Main Article

Rhino-Orbital-Cerebral Mucormycosis : Clinico-Epidemiologic Study in a Regional Centre in Eastern India during the Second Wave of COVID-19 Pandemic

https://doi.org/10.47210/bjohns.2022.v30i1.595

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ABSTRACT

Introduction

Rhino-orbital-cerebral mucormycosis (ROCM), a life-threatening acute fungal rhinosinusitis, has recently been reported in increasing numbers in post-COVID patients in the backdrop of uncontrolled hyperglycemia. We present our on-going experience with these patients.

Materials and Methods

A descriptive longitudinal study involving forty-three ROCM patients, during the 2nd wave of COVID -19, are presented here to discuss the epidemiology, clinical features, management approaches and outcomes.

Results

Commoner in males (65%), most ROCM patients belonged to lower socio-economic status and 41-50 years age group. Eighty six percent patients were known diabetics and confirmed COVID-19 illness were present in and 53% patients. Advanced disease (Stage-3&4) was found in 54% of patients at presentation. Diagnosis was confirmed by fungal culture and histopathological evidence of tissue invasion. All patients received injection Amphotericin B and undergone surgical debridement (endoscopic or external approach). Seventy two percent patients were discharged on oral antifungal post - debridement, 28% patients expired during course of treatment.

Conclusion

ROCM led to significant morbidity and mortality in post COVID patients due to its aggressive nature, late presentation and limited guidelines on management protocol. Early diagnosis in patients presented with suggestive background and a multidisciplinary team management approach is crucial. Randomized control trials on efficacy of various treatment modalities with duration of antifungal treatment will help in better management of these patients.

Keywords

COVID-19; SARS-CoV-2; Mucormycosis; Nose Diseases; Orbital Diseases; Magnetic Resonance Imaging; Debridement; West Bengal; India

Mucormycosis, an acute angio-invasive life-threatening fungal disease is caused by saprophytic fungus Rhizopus species under the order of Mucorales.[1] In India, the prevalence of mucormycosis is 70 times greater as compared to the global occurrence.[1] Mucormycosis is more commonly encountered in immunocompromised patients, particularly prevalent in association with diabetes mellitus.[1] Recently, a sharp rise in mucormycosis cases has been encountered during the 2nd wave of COVID- 19 pandemic and a cluster of cases either with ongoing COVID -19 disease or a recent history are being reported. A complex interplay of factors such as low oxygen (hypoxia), high glucose and immunosuppression (due to altered T cell- mediated immunity in SARS-CoV-2, steroid-induced or other comorbidities) in association

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with prolonged hospitalization with or without mechanical ventilators in COVID-19 patients are likely to predispose mucormycosis in these patients.[2] Rhino-orbital-cerebral form of the disease is often the most common form of the disease and carries a high mortality (20 - 80% approximately) even with medical and surgical treatments.[3] While presence of multiple co-morbidities and toxicity of anti-fungal treatment pose serious challenges in treating such patients, guidelines on optimum management strategies including extent of surgery, choice and/or duration of maintenance anti-fungal therapy are still lacking. Early detection with radical surgical debridement and systemic antifungal therapy are the key treatment of these cases. A descriptive study of forty-three ROCM patients is presented here, to discuss their socio demographic features, clinical manifestations with staging, management approaches and treatment outcome.

Materials and Methods

In total forty-six patients were admitted to our tertiary care (regional center for mucormycosis) hospital with possible rhino-orbital-cerebral mucormycosis (ROCM) during month of May to July, 2021. Amongst them, three patients were excluded as they did not show any suggestive disease radiologically with a negative histopathology and fungal culture. The remaining forty-three patients were included in this study.

This is a descriptive longitudinal study of 43 patients with rhino-orbital-cerebral mucormycosis (ROCM) presenting to a single tertiary care center at Bankura, West Bengal, India during May-July 2021.Patients and attainders were interviewed with a standard questioner and examined using a study proforma for maintaining uniformity and reducing bias.

Twenty-three patients were confirmed cases of COVID-19 disease by reverse transcriptase polymerase chain reaction (RT- PCR) testing within one month of current admission, nine patients had clinical features suggestive of COVID-19 but not tested for the same, and eleven patients did not have the background suggestive of COVID-19. Seven patients were RT-PCR positive on admission, the remaining patients were negative at the time of admission. Hyperglycemia, either in known diabetics or newly diagnosed was seen in most of the patients on admission.

