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Original Research Article

Post-COVID rhinocerebral mucormycosis: an otolaryngologists nightmare

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ABSTRACT

Background: Rhinocerebral mucormycosis which was considered to be a rare occurrence in the pre-COVID era is currently emerging as a life-threatening disease with seemingly poor prognosis in post COVID recovered patients. Prompt diagnosis with urgent surgical and medical management is vital to a positive outcome.
Methods: A retrospective observational study and analysis was done among patients of biopsy proven mucormycosis with preceding history of COVID 19 disease between March 2021 to April 2021 in a tertiary care state run hospital at Pune coinciding with the sudden surge and second COVID 19 wave.
Results: 20 0ut of 23 patients were having a history of type 2 diabetes mellitus for a mean duration of 4±3.5 years. The most common presenting complaint was unilateral facial swelling, periorbital pain, swelling and oedema in 18 out of 23 patients. All patients had COVID infection within the last one month of presentation with mean duration of 18±8.4 days. Out of 23 patients 16 survived while 19 patients had permanent vision loss and ophthalmoplegia.
Conclusions: Establishing the possibility of invasive secondary fungal infections in patients with history of COVID-19 infection especially in patients with pre-existing risk factors should raise high index of suspicion. Prompt early diagnosis and treatment should be started to reduce morbidity and mortality.

Keywords: Post COVID, Rhinocerebral mucormycosis, Functional endoscopic sinus surgery, Amphotericin

INTRODUCTION

Mucormycosis is an invasive fungal disease caused by mould fungi of the genus *Mucor*, *Rhizopus*, *Rhizomucor* and *Absidia*, which are in the Mucorales order of the Zygomycetes class.[1] Mucor can present in various forms as per anatomical location such as pulmonary, gastrointestinal, cutaneous, encephalic, and rhinocerebral. Frequently isolated species from the patients are *Apophysomyces (A. variabilis), Cunninghamella (C. bertholletiae), Lichtheimia [Absidia] (L. corymbifera L. raosa), Mucor (M. circinelloides), Rhizopus (R. arrhizus (oryzae) R. microsporus), Rhizomucor (R. pusillus), and Saksenaea (S. vasiformis*).[2] Considered to be indolent in immunocompetent patients, the aggressive course of disease in immunosuppressed patients such as poorly controlled diabetics is the commonest risk factor (36%), followed by hematologic cancers (17%), and hematopoietic stem cell or solid organ transplant (12%).[3]

The advent of the second wave of COVID 19 in India followed mandating the use of steroids as the first line of management and this is proving to be a double edged sword exacerbating diabetes which was previously well controlled or flaring up of latent or previously undiagnosed diabetes. The angio-invasive fungal form of this disease spread by fungal spores in a hyperglycemic environment causes luminal thrombosis resulting in mucosal infarction and necrosis, bony erosion which is rapidly progressive advancing into sino-nasal cavity,

orbit and eventually into the cranial cavity through retro orbital route.[4]

The sino-nasal/rhinocerebral disease most often clinically presents as purulent nasal discharge, headache, facial/periorbital swelling, blurring of vision/acute onset blindness, ptosis, proptosis, hard palate perforation and altered sensorium in case the disease has progressed to the cranial cavity amongst many other non-specific symptoms. Nasal cavity examination typically shows blackish eschar/necrosed mucosa though not pathognomonic raises a high index of suspicion.[5]

We at our tertiary care centre have witnessed a nearly four-fold rise in cases of mucormycosis in COVID-19 patients in the last 6 months. Immediate diagnosis and combined medical and surgical treatment is paramount and life saving for this disease which still remains highly morbid.

METHODS

Study design

A retrospective observational study was done among patients of biopsy proven mucormycosis with preceding history of COVID-19 disease between March 2021 to April 2021 in at B. J. Government Medical College and Sassoon General Hospital, Pune. All COVID recovered patients between 18-60 years of age with rhinocerebral mucormycosis who underwent either surgery/medical therapy were included in the study after written informed consent. All patients were subjected to computed tomography (CT) evaluation of the para nasal sinuses. Immediate diagnosis was established based on detailed history, thorough ENT, ophthalmic and neurological evaluation. KOH mount from nasal crusting was carried out to come to a provisional diagnosis.

Hereby we are reporting case series of 23 patients with confirmed diagnosis on KOH mount/biopsy followed by computed tomography of paranasal sinus in whom medical therapy and surgical debridement (FESS, Functional endoscopic nasal surgery) along with ophthalmic management was initiated.

