



Rhino-Orbito-Cerebral Mucormycosis During the Second Wave of Covid-19: The Indian Scenario

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Abstract Mucormycosis is a life threatening, opportunistic infection often seen in individuals with a weak immune system. With an upsurge of cases of Covid-19, a drastic increase in cases of Rhino-Orbito-Cerebral Mucormycosis is being witnessed at present. This article has been written with the purpose of understanding the factors responsible for it and the challenges it brings along for the Indian health-care system at present. Possible solutions for dealing with these problems have also been included in the manuscript. Google, PubMed and ENT Cochrane databases were searched without a time limit using key words like “Mucormycosis”, “Rhino-cerebral-mucormycosis” in conjunction with “COVID-19” and “SARS CoV-2”. We found 34 articles to be relevant and hence included them to write this review. Rhino-Orbito-Cerebral Mucormycosis is being seen due to coming together of the three entities—the agent, host and environment that constitute the epidemiological triad for this disease in India. Responsible factors are uncontrolled diabetes mellitus, overzealous use of steroids and antibiotics and other environment related issues. The solutions for these problems lie in spreading awareness about prevention of these practices along with early diagnosis and treatment of mucormycosis. To deal effectively with this situation, particularly when there is an existing overload on otolaryngologists and the rest of the

health-care system, a multipronged and multilevel collaborative approach is the need of the hour. With effective Standard Operating Procedures and guidelines promoting a multidisciplinary approach for early diagnosis and treatment, we can surely overcome this situation.

Keywords Rhino-orbito-cerebral mucormycosis · COVID-19 · Diabetes mellitus · Amphotericin-B · Steroids

Abbreviations

ROCM	Rhino-orbito-cerebral mucormycosis
CT	Computed tomography
MRI	Magnetic resonance imaging
IEC	Information, education and communication
DNE	Diagnostic nasal endoscopy
MDTs	Multi-disciplinary teams
DM	Diabetes mellitus
SOPs	Standard operating procedures

Introduction

Mucormycosis is an emergency situation caused by rapid progression of invasive fungal infection [1]. This acute, fulminant opportunistic infection which often results in fatality, is caused by fungi of family Mucoraceae residing in soil, decaying vegetation and agricultural residues. Hosts with a weak immune system due to certain conditions (such as HIV infection, hematological malignancies, diabetes mellitus or using long-term treatment of corticosteroids) are most often affected [2–5]. Fungal spores gain access through mucosa of oral and nasal cavities. Fungi have a

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tendency to invade sinus tissues very rapidly, in individuals having a compromised cellular and humoral immunity, hence demonstrating a fulminant course and spreading in less than four weeks [6, 7]. Mycotic tissue invasion results in vasculitis and thrombosis leading to hemorrhage, infarction and acute neutrophilic infiltration of the affected tissues [8]. Nasal obstruction, anosmia, facial pain, edema and headache are usual presenting symptoms in early stages. With disease progression, signs and symptoms of rhino-orbito-cerebral mucormycosis (ROCM) such as diplopia, proptosis, ptosis, ophthalmoplegia and neurological involvement start showing up [9, 10]. Although not very common, but the invaded necrosed tissue may appear as “black eschar”, due to which this condition has been commonly referred to as “Black Fungus”.

High degree of clinical suspicion and endoscopic findings supported by microbiological staining and culture reports confirm the diagnosis. CT scans help surgical planning by delineating the extent of the disease. For assessing intracranial and orbital involvement, MRI proved superior to CT [11], besides having role in follow-up. Prompt diagnosis followed by immediate and aggressive management is key to prevent morbidity and mortality. Amphotericin B is the standard antifungal drug of choice for ROCM. Surgical treatment involves repeated debridement/ excision of dead and necrotic tissues, the extent of which should be best decided upon by operating surgeon [12]. Adding both medical and surgical therapies together improves survival instead of adopting a single modality of treatment [11]. Even with aggressive medical and surgical therapy prognosis can remain poor in these patients and ranges from 33.3 to 80% [9, 13].

This article has been written with the objective to analyze the challenges faced by us with respect to mucormycosis during the covid-19 pandemic in detail and to find relevant solutions of problems at multiple levels for ensuring effective management.

Materials and Methods

Since our experience in dealing with covid-19 and cases of mucormycosis following recovery from it is limited, we carried out an extensive search on Google, PubMed, ENT Cochrane databases using key words like “Mucormycosis”, “Rhino-cerebral-mucormycosis” in conjunction with “COVID-19”, “SARC CoV-2”. Amongst the retrieved articles with extensive relevant filtering we found 37 articles to be relevant and hence included them to write this review.

