Indian J Otolaryngol Head Neck Surg
https://doi.org/10.1007/s12070-022-03134-w

ORIGINAL ARTICLE

Tracing, Tracking and Treating COVID-19 Associated Rhino-Orbito Cerebral Mucormycosis (ROCM)

Vijay Bidkar[1] · B. H. Shrikrishna[1] · Sandeep Dabhekar[1] · Kiran Kumar Prathipati[1] · Prashant P. Joshi[2] · Rasika Gadkari[3] · Meena Mishra[4] · Kalaiselvi Selvaraj[5] · Chetana Ratnaparakhi[6] · Avinash Prakash[7] · Rajesh Pattebahadur[8] · Anand Chellapan[9] · Raghunath Shanbag[10]

Received: 3 December 2021 / Accepted: 10 July 2022

Abstract Surge in the number of mucormycosis cases following second wave of coronavirus disease-19 (COVID-19) infection posed several diagnostic and prognostic challenges. This study was aimed to describe clinical, diagnostic features and survival outcomes among patients of mucormycosis in post COVID-19 context. Retrospective chart review. This study included 44 COVID-19 positive screened cases who presented with clinical features suggestive of mucormycosis. Demography, clinical profile, diagnostic findings, and the treatment outcome are studied. Medical and surgical outcomes are summarised as frequencies and percentages. The reliability of microbiological, and radiological findings against the pathological findings was analyzed using Kappa statistics (k). Based on constellation of microbiological, pathological and radiological findings 28 cases (63%) confirmed with mucormycosis infection. The mean (SD) age was 54.9 (12.9) years and two-third were males. The majority (90%) of cases presented with the feature of facial swelling, headache nasal blockade. Inpatient care for treatment of COVID-19 was recorded in 33 (75%). Diabetes mellitus was the commonest comorbidity in 27 (61.4%), 38 (86.4%) cases were treated by steroids and 30 (68.2%) were given oxygen therapy. There is a strong agreement (k = 0.83) between pathological and microbiological investigations. In thirty-eight cases (86.3%) remission was achieved when assessed after 8 weeks. Of the 44 cases, four patients died. The results of the current study suggest that the disease residues and/or recurrences in critical areas are frequent in mucormycosis. However, using the strategy of screening at risk patients, diagnosing, treating them with combination of antifungals, surgical debridement, and timely follow up may help in improving outcomes as compared to pre COVID-19 era.

Keywords Mucormycosis and covid-19 · Diabetes mellitus · Corticosteroids · Endoscopic sinus surgery · Maxillectomy · Amphotericin-B

✉ Vijay Bidkar
dr.vijaybidkar@gmail.com

1 Department of Otorhinolaryngology-Head and Neck Surgery, All India Institute of Medical Sciences, Nagpur, Maharashtra, India

2 Department of General Medicine, All India Institute of Medical Sciences, Nagpur, Maharashtra, India

3 Department of Pathology, All India Institute of Medical Sciences, Nagpur, Maharashtra, India

4 Department of Microbiology, All India Institute of Medical Sciences, Nagpur, Maharashtra, India

5 Department of Community Medicine, All India Institute of Medical Sciences, Nagpur, Maharashtra, India

6 Department of Radio-Diagnosis, All India Institute of Medical Sciences, Nagpur, Maharashtra, India

7 Department of Anaesthesiology, All India Institute of Medical Sciences, Nagpur, Maharashtra, India

8 Department of Ophthalmology, All India Institute of Medical Sciences, Nagpur, Maharashtra, India

9 Department of Nephrology, All India Institute of Medical Sciences, Nagpur, Maharashtra, India

10 Department of Otorhinolaryngology-Head and Neck Surgery, SDM College Medical Sciences & Hospital, Dharwad, Karnataka, India

Published online: 18 August 2022

Introduction

The otolaryngologist across the country got alerted on rising number of mucormycosis infection. Special screening units were set up to detect rhino-orbito-cerebral mucormycosis (ROCM) infections in patients who are tested positive for Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV2) in recent times or in the past. Individuals having suspicious clinical feature involving the nose, sinuses, face and or orbit were considered as potential suspects of this invasive, opportunistic fungal infection.

Multiple factors are implicated in occurrence of ROCM in patients of Corona Virus disease -19 (COVID-19) infection which included, preexisting co-morbidities: the immunosuppression caused by the virus itself [1], uncontrolled or undiagnosed diabetes mellitus (DM) leading to alarming hyperglycemia [2], prolonged corticosteroid administration [3] and the prothrombotic state induced by COVID-19 itself [4].

The mechanism by which COVID-19 influences occurrence of ROCM includes; hypoxemia, high glucose, acidic medium, increased ferritins and reduced phagocytosis as a result of immune dysregulation caused by the virus itself, steroids and decompensated comorbidities in these patients. Other external factors like prolonged hospitalization with or without oxygen therapy further facilitated ubiquitous fungus of mucorales order to invade in favorable environment [5].