Data was then compiled and analysed using IBM Statistical Package for Social Sciences (SPSS) Software to calculate mean, standard deviation and distribution.

RESULTS

Our case series had 23 patients who presented between March 2021 to April 2021. 15 were male and 8 were female. The mean age was 58.9 years with standard deviation of 11.59 years. 20 out of 23 patients were having a history of type 2 diabetes mellitus for a mean duration of 4±3.5 years but were well controlled on oral hypoglycaemic agents. 3 cases were that of a newly diagnosed diabetic concurrently on admission for COVID-19. The fasting blood sugars was grossly deranged in all the patients with a mean of 332±90 mg/dl with one patient having frank diabetic ketoacidosis. All the patients had to be managed on subcutaneous insulin proportional to their blood sugars.

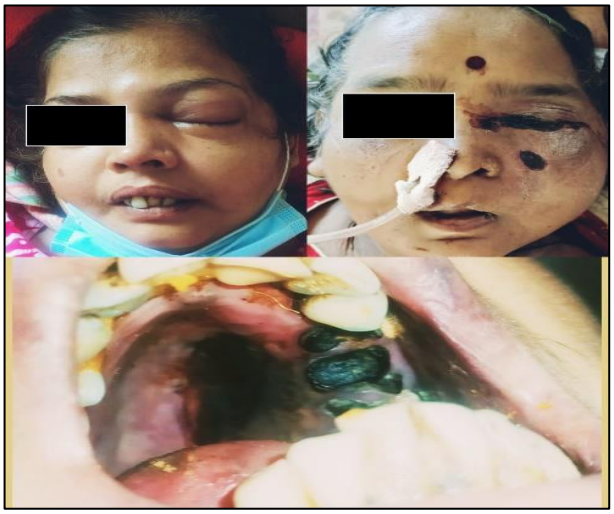

Figure 1: Clinical picture on presentation.

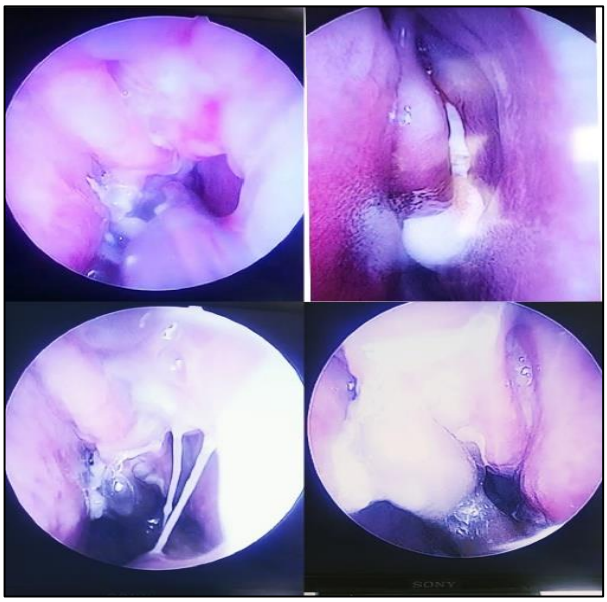

Figure 2: Diagnostic nasal endoscopy.

The most common presenting complaint was unilateral facial swelling, periorbital pain, swelling and oedema in 18 out of 23 patients. Mean duration of onset was 4 days. Except for four cases, all other patients had complete ptosis, chemosis, eyelid and periorbital oedema and no perception of light. (Figure 1) Purulent discharge and black eschar was observed in the nasal cavity of all cases except for two cases who just complained of nasal blockage. 14 patients also had hard palate perforation/eschar. (Figure 2) General condition was moderate barring four patients who were clinically unstable.

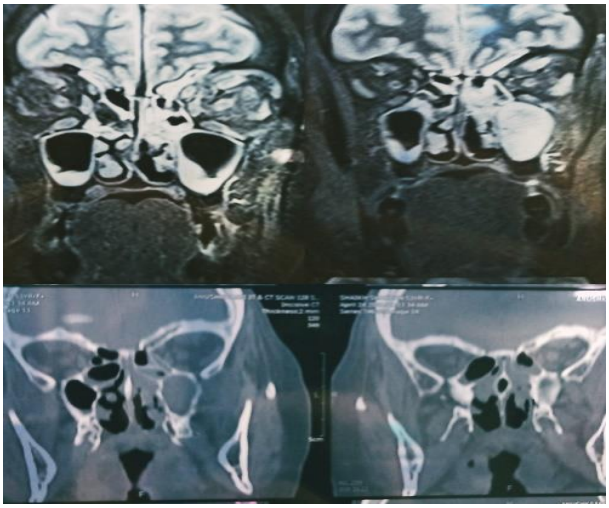

Figure 3: Radiological images of paranasal sinus.