Patients with suspicious clinical features including pain and facial swelling, periorbital inflammation with ophthalmoplegia or visual disturbances, necrosis or eschar formation in nasal cavity, face, and/or palate with or without loosening of tooth in the suggested background of hyperglycemia and COVID-19 illness were subjected to routine pre-operative blood checks and radiological investigations with contrast-enhanced CT/ MRI of nose and paranasal sinuses (PNS), orbit, and brain. Representative tissue sampling for potassium hydroxide (KOH) mount/fungal culture and histopathological examination to look for tissue invasion were arranged for confirmation of diagnosis.

All patients received Injection Amphotericin B deoxycholate 1mg/kg/day infusion in 5% dextrose solution (0.1mg/ml solution) along with hyperglycemia control by insulin, intravenous antibiotics and analgesics as appropriate. Liposomal Amphotericin -B (5mg/kg/day) was used in patients with radiological evidence of cerebral involvement. Physician and ophthalmologist's opinion was sought for all patients from time to time and their suggestions followed.

Radical surgical debridement by either endoscopic (modified Denker's approach, fronto-spheno-ethmoidectomy, septectomy) or open procedures by lateral rhinotomy approach for maxillectomy with or without orbital exenteration, external fronto-ethmoidectomy was carried out under general anesthesia and operation notes including extent of disease involvement were documented. Post-operative patients were subjected to routine blood investigations including complete hemogram, renal function tests, liver function tests and electrolytes, and strict monitoring of vital signs and blood sugar levels were done. Post-operative MRI was done in patients after 2-3 weeks or before in patients with new onset or persisting symptoms. Re-debridement procedure is done for three patients due to involvement of the opposite side or presence of necrotic tissue on post –operative diagnostic nasal endoscopy and on MRI. Nasal

endoscopy and suction cleaning of operated cavities are done at regular intervals.

In view of deranged kidney functions, two patients have undergone hemodialysis under medical team monitoring.

Results

This study includes a total of 43 patients, among them 28 were males (65%) and 15 females (35%).

Age distribution: Maximum number of patients were between age group 41 and 50 having thirteen patients in this group (30%),followed by ten patients(23%) in the age group 51 to 60, nine patients (21%) in the age group 61 to 70, and eight patients(19%) in the age group 31 to 40. Two patients were more than seventy years(5%) and one patient (2%) was there in the age group 21 to 30. (Fig. 1)

Socio-economic status: Two patients belonged to the upper-income group, six patients belonged to the middle-income group and thirty-fivepatients belonged to the lower-income group.[4]

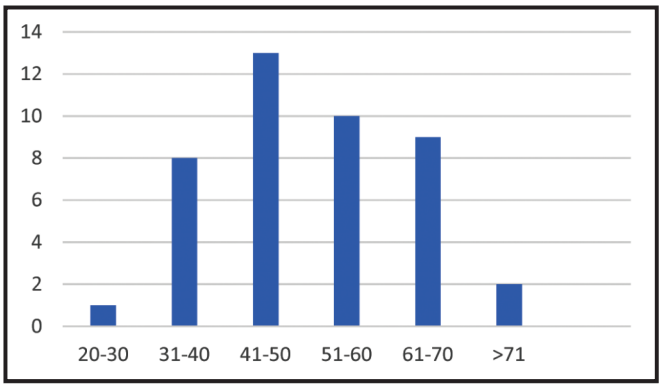

Fig. 1. Age distribution

Co-morbidity/ Diabetes: All patients suffered from hyperglycemia on admission. Thirty- seven patients were known diabetics with or without treatment with oral hypoglycaemics or insulin, whereas six patients were newly dignosed to have hyperglycaemia. All patients received subcutaneous insulin as per physician recommendation (Fig.2).