Interestingly, DM which is the most common risk factor in occurrence of ROCM is highly prevalent in India. This led to rising incidence of ROCM to 80 times higher in comparison to developed countries [6]. On the contrary in western countries recipients of organ transplant and patients of blood/solid organ malignancies were common victims to this infection. [7]

The surge in the number of mucormycosis cases following coronavirus disease-19 (COVID-19) infection posed several challenges in diagnosis and predicting the prognosis. The clinical course of disease has taken different trajectories compared to cases reported in pre-covid context. Though the recent surge is observed in many developing countries like India there is paucity of literatures on their diagnostic and treatment outcome. Hence, in this study we aimed to describe clinical, diagnostic and survival outcomes among patients undergoing treatment for ROCM in post covid context.

Material and Methods

Study Design

This is a facility based retrospective chart review.

Study Population

The COVID- 19 positive cases presenting with symptoms of ROCM were identified based on recommendations laid down by Research Consortium of European Confederation of Medical Mycology in cooperation with Mycoses Study Group Education and Research Consortium for detection of mucormycosis [8].

Inclusion Criteria

Suspects presenting with symptoms suggestive of ROCM like-

- Fever
- Headache
- Facial pain, Swelling
- Nasal discharge (blood stained), vomiting
- Visual disturbances, chemosis
- Shortness of breath
- Seizures

Exclusion Criteria

Non COVID-19 patients.

Study Site

This study was conducted in a tertiary care settings. In the study setting, all clinically suspected mucormycosis initially reported to exclusive mucormycosis screening area. All suspects had detailed clinical evaluation by the multi-disciplinary team consists of specialists from ENT, Ophthalmology, and Dentistry. Also the details on history of COVID-19 in the recent past, co-morbidities and treatment details were collected. Based on the clinical suspect criteria, further the suspects were admitted in Mucormycosis wards for inpatient follow-up treatment. This included diagnostic nasal endoscopy (DNE), Potassium hydroxide (KOH) scrapings from nasal cavity, culture and cytology reports. Similarly, radiological evaluation by computed tomography (CT) and Magnetic resonance imaging (MRI) of nose, paranasal sinus (PNS), orbit and brain (plain + contrast) was done for assessing involvement of soft tissue and bony structures before and post-surgery/medical therapy separately**.** Intraoperative findings for the involvement of different sub sites was extracted from surgical notes. Histopathological examination (HPE) reports were analyzed.

The relevant data is extracted from the suspected patients records admitted to Mucormycosis ward.

Study Duration

4 months (April–July 2021)

Sample Size

This is a case series which includes 44 patients with suspected features of mucormycosis screened from 180 cases presented to screening unit since April to July 2021.

Data Collection (Recruitment and Participants)

Details related to clinical, microbiological, pathological radiological characteristics was extracted from patients records. Data regarding COVID-19 treatment including oxygen therapy, steroid use, length of hospital stay (indoor therapy for 5 or more days), day of developing first symptom following COVID-19 infection were collected as a part of clinical case work up. Their positivity for microbiological and pathological evaluation of nasal swabs were also extracted from laboratory report and imaging reports.

Surgical Plan

On the basis of pre-operative clinical (Fig. 1A, B) and radiological findings decision of endoscopic sinus surgery or maxillectomy by open approach alone or combination was done. Endoscopic middle meatus antrostomy, anterior and posterior ethmoidectomy, sphenoidotomy is done on the side affected as standard procedure (Fig. 1C, D). Patients having disease in premaxillary or peri-antral region underwent modified endoscopic modified Denker's procedure for removing osteomyelitis bone from anterior wall of maxilla and as an approach to remove disease behind posterior maxillary wall in pterygopalatine fossa. Crusts were sent for analysis by KOH mounts and culture. Abnormal mucosa from lateral wall of nose and sinuses was sent for frozen section for confirmation of presence of fungal hyphae. In case of involvement of orbit floor or zygomatic extension, the Weber Ferguson incision was used and necrotic tissue was debrided. Disease involving the alveolar bone was excised by infrastructure maxillectomy using sub-labial approach (Fig. 1E, F).

Post operatively patients received intravenous antibiotic coverage and Amphotericin B deoxycholate (AMB) (1 mg/kg) with adequate pre and post hydration using appropriate fluids. Patients were given Liposomal Amphotericin (7 mg/