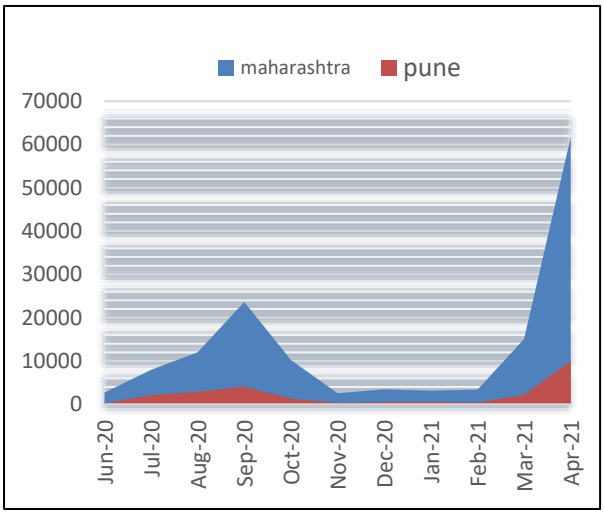

Figure 4: The second wave of April showing thrice the number of cases as compared to first wave in September 2020.

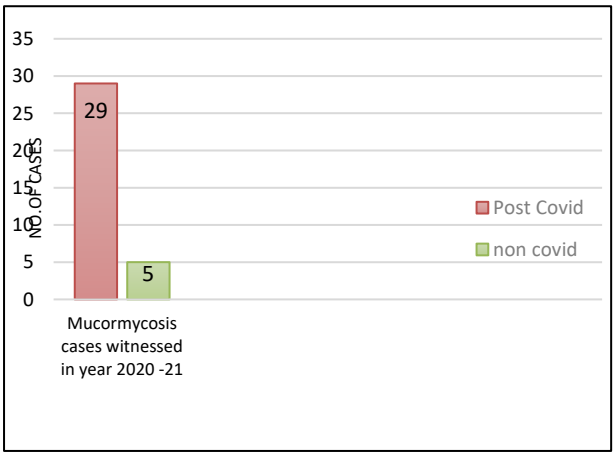

Figure 5: The number cases of mucormycosis received post COVID versus the number without prior COVID history.

On computed tomography of the para nasal sinuses, all patients had thickened mucosal lining and sinus opacification of maxillary, ethmoid, sphenoid and frontal sinus. (Figure 3) There was patchy bony resorption followed by intra orbital extension in 19 out 23 patients. 6 patients had extension into the orbital apex reaching the cavernous sinus.

All patients had COVID-19 infection within the last month with mean 18±8.4 days. All 23 patients had requirement of oxygen and were treated for moderate to severe covid disease as per Indian Council of Medical Research (ICMR) guidelines for COVID-19 management which includes anti-inflammatory or immunomodulatory therapy. Injection Methylprednisolone 1 to 2 mg/kg IV in 2 divided doses (or an equivalent dose of dexamethasone) usually for a duration 5 to 10 days 6. Disease progression was aggressive and out of 23 patients who presented to us had 19 already lost their vision (no perception of light on examination) within 3 to 4 days of onset of first symptom.

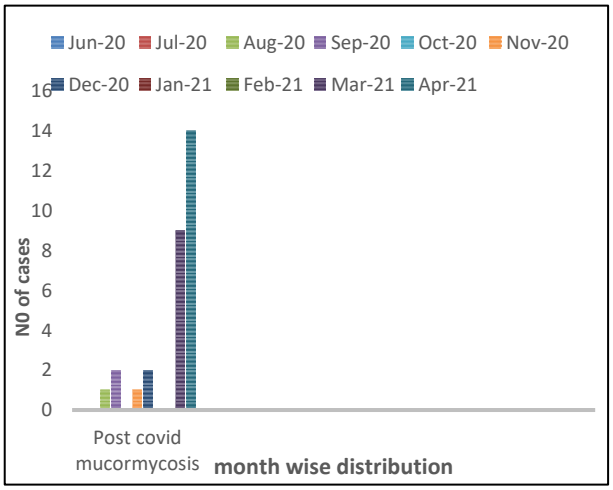

Figure 6: Month wise distribution of COVID cases, surge witnessed coinciding with the second COVID wave.