Present Day Challenge

Mucormycosis is not a very common disease. In India estimated prevalence of this disease is 140 cases per 10,00,000 population, out of which nearly 52% present as rhino-orbito-cerebralmucormycosis (ROCM) [3, 4]. With the upsurge of Covid-19 disease, a drastic increase in number of cases of ROCM is expected as there are high chances of coming together of the three important entities—the agent, host and environment constituting the epidemiological triad in India (Fig. 1: Epidemiological triad of ROCM). We tried to analyze the problem in India from the epidemiological point of view and after dissecting the problem in details, we felt that following are the concerned aspects of it.

COVID 19

Covid 19 disease is known to result in overexpression of ACE-2 receptors in pancreatic islet cells and leads to high insulin resistance in body causing biochemically diabetogenic condition [14]. Severe disease associated with Covid 19 results in altered iron metabolism leading to high serum ferritin levels [15]. IL-6 which is a key mediator of cytokininstrome in severe disease, also promotes ferritin synthesis. This high ferritin level results in free radical mediated tissue damage and circulatory overload of free iron. Circulatory free iron along with acidosis becomes an important risk factor for mucormycosis in these patients [16]. Disease severity in terms of multisystem failure and

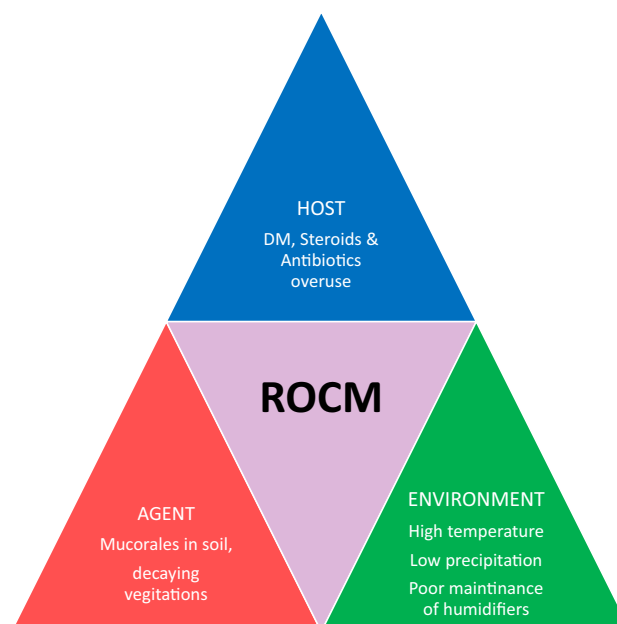


Fig. 1 Epidemiological triad of ROCM

ARDS hinders prompt diagnosis by utilizing diagnostic radiology and thus delays treatment.

Diabetes mellitus (DM)

DM is recognized as an important risk factor for mucormycosis [17]. Patients with DM who develop mucormycosis have been seen to have high morbidity and mortality. At present India accounts for the second largest number of diabetic individuals, with China topping the list [18]. India is also expected to be the diabetic capital of the world by 2025, having maximum number of affected individuals (approx. 68 millions) in a country [19]. In a recent study about mucormycosis and its association with diabetes and Covid 19, the majority of the patients were reported from India [20]. The second wave of Covid affecting a large number of people in India, will surely affect diabetics more as hyperglycemia is known to be responsible for dysfunction of immune response [21].

Steroids

The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial showed that uses of dexamethasone 6 mg once daily for upto 10 days reduced 28 day mortality in hospitalized patients [22]. It was also seen that dexamethasone uses were associated with higher likelihood of discharge at 28 days among patients who were receiving oxygen or invasive mechanical ventilation [22]. A sudden rise in cases of covid-19 in India, created a near-emergency situation creating panic across the nation. Usage of steroids was misinterpreted and they were being looked upon as the only lifesaving drugs. Lack of expert advice, self-medication and over the counter availability in black-market lead to the injudicious use and abuse of these medications. Steroids in excess are known to cause hyperglycemia and insulin resistance [23]. Steroids also exert potent immunosuppressive and anti-inflammatory effects [24]. Hence this overzealous abuse of steroids during the management of Covid cases paved the way for mucormycosis by enhancing susceptibility of hosts for the fungal invasion.

Medications

Self-medication and over the counter availability of antibiotics combined with incomplete knowledge imparted by social media during these unprecedented times also resulted in excessive and unethical use of antibiotics in India. Antibiotic overuse is strongly linked with increased incidence of fungal infections, both invasive and non-invasive [25]. Another important aspect from the medicine point of view is that the sudden expected rise of cases of ROCM is bound to increase the demand of Amphotericin

B. The availability of this drug will depend on manufacturing capacity of pharmaceuticals. Hence there is a possibility of unavailability due to black-marketing, panic buying and abusive consumption of the drug.