COVID-19 infection status: More than 50% of these patients (23) had RT PCR confirmed COVID-19 illness

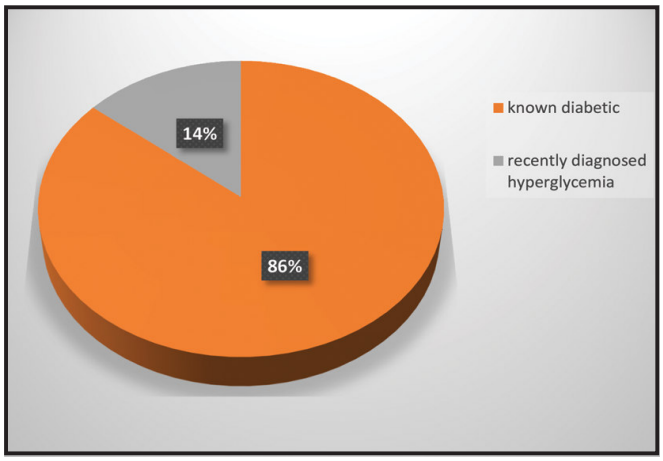

Fig. 2. Co-morbidity/ Diabetes

during the past one month duration, 21% patients (9)had suggestive history of COVID-19 infection and 26% of patients (11) did not give any history suggestive of COVID-19 (Fig.3).

Clinical manifestations[5] and staging[6]: Clinical features were varied and many patients presented late in the course

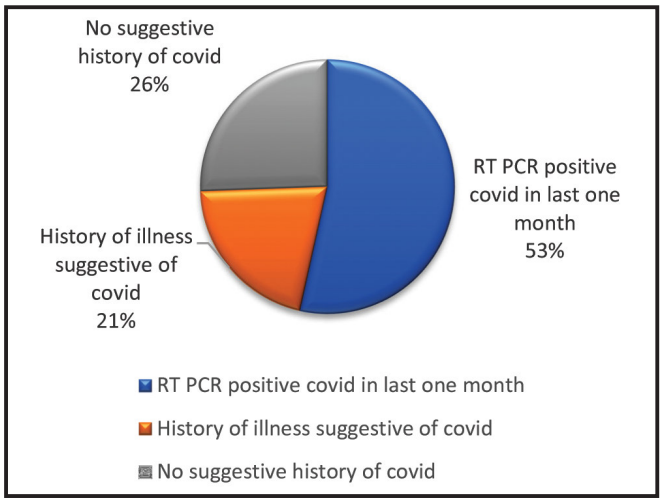

Fig. 3. COVID-19 infection status

of disease. Most patients with ROCM presented with complaints of facial pain, numbness and swelling (37 cases). Nasal discharge or stuffiness (12 patients) was also a common complain, along with variable ophthalmic symptoms ranging from swelling or shrinking of eye (10 cases), pain around or behind eyes and double vision (9cases), dimness of vision and/or loss of vision