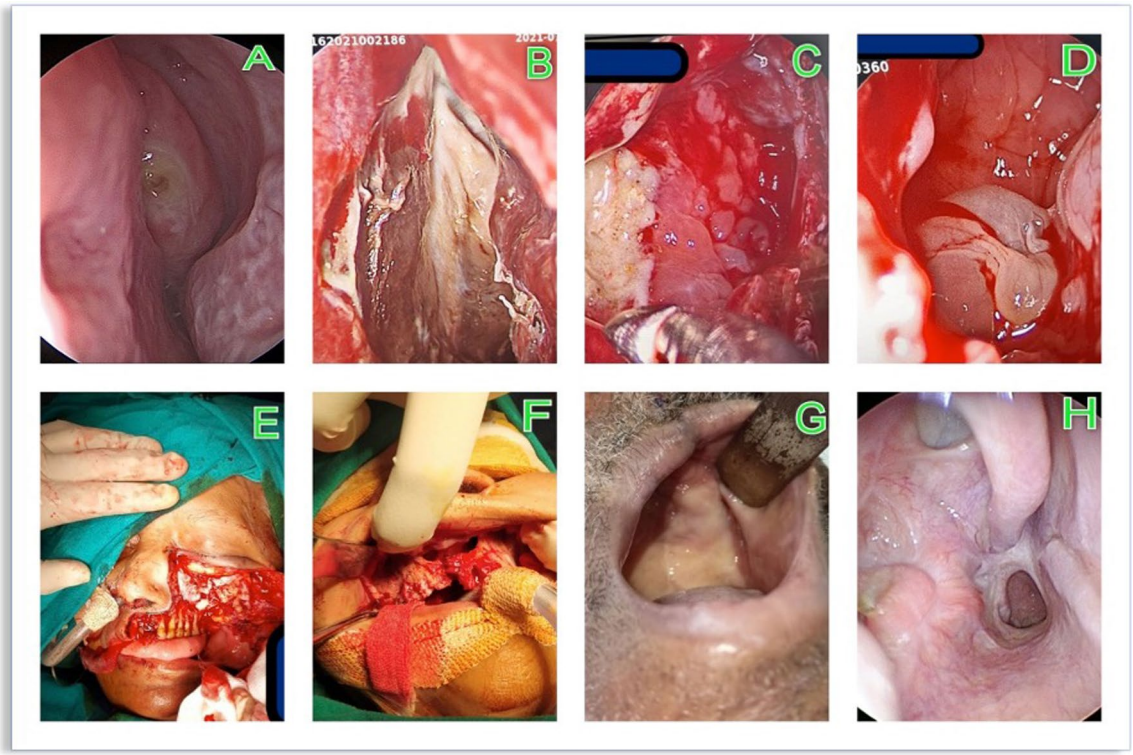


Fig. 1 **A**, **B** Preoperative nasal endoscopy showing normal and necrotic (eschar) mucosa; **C**, **D** Intra operative nasal endoscopy showing congested, cobble stone to polypoidal mucosa in maxillary and sphenoid sinus respectively; **E**, **F** Open surgical approaches; **G**, **H** Follow up evaluation showing well healed gingiva buccal sulcus and intranasal sinus cavity

Kg) if nephrotoxicity sets in with conventional AMB or as in case needed for extended period of administration (intracranial extension). Extended oral Posaconazole was given for 3 months following completion of intravenous AMB.

Patients renal function tests, serum electrolytes levels and C-reactive protein (CRP) level assessment was done on alternate day basis to understand trend and disease recurrence or remission. The radiological investigation was done at 1 week for follow up and as per necessity.

Clinical and endoscopic evaluation was done at interval of 1 week, 4 week and 8 weeks for detecting residual, recurrences (Fig. 1G, H). Revision surgery is planned according to evidence of disease.

Ethical Issues

Ethical committee approval was taken from independent institutional committee (IEC/Pharmac/2021/290). The information of the participants was kept confidential. The study was conducted according to Good Clinical Practice guidelines.

Data Analysis Plan

Data is entered in Microsoft Excel spread sheet. Patient related demographic (gender, age COVID category), clinical profile (symptoms and signs), microbiological, pathological and radiological findings is summarised as frequencies and percentages. Reliability of microbiological, and radiological findings against the histopathological findings was analysed using Kappa statistics. The treatment outcome at the time of discharge also is summarised as percentages. Patients who received full course of Amphotericin B and follow up for 15 days post-operative and has no evidence of residual or recurrence as per clinical, biochemical, radiological and endoscopic features was considered to be in remission.

Results

Demographic Characteristics

Twenty eight (63%) were diagnosed as cases of mucormycosis by microbiological and/ or histopathological studies. The mean (*SD*) age was 54.9 (12.9) years. About two third were males. Majority (~90%) of the suspects presented with the feature of facial swelling, headache nasal blockade along with fever in initial 24 h and followed by others (Table 1).

Co-Morbidity Profile

Apart from recent or ongoing COVID-19 infection, twenty seven (61.4%) had history of DM while 14 (31.8%) had immune compromising condition other than DM, like haematological or solid organ malignancy. In-patient care for treatment of COVID-19 was recorded in 33 (75%) cases. Further 38 cases (86.4%) were treated by steroids while 30 (68.2%) patients were given oxygen therapy.

Table 1 Clinical characteristics of patients admitted with Mucormycosis like features (N = 44)

Clinical symptoms	No. of patients (%)
Headache	40 (90.9)
Facial swelling	40 (90.9)
Nasal blockage	40 (90.9)
Hypesthesia	38 (86.4)
Loosened teeth	11 (25)
Orbital swelling	8 (18.2)
Nasal discharge	6 (13.4)
Palatal Eschar	6 (13.6)
Diplopia	5 (11.4)

Microbiology and Pathology Profile

Of the 44 suspected patients with probable mucormycosis, histopathology confirmed the diagnosis in 28, of whom 25 also had fungal cultures that grew a Mucorales species. Of the remaining 16 patients, 12 had histopathology performed and, this showed nonspecific rhinosinusitis which was negative for fungal growth on culture. (Fig. 2).

The KOH preparation on direct microscopy demonstrated (Fig. 3A) pauci-septate fungal hyphae of mucorales order fungus was seen in 33 (75%), while growth on culture was seen in 25 of 43 patients (58.13%) cases. Remaining 8 patients who were culture negative also turned to be non-fungal sinusitis on HPE.