Environment

Cases of Sino-pulmonary mucormycosis which are not very commonly seen, have been seen recently in association with high temperature and low precipitation especially in the period between June and August [26]. Unfortunately we are about to enter the aforementioned climatic conditions favoring mucormycosis. In treatment of patients affected with Covid, humidifiers have an important role, but poor maintenance of these also results in patients acquiring infection particularly when one is otherwise susceptible to the infection.

Health Care Infrastructure and Otorhinolaryngologists

We have been dealing with the ongoing pandemic for more than a year and a half. As a result the over-burdened health care system is getting fatigued. Constant consumption and superadded demand of healthcare infrastructure due to sudden rise in cases is a big challenge. Loss of health care workers due to Covid-19 disease in recent past has been very unfortunate and adds to the miseries. As far as Covid-19 disease is concerned, the Indian health care workers from all other specialties were trying to manage it well by working under the guidance of Medicine/pulmonary medicine and critical care specialists. But now with the threatening upsurge of ROCM, health care system will be facing new challenges as managing this entity requires a lot from otorhinolaryngologists in terms of surgical skills. The doctor population ratio in India is nearly 1:1800 which is far less than the WHO recommendations of 1:1000 [27]. If this ratio is to be assessed in view of Otorhinolaryngologist, it will yield further shortage. There have been concerns in Indian medical graduates towards opting Otorhinolaryngology as a choice [28]. The training of developing key surgical skills for candidates in Otorhinolaryngology also suffered a lot in recent past, as the elective surgeries were abandoned and the health care force was diverted to manage Covid-19. Similar concerns regarding lack of training opportunities in otolaryngology residency training have been raised in other nations [29]. All these factors add up to create a deficiency of specialist otorhinolaryngologists available to deal with the upcoming menace.

Immunity and immunosuppression

The outcome of COVID 19 related illness is mainly determined by imbalance in the host immune system. Positive primary immune response from the host clears viral load in a large number of cases. However a secondary exaggerated immune response often referred to as the cytokine storm is usually responsible for adverse disease outcome that eventually leads to multiple organ failure and death. Recent literature proves that there is not much difference between immunocompromised individuals and general population when it comes to the risk of acquiring COVID 19 infection. [30]. However people with a weaker immune system are often seen developing severe complications of the disease as they are unable to mount regulated immune response. For this reason, studies advocated the consumption of a healthy, balanced diet rich in vitamins A, B, C, D, E, and K, and some micronutrients such as zinc, sodium, potassium, calcium, chloride, and phosphorus to support immune system [31]. This lead to overuse of pharmacological supplements containing vitamins and other micronutrients during this time. Fungal pathogens require sufficient quantities of zinc from their host in order to proliferate and cause disease [32]. Hence, the overzealous consumption of zinc could have paved the way for a sudden outbreak of mucormycosis in current context. However, this belief still needs to be proven and numerous research studies are being undertaken for it.

Discussion

As the Covid-19 pandemic is not yet over, new manifestations and the complications are being reported as we grow in our experience with the disease. Covid-19 associated ROCM is one such fulminant disease which can be considered a sequel/complication of SARS-CoV-2 infection. As discussed earlier, due to involvement of multiple factors, expecting a sudden surge in RCMM cases will not be unwise. In order to deal with it effectively utilizing the already overburdened health-care system, a multi-prong, multi-level approach will be required. Contribution from other sectors besides healthcare will also prove equally beneficial. In our opinion the efforts are needed at multiple levels for dealing with the challenges faced by India at present. We believe that the following measures will be relevant in the Indian scenario and ensure effective management of mucormycosis during these times.

1. Efforts needed at national level

These include active involvement of Information Technology sector:

(A) *To spread disease awareness* This infection is less likely to develop in those individuals who have good immunity, as the inhaled fungal spores are usually phagocytized by cells contributing to cellular immunity. The disease could only affect those susceptible hosts who lack a competent immune system to do so (i.e. those with uncontrolled diabetes, using immunosuppressant drugs, hematological malignancies) [33]. Although the steroid use in treatment of Covid-19 has been linked with associated ROCM [34], not all patient using steroids for treating Covid-19 will develop it, especially those who used it in prescribed format and for shorter durations. This information should be relayed to the general public by means of effective IEC (information, Education and communication) activities. Similar IEC activities can also be planned for promoting environmental hygiene (like explaining proper maintenance of humidifiers for the patients) and curtailing steroid abuse. Various organizations, different social media platforms, self-help groups and eminent individuals can help in this information spread.