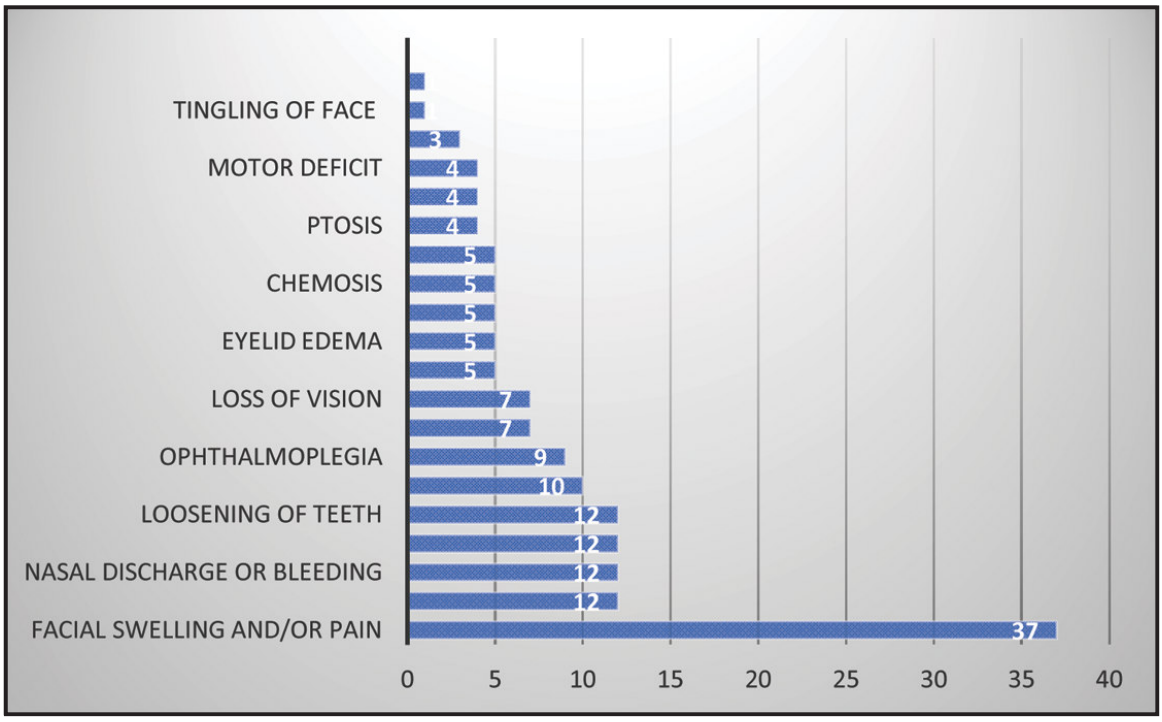

Fig. 4. Clinical features

(7patients), redness and/or watering from eyes (5 cases). Loosening of teeth and dental pain were also complained (12cases) by significant number of patients. Necrosis of palate and skin involvement were noted in some patients (7 & 5 patients respectively). Trismus was seen with extension of pathology to infratemporal fossa (three cases). One patient presented with facial palsy. Slurring of speech, weakness of limbs and altered sensorium were seen in four patients with cerebral involvement (Figs. 4 & 5).

Patients were staged according to their extent of involvement[6] as evident from clinical signs and radiology (Figs. 6 & 7). Patients with advanced disease (stage 3 &4) included 48% of ROCM cases. Nineteen patients (44%) presented in stage 2 (involvement of nose and PNS), twelve (28%) presented in stage 3 (involving nose, PNS and orbit), eleven patients (26%) were in stage 4(involving brain), and one patient (2%) came in stage 1 (isolated lesion in nasal cavity) (Fig.8).

Operative procedures: Twenty patients (47%) undergone endoscopic surgical debridement using modified Denker's

Fig. 5. Involvement of palate and orbit in ROCM

maxillectomy[7] with fronto-spheno-ethmoidec-tomy while external maxillectomy (lateral rhinotomy incision with Lynch-Howarth extension) with fronto-spheno-ethmoidectomy was done in 17 patients (40%). Among

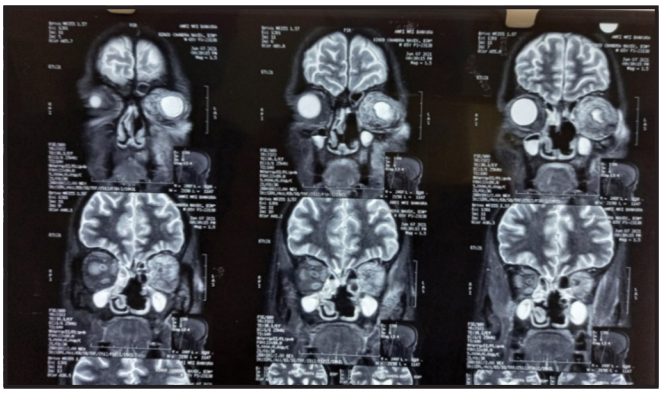

Fig. 6. MRI T2 coronal fat supression image showing heterogenous intensity soft tissue swelling in left periorbital region involving the orbital globe