Of 28 patients with positive histopathology, all showed fungal hyphae invasion in tissue (Fig. 3B) with (n = 5) or without (n = 21) angioinvasion. In addition, bony necrosis was seen in 2 of these 28 patients. There is a strong agreement (k = 0.83) between pathological and microbiological investigative modalities.

Radiological Profile

All patients underwent CT and MRI scan showed sinus involvement of single or multiple sinus causing opacification and altered intensities. The orbital and brain parenchymal involvement is well studied on MRI. The bone necrosis was more evident on CT images. (Fig. 4A, B) Orbital involvement was seen in 6 patients ranging from minimal extraconal collection, bulky recti muscles, and fat stranding. Three patients showed involvement of skull base at lateral wall of sphenoid sinus, clivus and lesser wing of sphenoid.

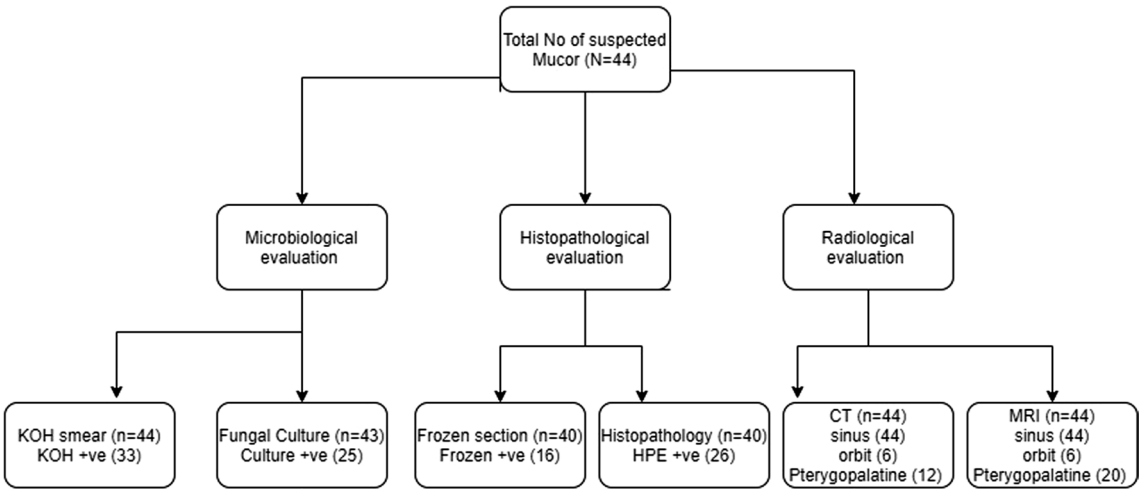


Fig. 2 Mucormycosis diagnostic (microbiological, histopathological and radiological) profile

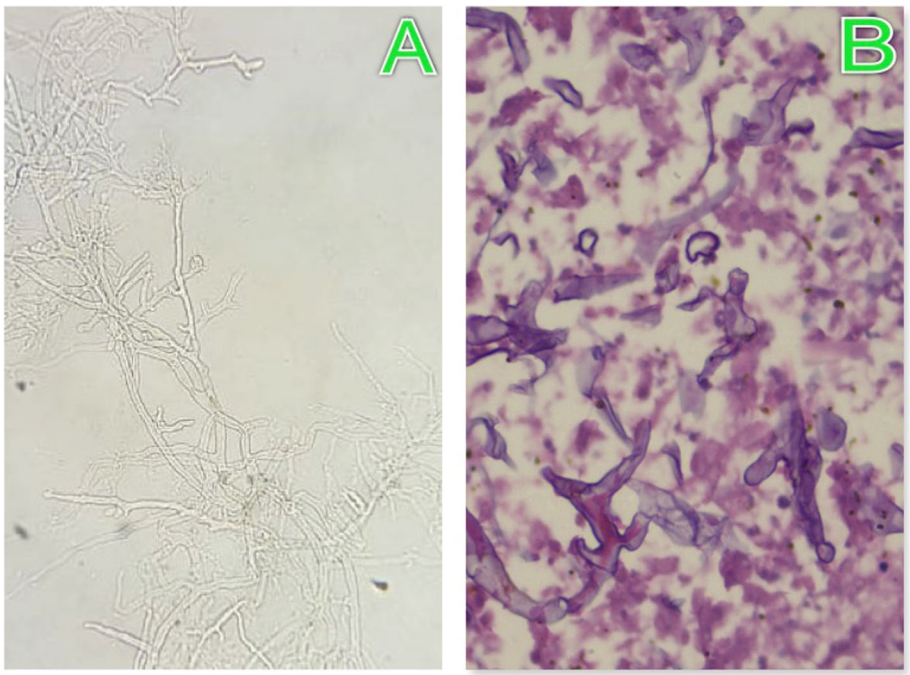


Fig. 3 **A** Direct microscopic (40X) KOH preparation showing pauciseptate (coenocytic) hyphae with nonparallel sides. Branching is nondichotomous, irregular and sometimes at right angles, **B** Broad, aseptate, ribbon like hyphae seen along with many twisted, bizarre and hollow tube like forms also seen, (HE, 40X)

One patient had intracranial extension demonstrable on MRI in gyrus rectus region. In twenty cases MRI scans showed involvement of pterygopalatine region during follow up which detected residual and/recurrences. Alveolar bone of ipsilateral maxilla showed osteomyelitis features on CT scan in 15 patients.