(B) *To unburden health care system* The fear mongering due to false and incomplete information should be checked by the Information Technology regulatory Boards/concerned Government Bodies. This can help the overburdened health-care system by lowering the numbers of unnecessary visits made by apprehensive individuals. It also helps by awaking awareness in high risk individuals to seek timely medical help. Planning for these activities should be very detailed and in consultation with the subject experts, as it can serve as double edged sword if not done properly. This can help reduce the panic in general public.

2. Efforts needed at the level of Health-care providers/Hospitals:

(A) *Interdepartmental collaboration* ROCM may not always present to otorhinolaryngology, as the myriads of symptomatology also includes ocular symptoms (i.e. periorbital swelling, ptosis, ophthalmoplagia and decreased vision) [35, 36] as well as symptoms pertaining to dentistry (loosening of tooth, palatal ulcer)/Neurology. A high index of clinical suspicion will help all the clinical specialties diagnosing these patient early. Even though for diagnosing invasive fungal disease, radiology alone would not be enough to provide sufficient sensitivity and specificity [37], but keeping a low threshold for diagnostic imaging in strongly suspected cases, will surely help in early diagnosis. Optimizing the patient biochemically before surgical management, should be aimed for in consultation with medicine/

endocrinology/nephrology specialists, as the patients usually have related co-morbidities

- (B) *Administrative support* Dedicated multidisciplinary teams (MDTs) can be made to deal with ROCM. These should include Otorhinolaryngologists, ophthalmologists, neurosurgeon, neurologists, nephrologists endocrinologists, critical case specialists, dental/ maxillofacial surgeon, microbiologists, pathologists and expert dietician, as all of them have certain concerns with majority of ROCM patients. Detailed and customized standard operating procedures (SOPs) can thus be made by help of these MDTs for every institution in order to ensure early diagnose and effective management. Administration should also be quick and supportive in providing required logistic support without friction.
3. Efforts at the level of Otorhinolaryngologists
- (A) *Administrative planning* As the key surgical role will be played by otorhinolaryngologists in managing ROCM, every hospital should make arrangements of sparing them from Covid management related duties for the time being.
- (B) *Academic planning* In the past one year, post-graduated trainees in otolaryngology could not develop the necessary skills, including basic procedures like diagnostic nasal endoscopy (DNE) due to abandoning elective services. This puts an additional diagnostic workload on seniors in the department, which otherwise could have been avoided. This should be compensated for by dedicating fixed hours of active teaching in every Otorhinolaryngology department across the nation. This can surely unburden the senior experts in the department, who can divert their efforts from diagnostic activities towards therapeutic surgeries for management of mucormycosis during these times.
- (C) *Ergonomic planning* In an attempt to save time and effort, the endoscopic diagnostic and therapeutic attempts of surgeons can be clubbed together in patients who are clinical suspects of Mucormycosis and have radiological evidences to support the diagnosis. This can avoid duplication of work. Active participation of trainees in these surgical procedures should be encouraged to improve their learning and to have more helping hands as these patients require multiple attempts of subsequent surgical debridement.
- (D) *Workload management planning* Close collaboration with eye surgeons and neurosurgeons can also help in avoiding multiple surgeries in patients who also need surgical treatment from these departments as well. Maxillofacial surgeons also be clubbed with

otorhinolaryngologists if required, as they are also familiar with open surgical approaches in the required surgical field.

Conclusion

Due to various factors impacting host immunity such as diabetes mellitus, overuse of steroids and antibiotics in patients who were being treated for covid-19, along with favorable environmental factors such as high temperature and low precipitation, a sudden surge in cases of Rhino-Orbito-Cerebral Mucormycosis is being seen in India. In order to deal with this situation effectively, particularly when there is an existing overload on otolaryngologists and the rest of the health-care system, a multipronged and multilevel collaborative effort is the need of the hour. With effective Standard Operating Procedures and guidelines promoting a multidisciplinary approach for early diagnosis and treatment, we can surely overcome this menace. Moreover we suggest taking essential precautions to strengthen one's immunity but do not advocate the consumption of unprescribed medications. As the role of Zinc in mucormycosis during the ongoing pandemic is still being looked into, its intake as an immunity booster is not advisable at the moment. In our opinion, these measures need to be taken irrespective of whether one has been infected with covid-19 or not, as the threat of acquiring both covid-19 infection and mucormycosis following recovery from it is bound to persist in times to come.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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