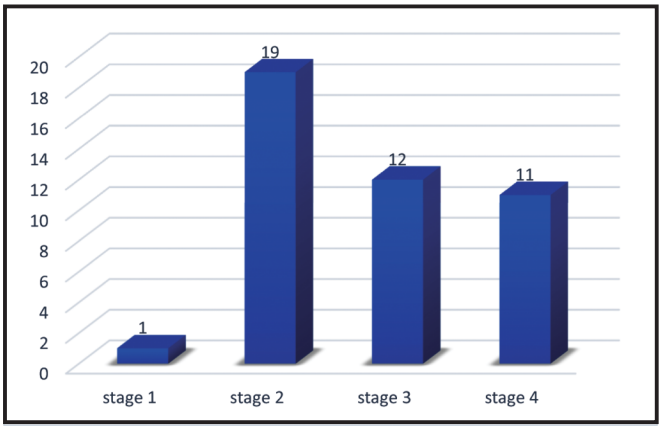

Fig. 8. Clinical staging

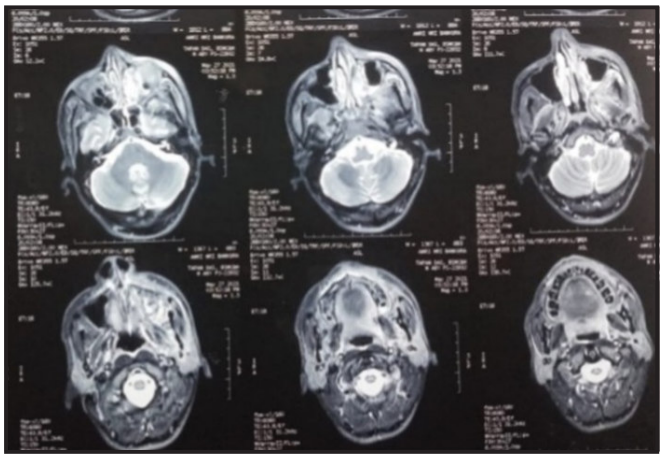

Fig. 7. MRI of ROCM showing heterogenous density in paranasal sinuses and involvement of perisinus spaces

them, total maxillectomy with fronto-ethmoidectomy was done in 5 cases (12%) and partial maxillectomy with fronto-ethmoidectomy was done in 7 patients (16%). Orbital exenteration was undertaken in cases with loss of vision and unsalvageable orbital involvement, either with total maxillectomy and fronto-ethmoidectomy, done in 3 patients (7%) or with partial maxillectomy in the form of medial or infrastructure maxillectomy and fronto-ethmoidectomy, done in 2 patients (5%). (Figs. 9, 10, 11)

Six patients expired before any surgical debridement was undertaken.