Surgical, Medical Intervention and Outcome

Forty patients underwent endoscopic sinus surgery. Combined endoscopic and open approach maxillectomy was done in nine patients in the form of infrastructure segmental maxillectomy for alveolar osteomyelitis of maxilla. Endoscopic appearance in these cases differed from congested oedematous mucosa, cobble stone appearance, polyps and granulation in 39 (97.5%) patients. (Fig. 4C, D) Typical intranasal mucosal blackish eschar was seen in 4 patients only. Peri-antral soft tissue involvement was seen in 9 patients which was correlating with radiological investigations. Out of 40 patients, 12 needed a revision surgery which included endoscopic, open surgical alone or combined approach. The pterygopalatine fossa, alveolar bone and orbit were the sites for recurrences at the end of 1 week and onwards. Further, in 3

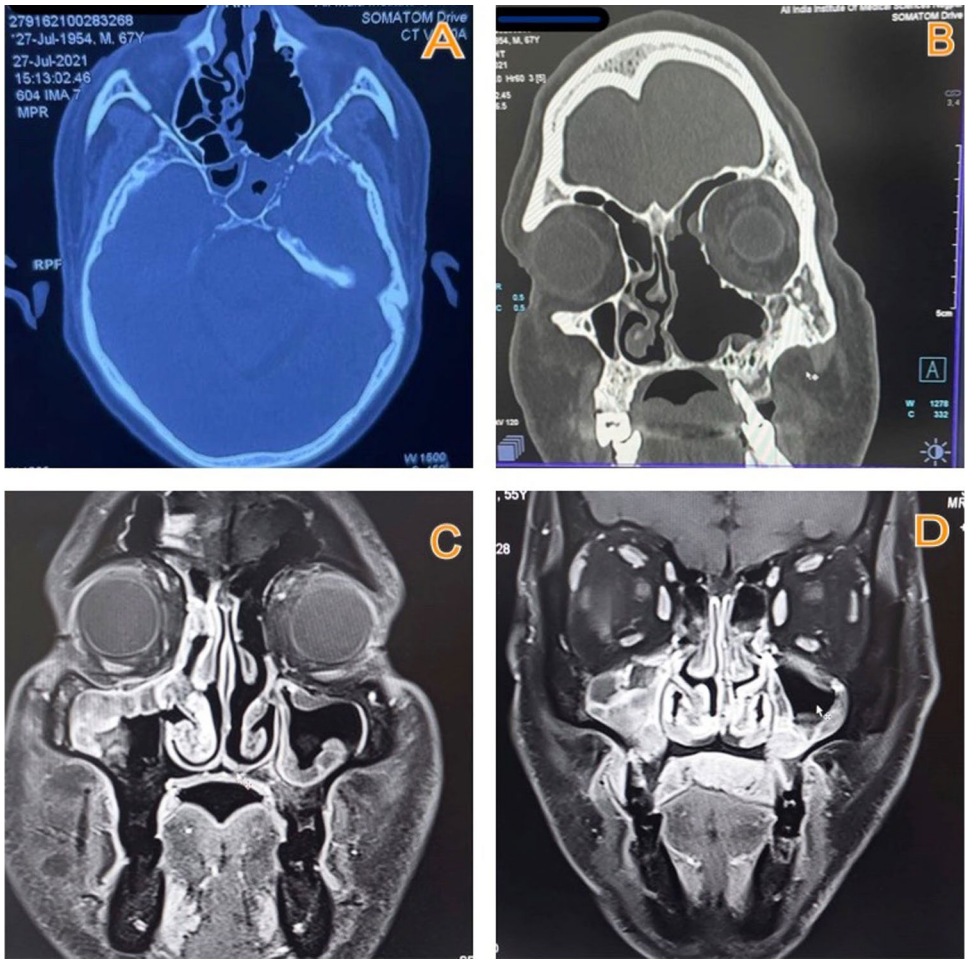


Fig. 4 **A** Plain Axial CT image showing sphenoidal mucosal thickening and lateral wall erosion, **B** Plain Coronal CT image showing orbital collection in operated case, **C**, **D** Post contrast MR coronal image showing hyperintense signals from sinus mucosa

cases newer skull base involvement either in lateral wall, grater wing of sphenoid or the Clivus was involved which were labelled as site of recurrence.

The cases having residual and recurrences in these subsites (12 of 40) underwent revision surgery. One patient having involvement of gyrus rectus was treated conservatively by increasing dosage of liposomal AMB to 7 mg/kg and kept under strict follow up.

Acute adverse reaction like fever, chills, nausea after AMB administration was seen commonly in all the patients after initiating therapy for the first time. Regular monitoring of serum electrolyte and creatinine levels helped detection of renal toxicity earlier in 13 (66.7%) of 21 patients. Oral Posaconazole was administered in 2 patients who could not tolerate Amphotericin B injectable.

