papyracea to involve medial rectus first which lies in close proximity of medial wall of orbit. Strikingly, isolated lateral rectus palsy though infrequent, was present in some subjects.
   e) Appreciable perception of basis of ophthalmoplegia depicted it might result from involvement of extraocular muscle/s; of nerve fascicles at level of superior orbital apex, cavernous sinus, subarachnoid space or involvement of corresponding cranial nerve nucleus supplying the muscles at the level of brain stem intra-axially. Ophthalmoplegia might also stem from neuromuscular junction pathology or due to involvement of retro-orbital soft tissue encircling the muscles. In present study, clinical correlation with neuroimaging and CSF examination in selective cases unfurled, fungal invasion into extraocular muscles and surrounding soft tissue was the leading cause of ophthalmoplegia, restrictive type, substantiated

by positive forced duction test (in 25 subjects,45.45%). This was followed by neurogenic ophthalmoplegia evidenced by involvement of nerve fascicles at the level of superior orbital apex, cavernous sinus and subarachnoid space respectively. None were found due to neuromuscular junction or brain stem involvement. Isolated lateral rectus palsy was attributed to involvement of infranuclear fascicular involvement of sixth cranial nerve or lateral rectus muscle infiltration [36].

f) Direct and consensual pupillary reflex were absent on the side of optic nerve involvement. However, preserved direct pupillary reflex but absent consensual reflex in relatively normal eye, indicated internal ophthalmoplegia (probably at the level of ciliary ganglia). This sign though infrequent was observed in few cases [37].

g) Radiological intensity changes over muscles (invasion and infiltration) in cases of external ophthalmoplegia correlated well and was present in substantial number of cases. However external ophthalmoplegia without radiological intensity changes over muscles, leaves room for insight, also wasn't uncommon in our study.

h) Radiological lesions over extraocular muscles, retro-orbital soft tissue, superior orbital apex, and cavernous sinus in clinically asymptomatic patients (no diplopia/ external ophthalmoplegia) though infrequent, was present in some.This time gap probably represents the clinic-radiological dissociation, indicating the importance of imaging for earlier diagnosis and treatment initiation [38].

I) Clinically unilateral external ophthalmoplegia but radiologically bilateral extraocular muscles involvement were infrequent but deceptive, indicating radiological progression preceded clinical progression in few [39].

8) **Bulbar dysfunction**: Apart from subjects with destructive surgery, only few (five) had bulbar symptoms (nasal intonation and nasal regurgitation of liquid) due to palatal and pharyngeal muscles weakness, substantiated by imaging which showed intensity changes over palatal and pharyngeal muscles along with surrounding soft tissue, representing direct invasion of fungus.

9) **Stroke in mucormycosis**: Stroke in mucormycosis is not uncommon. High degree of suspicion is needed, as symptoms and signs were subtle, most of the time ranging from being completely asymptomatic to focal limb weakness with or without aphasia. Striking observations include:

a) All Strokes were primarily due to ICA involvement at the level of cavernous sinus. Mechanisms of ICA involvement being hypothesized as external compression (by necrotic soft tissue debris), intraluminal obstruction, microscopic angioinvasion and vasospasm.

b) All strokes were superficial and deep watershed infarctions with involvement of the periventricular region and centrum semiovale. Four such cases additionally had infarcts which involved ACA-MCA and MCA-PCA watershed zone, further establishing involvement of large artery (ICA) on the side of ROCM, and two had haemorrhagic transformation. One case evolved from a watershed infarct to involvement of the entire ACA/MCA territory [40].

c) Radiological evidence of ICA involvement at the level of cavernous sinus substantiated well with imaging as evidenced by absent flow void of ICA on affected side in T2 MR imaging and decreased flow in ICA in MRA in majority cases. However in 1 subject with stroke, there was no evidence of structural involvement of ICA, thereby suggesting an intriguing relationship between stroke with microscopic invasion by fungus and vasospasm of ICA, apart from structural compression from outside and intraluminal obstructions [41–45].

10) **Meningeal and invasive parenchymal involvement, seizure, and disorientation**: Meningeal involvement though common in our study, was focal in all cases with primary involvement of meninges over temporal (medial and anterior) and frontal lobe. Absence of features of neck rigidity was characteristic, possibly due to focal involvement. Brain parenchyma invasion by deadly fungus was characterized by predominant involvement of frontal and temporal lobe, hypothesized to be due to close proximity which facilitates contiguous invasion of fungus from frontal sinus and cavernous sinus respectively. Seizure as clinical manifestation was present in only one subject.Disorientation, in majority proved to be due to underlying sepsis and/or metabolic perturbations, barring only one subject with frontal lobar involvement without features suggestive of sepsis or any metabolic disruption [46–50].

5. Conclusion

To conclude, lower middle class, middle aged, rural males were most affected. COVID-19 infection in recent past and diabetes (pre-existing or new onset; diagnosed during COVID-19) are the two most important risk factors, though most often ROCM is associated with the simultaneous presence of multiple risk factors.

ROCM though predominantly unilateral, often becomes a bilateral disease with delay in diagnosis. Sinus and eye symptoms were common, albeit most of the time correlated with appropriate imaging, still clinically asymptomatic or mild disease, evident on radiological imaging were not uncommon.

New onset upper jaw toothache and loosening of teeth was frequently observed, often as the first presenting manifestation.It should prompt a search for mucormycosis on war footing in the backdrop of a diabetic patient with recent history of COVID-19 disease, as they might signal early disease before involvement of other axes and provide a window of opportunity to improve outcome.

Neuroaxis involvement was characterized by myriad of clinical symptoms and signs among which proptosis/ptosis, external ophthalmoplegia, diminution of vision/loss of vision, stroke, facial numbness and facial palsies were most common.

Paramount importance of neuroimaging can't be ignored for localization of disease, delineation of it's extent and for early diagnosis of clinically asymptomatic lesion for appropriate treatment at the earliest.

Declaration of competing interest

Authors declare no conflict of interest.

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