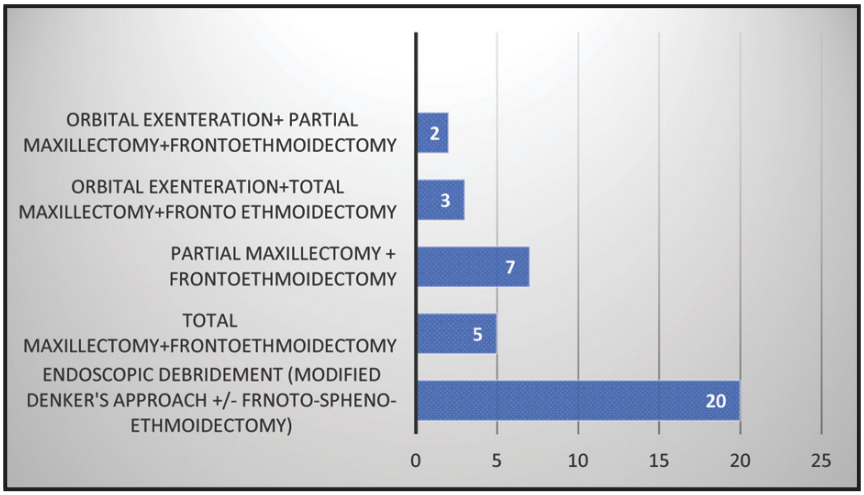

Fig. 9. Operative procedures

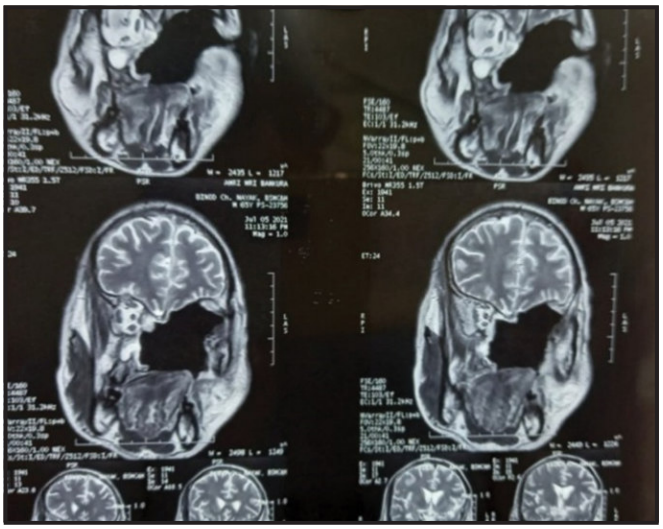

Fig.10. Post opeartive MRI of patient of Fig.11

Fig. 11. Post-operative maxillectomy with right orbital exenteration

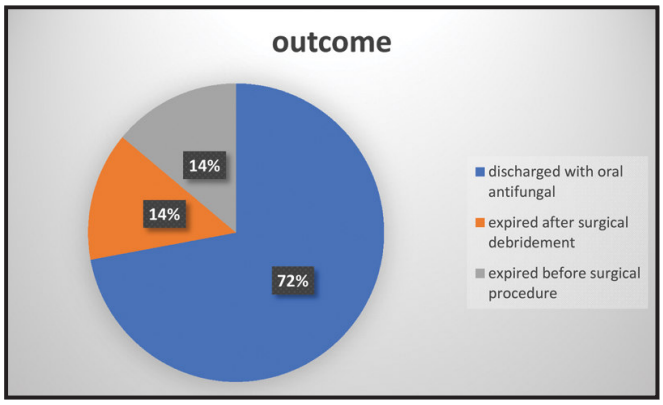

Fig. 12. Outcome

Repeated surgical procedures were done in three patients due to persisting or worsening symptoms with evident disease on repeat nasal endoscopy. Here we have mentioned the final surgical procedure. All patients were subjected to diagnostic nasal endoscopies and suction cleaning of post operative cavities at 2 days intervals.

Outcome: After surgical debridement and 1500 mg of cumulative doses of intravenous Amphotericin B (average duration 3 weeks), thirty-one patients (72%) showed clinical improvement and were discharged with oral Posaconazole treatment. Six patients (14%) expired after surgical debridement, four amongst them presented with CNS involvement and another six patients (14%) died during the course of treatment, prior to any surgical intervention. (Fig.12.)

Patients discharged on oral Posaconazole therapy (300mg per day) are being followed up by diagnostic nasal endoscopies in regular intervals.

Discussion

Rhino-orbital-cerebral mucormycosis (ROCM) is an acute fulminating fungal infection involving the nose, paranasal sinuses, oral cavity/hard palate with alveolus, orbits and central nervous system. Although rare in otherwise healthy subjects, ROCM is associated with various immunocompromised and co-morbid conditions such as uncontrolled DM with or without ketoacidosis, organ transplantation, recent glucocorticoid use, blood or other malignancies, iron overload or deferoxamine

therapy, acquired immunodeficiency syndrome (AIDS), and neutropenia.[2] Increase in cases of mucormycosis in patients with recent COVID-19 infections has become a raising concern in India and rest of the world. Prompt attention to these patients for early diagnosis and aggressive treatment are key factors in achieving optimum response and improved mortality.[6] Depending on the area of involvement, mucormycosis can be rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, or disseminated, ROCM being the most common form of mucormycosis encountered worldwide.[8]

The initial clinical manifestation of ROCM includes eye or facial pain and numbness, conjunctival suffusion and blurred vision. Infection usually spreads from ethmoid sinuses to orbit producing ophthalmoplegia and proptosis with chemosis. From the orbit, spread via hematogenous or contiguous route leads to frontal lobe involvement or cavernous sinus involvement via venous drainage. Involvement of the contralateral eye with proptosis, chemosis, and ophthalmoplegia or vision loss signifies cavernous sinus thrombosis. Initially the infected tissue may appear normal, progressing through an erythematous stage to a violaceous appearance and finally development of a black necrotic eschar.[5] Extension of disease from sinuses to mouth leads to toothache with loosening of teeth and ultimately painful necrotic ulcerations in hard palate. A high index of suspicion in clinically suggestive cases along with a positive culture from a representative site or histopathology confirmed presence of tissue invasion establishes the diagnosis. A patient with clinical features suggestive of mucormycosis in the clinical setting of COVID positive status along with hyperglycemia, use of mechanical ventilator or oxygen support is regarded possible ROCM. Clinical features along with positive diagnostic nasal endoscopy and contrast imaging findings can be considered as probable ROCM. Clinico-radiological features along with histopathological or microbiology confirmation entitles proven ROCM.[6]

A rapid response multidisciplinary team including experts from radiology, microbiology, pathology, medicine, critical care, otolaryngology, ophthalmology, and neurosurgery, is essential in managing such patients.[9] In our set up, all cases were admitted in special mucormycosis ward under the department of otolaryngology. The management of ROCM involves radical surgical debridement of nose and paranasal sinuses with the clearance of orbital and cerebral disease along with systemic antifungal therapy and strict glycemic control.[10] Liposomal Amphotericin B is the recommended antifungal although Amphotericin B deoxycholate or lipid complex are used in the area of resource constraints.[6] Salvage therapy with intravenous or oral Posaconazole can be used with a duration of treatment usually 6 weeks or more. Mortality rates of ROCM ranges from 20% to 80% depending on the underlying conditions.[3,11]