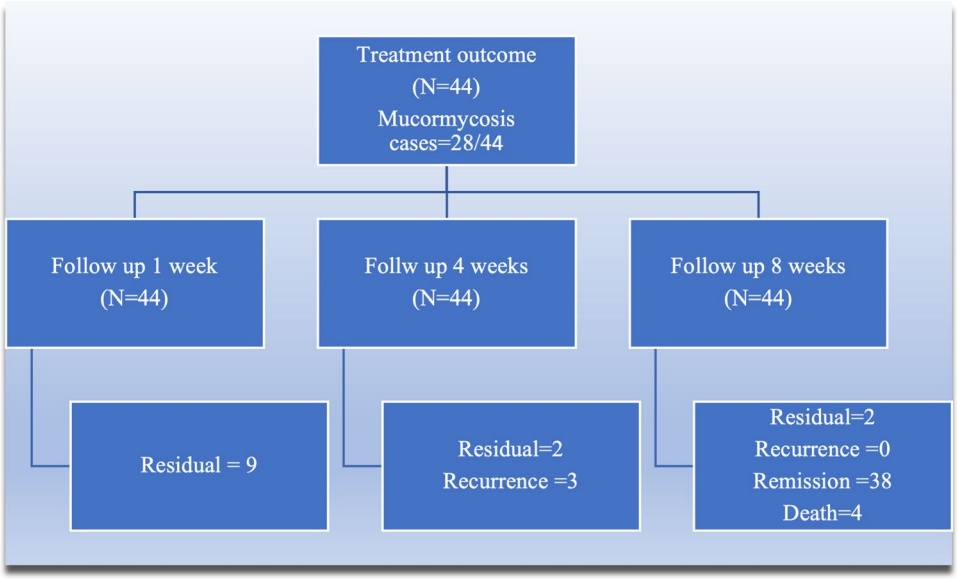
At the end of 8 weeks 38 patients were in remission while 2 patients, having intracranial extension and skull base involvement (clivus and lateral wall of sphenoid) had residual left which was treated conservatively (Fig. 5).

Discussion

The sino-nasal mucormycosis is an aggressive fungal infection known for preferential involvement for nose which may spread to orbit and brain. The opportunistic nature of fungi in Mucorales order especially in COVID-19 patients with co-morbidities is sometimes quiet but it is certainly more harmful. Recent estimate of increase in its prevalence in India (0.14 per 1000) as compared to the rest of world is reflective of ongoing problem [6]. The management in such cases is challenging in view of existing comorbidities, disease residuals and recurrences occurring over longer duration in follow up period.

The complex interaction between COVID-19 in presence of other co-morbidities and use of corticosteroids in its treatment increases the chances of occurrence of invasive fungal infection. In a systematic review, Singh et al. has hypothesised the virtue by which COVID-19 influences chances of once acquiring Mucormycosis which includes 1. increase in reactive oxygen specimen, 2. Endothelial receptor glucose

Fig. 5 Clinical course outcome



regulated protein 78 (GRP-78) and 3. Mucorale adhesin spore coat protein homologous (Cot-H) [5] The study population (n = 44) in this retrospective analysis included all COVID-19 infected patients.

The RECOVERY trial has given clear guidelines on usage of corticosteroids and hospitalization. It has suggested about possibility of secondary bacterial and fungal infection upon imprudent use [9]. In the current cohort most of the suspects were either recovered from or had an ongoing COVID-19 infection. Eighty six percent of cases received in the hospital treatment with systemic steroid administration during their management and the findings remains similar in other countries as well. [10]

Clinically, ROCM can present with nasal, sinus, orbital or neurological symptoms [11]. Unilateral headache, hypoesthesia and swelling were the most common and detected early (within 1st week) features in our series. Delayed orbital and palatal symptoms appeared in fewer (18% and 13%) patients respectively after second week. Classical palatal eschar was visible in 2 cases only who developed mucormycosis during on-going severe COVID-19 infection. The appearance of first clinical feature varied from one week to a month in COVID-19 recovered patients. Intracranial extension (1 case) or other systemic involvement (pulmonary (one case) or gastrointestinal) had rapid progression and worsening of clinical conditions leading to case fatality in three of the cases who had ongoing sever COVID-19 infection.

Nasal cavity scrapings for KOH is basic and well accepted investigation modality [12]. However, it is a blind procedure and chances of false negative remains a concern. The dried nasal cavity crust may preclude the swab head touching mucosal surface for collecting appropriate specimen sample. Endoscope guided sampling can overcome this limitation. The best practice is to collect crusts in sterile container and same may be evaluated for making smear and culture. The culture growth was visible in 21 cases and amongst these 4 had mixed growth of aspergillus.

The extent of involvement of adjacent soft tissues and bone is best done by radiological investigation viz. MRI and CT of PNS with orbit and brain. On MRI, T2 weighted images (T2WI) and T2 Fat Suppressed Images (T2FSI) are informative showing hyper-intense signals in the affected areas. The gadolinium contrast enhanced MRI, show variable enhancement from homogenous to heterogenous and at times without any enhancement typically causing characteristic signal void. The necrosis particularly along the lateral nasal wall and the turbinates have signal voids [13]. Altered signal intensities from pterygopalatine fossa, infra-temporal fossa, and cavernous sinus are suggestive of mucormycosis in immunocompromised patients [14]. These patients (45.6%) had poorer prognosis in this series in terms of recurrence or intracranial extension.