In our study, forty-six patients were admitted during the study period with suggestive clinical background among which three were excluded and forty-three cases were confirmed to have ROCM both by radiological and histopathology/fungal culture results. Most of these patients (23) were in stage 3 and 4,[6] followed by stage 2 (19). Only one patient came in stage 1. Insulin therapy had been initiated in patients with hyperglycemia as per the physician consultation. All of our study patients received intravenous Amphotericin B deoxycholate and Liposomal Amphotericin B was given to patients with cerebral involvement. Surgical debridement was undertaken for thirty-seven patients either by endoscopic approach for twenty patients or external approach in seventeen cases.[9] Orbital exenteration was done in five patients due to unsalvageable orbital involvement after consulting ophthalmologists and after obtaining proper informed consent.

Thirty-one patients showed significant clinical improvement post debridement and after a cumulative Amphotericin B dose of 1500 mg with average duration of three weeks therapy, they were discharged with oral Posaconazole therapy with an advice for a follow-up MRI in 2 weeks. Six patients expired after surgical debridement, four amongst them had cerebral involvement. Six patients succumbed prior to surgical debridement, during their course of treatment, due to cardiac arrythmia, acute respiratory distress syndrome and metabolic encephalopathy. Patients who were

discharged on oral Posaconazole are currently undergoing regular follow up by serial nasal endoscopies and MRI to look for evidence of any recurrence.

Conclusion

ROCM is a life-threatening angioinvasive fungal disease with a stormy course and challenging outcome even with best possible care. The increase in the incidence of ROCM cases in the background of COVID-19 illness in patients with uncontrolled hyperglycemia adds to the morbidity and mortality burden of COVID-19 disease spectrum. Early diagnosis and initiation of systemic antifungal therapy along with surgical debridement of necrotic tissue are crucial to the management of these patients. Involvement of multi-disciplinary teams including critical care specialists, otolaryngologists, ophthalmologists, radiologists, pathologists, and microbiologists are essential to deal with such patients. Clinical trials to determine the appropriate duration, and protocol of medical and surgical therapies for ROCM should be done in future to streamline the therapeutic approaches and improve the outcome.

References

1. Prakash H, Chakrabarti A. Epidemiology of Mucormycosis in India. Microorganisms. 2021; 9:523. Published 2021 Mar 4
2. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr. 2021; 15:102146. doi: 10.1016/j.dsx.2021.05.019
3. Hernández JL, Buckley CJ. Mucormycosis In: Stat Pearls. Treasure Island (FL): StatPearls Publishing; June 26, 2021
4. Saleem S M, Jan S S, Modified Kuppuswamy socioeconomic scale updated for the year 2021. Indian J Forensic Community Med 2021; 8:1-3
5. Spellberg B, Ibrahim Ashraf S. Mucormycosis Harrison's Principles of Internal Medicine,20e, Part 5; Chapter 213.p1537-41
6. Honavar SG. Rhino-orbito-cerebral mucormycosis– Guidelines for diagnosis, staging, and management. Indian J Ophthalmol. 2021; 69
7. Upadhyay S, Dolci RL, Buohliqah L, Prevedello DM, Otto BA, Carrau RL. Endoscopic endonasal anterior maxillotomy. Laryngoscope 2015; 125:2668-71
8. Peterson KL, Wang M, Canalis RF, Abemayor E. Rhinocerebralmucormycosis: evolution of the disease and treatment options. Laryngoscope. 1997 Jul; 107(7):855-62
9. Abdollahi A, Shokohi T, Amirrajab N, et al. Clinical features, diagnosis, and outcomes of rhino-orbito-cerebral mucormycosis- A retrospective analysis. Curr Med Mycol. 2016; 2:15-23
10. Nehara HR, Puri I, Singhal V, et al. Rhinocerebral mucormycosis in COVID-19 patient with diabetes a deadly trio: Case series from the north-western part of India. Indian J Med Microbiol. 2021
11. Cornely OA, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis. 2019; 19: e405-e421.