The role of frozen section is under rated with reference to evaluation of infectious aetiologies like Mucormycosis. However, in our study, we found the intra-operative frozen section is quiet helpful for detection of presence of fungal hyphae as around two third of pathologically confirmed cases were confirmed in Frozen section itself. Hence, decision making in case of suspicious mucosal changes or status of disease margins may be done confidently. This was further confirmed by culture and histo-pathological evaluation(HPE) using special stains such as periodic acid-Schiff (PAS) in all the cases [15]. Ten cases were diagnosed on HPE, who were reported negative on frozen section study.

An aggressive surgical treatment at the earliest on diagnosis of ROCM is the key for better outcomes in these patients. [16]

The prognosis remained poor in cases with disseminated fungal infection in presence of decompensated co-morbidities as in the other study as well [17]. The survival rate in various studies for acute invasive fungal sinusitis ranges from 20 to 80%. NoahEl-Kholy reported better survival of 63.89% in COVID-19 associated mucormycosis and attributed this to early diagnosis. [18] The overall survival rate in the current cohort is 86.3% with reported residual in 2 and mortality in 4 enrolled patients at the end of study.

The Amphotericin-B deoxycholate injection is the mainstay of medical management in all the patients [19]. Posaconazole therapy is helpful replacement in cases of severe allergy to AMB as salvage therapy but definitely not as replacement. [16]

This study elaborates treatment outcomes of mucormycosis from India especially in the COVID-19 context with significant duration of follow-up. Though this is an observational retrospective cohort study from routine clinical care settings, the missing data is negligible. This study identifies the potential areas for future research to confirm the areas such as factors associated with residuals or recurrence and the differential rate of survival between concurrent mucormycosis cases.

The smaller sample size and short period of follow up are the shortcoming of this study which can be taken in to consideration in future research. In thirty eight cases (86.3%) of the study population, the remission was achieved when analyzed after 8 weeks. In our view early diagnosis and treatment is helpful in accomplishing better outcome. However, early residual in 9 and recurrence in 3 cases at 1 week and four weeks respectively indicated resilient nature of the fungus. Strict follow up with biochemical, endoscopic and radiological investigations were helpful for achieving remission.

Conclusion

The results of the current study suggest that the disease residues and/or recurrences in critical areas are frequent in mucormycosis. However, using the strategy of screening at risk patients, diagnosing, treating them with combination of antifungals, surgical debridement, and timely follow up may help in improving outcomes as compared to pre COVID-19 era.

Acknowledgements We acknowledge contribution from Department of Dentistry, All India Institute of Medical Sciences, Nagpur and Department of Oral & Maxillofacial Surgery, Government Dental College, Nagpur. Maharashtra

Funding Not funded.

Declarations

Conflict of interest None.

Consent to Participate Verbal informed consent of participant taken.

Consent for Publication All authors provide consent to publish.

Ethics Approval Institutional Ethical Committee, All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration.

References

1. Pemán J, Ruiz-Gaitán A, García-Vidal C, Salavert M, Ramírez P, Puchades F, García-Hita M, Alastruey-Izquierdo A, Quindós G (2020) Fungal co-infection in COVID-19 patients: Should we be concerned? Rev Iberoam Micol 37(2):41–46. https://doi.org/10.1016/j.riam.2020.07.001 (Epub 2020 Sep 14. PMID: 33041191; PMCID: PMC7489924)
2. Sharma S, Grover M, Bhargava S, Samdani S, Kataria T (2021) Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum. J Laryngol Otol 135(5):442–447. https://doi.org/10.1017/S0022215121000992 (Epub 2021 Apr 8. PMID: 33827722; PMCID: PMC8060545)
3. Ahmadikia K, Hashemi SJ, Khodavaisy S, Getso MI, Alijani N, Badali H, Mirhendi H, Salehi M, Tabari A, Mohammadi Ardehali M, Kord M, Roilides E, Rezaie S (2021) The double-edged sword of systemic corticosteroid therapy in viral pneumonia: a case report and comparative review of influenza-associated mucormycosis versus COVID-19 associated mucormycosis. Mycoses 64(8):798–808. https://doi.org/10.1111/myc.13256 (Epub 2021 Mar 5. PMID: 33590551; PMCID: PMC8013756)
4. Moorthy A, Gaikwad R, Krishna S, Hegde R, Tripathi KK, Kale PG, Rao PS, Haldipur D, Bonanthaya K (2021) 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 20(3):1–8. https://doi.org/10.1007/s12663-021-01532-1 (PMID: 33716414; PMCID: PMC7936599)
5. Singh AK, Singh R, Joshi SR, Misra A (2021) Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes Metab Syndr 15(4):102146. https://doi.org/10.1016/j.dsx.2021.05.019 (Epub 2021 May 21. PMID: 34192610; PMCID: PMC8137376)
6. Skiada A, Pavleas I, Drogari-Apiranthitou M (2020) Epidemiology and diagnosis of mucormycosis: an update. J Fungi (Basel) 6(4):265. https://doi.org/10.3390/jof6040265 (PMID:33147877; PMCID:PMC7711598)
7. Prakash H, Chakrabarti A (2019) Global epidemiology of mucormycosis. J Fungi (Basel) 5(1):26. https://doi.org/10.3390/jof5010026 (PMID:30901907;PMCID:PMC6462913)
8. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hochhegger B, Hoenigl M, Jensen HE, Lagrou K, Lewis RE, Mellinghoff SC, Mer M, Pana ZD, Seidel D, Sheppard DC, Wahba R, Akova M, Alanio A, Al-Hatmi AMS, Arikan-Akdagli S, Badali H, Ben-Ami R, Bonifaz A, Bretagne S, Castagnola E, Chayakulkeeree M, Colombo AL, Corzo-León DE, Drgona L, Groll AH, Guinea J, Heussel CP, Ibrahim AS, Kanj SS, Klimko N, Lackner M, Lamoth F, Lanternier F, Lass-Floerl C, Lee DG, Lehrnbecher T, Lmimouni BE, Mares M, Maschmeyer G, Meis JF, Meletiadis J, Morrissey CO, Nucci M, Oladele R, Pagano L, Pasqualotto A, Patel A, Racil Z, Richardson M, Roilides E, Ruhnke M, Seyedmousavi S, Sidharthan N, Singh N, Sinko J,

Skiada A, Slavin M, Soman R, Spellberg B, Steinbach W, Tan BH, Ullmann AJ, Vehreschild JJ, Vehreschild MJGT, Walsh TJ, White PL, Wiederhold NP, Zaoutis T, Chakrabarti A; Mucormycosis ECMM MSG Global Guideline Writing Group (2019) 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. 19(12):e405–e421. https://doi.org/10.1016/S1473-3099(19)30312-3. Epub 2019 Nov 5. PMID: 31699664

9. Recovery Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ (2021) Dexamethasone in hospitalized patients with covid-19. N Engl J Med 384(8):693–704. https://doi.org/10.1056/NEJMoa2021436 (Epub 2020 Jul 17. PMID: 32678530; PMCID: PMC7383595)
10. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y (2020) 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 8(5):475–481. https://doi.org/10.1016/S2213-2600(20)30079-5 (PMID: 32105632; PMCID: PMC7102538)
11. Vairaktaris E, Moschos MM, Vassiliou S, Baltatzis S, Kalimeras E, Avgoustidis D, Pappas Z, Moschos MN (2009) Orbital cellulitis, orbital subperiosteal and intraorbital abscess: report of three cases and review of the literature. J Craniomaxillofac Surg 37(3):132–136. https://doi.org/10.1016/j.jcms.2008.10.007 (Epub 2008 Dec 4 PMID: 19062300)
12. Selarka L, Sharma S, Saini D, Sharma S, Batra A, Waghmare VT, Dileep P, Patel S, Shah M, Parikh T, Darji P, Patel A, Goswami G, Shah A, Shah S, Lathiya H, Shah M, Sharma P, Chopra S, Gupta A, Jain N, Khan E, Sharma VK, Sharma AK, Chan ACY, Ong JJY (2021) Mucormycosis and COVID-19: an epidemic within a pandemic in India. Mycoses. https://doi.org/10.1111/myc.13353 (Epub ahead of print. PMID: 34255907)
13. Herrera DA, Dublin AB, Ormsby EL, Aminpour S, Howell LP (2009) Imaging findings of rhinocerebral mucormycosis. Skull Base 19(2):117–125. https://doi.org/10.1055/s-0028-1096209 (PMID:19721767;PMCID:PMC2671302)
14. Raab P, Sedlacek L, Buchholz S, Stolle S, Lanfermann H (2017) Imaging patterns of rhino-orbital-cerebral mucormycosis in immunocompromised patients : when to suspect complicated mucormycosis. Clin Neuroradiol 27(4):469–475. https://doi.org/10.1007/s00062-017-0629-1 (Epub 2017 Oct 12 PMID: 29026931)
15. Skiada A, Lass-Floerl C, Klimko N, Ibrahim A, Roilides E, Petrikkos G (2018) Challenges in the diagnosis and treatment of mucormycosis. Med Mycol 56(suppl_1):93–101. https://doi.org/10.1093/mmy/myx101 (PMID: 29538730; PMCID: PMC6251532)
16. Spellberg B, Walsh TJ, Kontoyiannis DP, Edwards J Jr, Ibrahim AS (2009) Recent advances in the management of mucormycosis: from bench to bedside. Clin Infect Dis 48(12):1743–1751. https://doi.org/10.1086/599105 (PMID:19435437;PMCID: PMC2809216)
17. Jung SH, Kim SW, Park CS, Song CE, Cho JH, Lee JH, Kim NS, Kang JM (2009) Rhinocerebral Mucormycosis: consideration of prognostic factors and treatment modality. Auris Nasus Larynx 36(3):274–279. https://doi.org/10.1016/j.anl.2008.07.003 (Epub 2008 Sep 10 PMID: 18786790)
18. El-Kholy NA, El-Fattah AMA, Khafagy YW (2021) Invasive fungal sinusitis in post COVID-19 patients: a new clinical entity. Laryngoscope. https://doi.org/10.1002/lary.29632 (Epub ahead of print. PMID: 34009676; PMCID: PMC8242424)
19. Scheckenbach K, Cornely O, Hoffmann TK, Engers R, Bier H, Chaker A, Greve J, Schipper J, Wagenmann M (2010) Emerging therapeutic options in fulminant invasive rhinocerebral mucormycosis. Auris Nasus Larynx 37(3):322–328. https://doi.org/10.1016/j.anl.2009.09.001 (Epub 2009 Oct 25 PMID: 19857939)