All patients were started on broad spectrum antibiotics, subcutaneous insulin, two patients received liposomal amphotericin 4-8 mg/kg while 21 patients received intra venous amphotericin B 1-3 mg/kg titrated as per creatinine clearance for 21 days.[16] 20 out of 23 patients were urgently posted for endoscopic surgical debridement along with intravenous amphotericin, sugar control, broad spectrum antibiotics. Serum electrolytes and renal function tests were rigorously monitored on a daily basis. 16 out of 23 patients survived while 19 patients had permanent vision loss and ophthalmoplegia.

DISCUSSION

Mucormycosis regardless of the type of fungi has been identified as a highly fatal disease with rapid progression and hence needs to be treated aggressively. The incidence

of mucor in India is estimated to be 70 times more than the global estimate. The Leading International Fungal Education (LIFE) portal has estimated the annual global prevalence of mucormycosis to be approximately as 10,000 cases excluding the Indian data. After inclusion of Indian data, it became 910,000 cases annually. In India 57% of the patients had uncontrolled diabetes with 10% in diabetic ketoacidosis.[7]

Rhinocerebral mucormycosis infection starts in the nasal cavity after inhalation of fungal spores. In uncontrolled diabetic patients the hyperglycemic environment depletes the patients immunity along with disruption of the local inflammatory response thus making it difficult to tackle the spread and this leads to spread of infection to adjoining paranasal sinuses. The angio-invasive nature of the disease leads to early implantation of fungi most commonly in the maxillary sinus as a fungal ball. The site involved in decreasing frequency is believed to be middle turbinate, followed by middle meatus and septum. As the duration progresses the necrosis of involved mucosa and bony resorption is inevitable. Progression into the brain is via either ethmoid sinuses, orbital apex, ethmoid fovea or angio-invasion of sphenopalatine or internal maxillary artery. The unique pathogenesis of blood invasion damaging the endothelium causing clot and occlusion resulting in ischemia is an attributing factor to early necrosis of the surrounding tissue.[8]

Study by Hoseini et al, suggests that pterygopalatine fossa is considered to be the main reservoir for rhinocerebral mucormycosis, and further extension into the orbit and facial soft tissues is preferably by this route. Initial proliferation in the nasal cavity, the spread to the pterygo-palatine fossa, inferior orbital fissure and finally the retro-global space of the orbit, results in ocular signs and eventually loss of vision and total ophthalmoplegia.[9]

The alarming addition to global burden of mucormycosis by India is mainly due to the huge susceptible population suffering from diabetes mellitus which is the most common attributed risk factor for developing mucormycosis. The number of people with diabetes in India has increased from 26.0 million (95% UI 23.4-28.6) in 1990 to 65.0 million (58.7-71.1) in 2016. The prevalence of diabetes amongst adults aged 20 years or older in India has increased from 5.5% (4.9-6.1) in 1990 to 7.7% (6.9-8.4) in 2016.[14] The large chunk of population which is still un-diagnosed until late stages, those with poorly controlled blood sugars, irregular follow up and inadequate management are all contributory.

The COVID-19 pandemic at present has caused massive surge in incidence of mucormycosis by exposing the susceptible population mainly diabetics. Our institution BJGMC and SGH is a tertiary care centre catering to the district of Pune.[15] Maharashtra currently is one of the worst hit states in India and Pune has emerged as the hotspot (Figure 4). The average growth rate in active cases in the month of April was 1.3% with a case fatality of 1.5%. This has created a major burden on our healthcare infrastructure. We at our institute having a capacity of 500 beds exclusively for treating covid infected patients and including 130 ICU beds for severe covid disease patients. We have been catering to an explosive surge of COVID rise in the month of March and April 2021 (Figure 5 and 6). The rise in Post COVID mucormycosis is proving to be an upcoming wildfire and aftermath of the COVID-19 complication.

The immune alteration and cytokine storm which is common occurrence in moderate to severe covid diseases is managed by intravenous methylprednisolone 0.5-1 mg/kg/day for three days in moderate cases and 1-2 mg/kg/day in severe cases as per current protocols.[10] The National Institute of Health recommends the use of dexamethasone (6 mg per day for a maximum of 10 days) in patients who require mechanical ventilation or oxygen supplementation.[11] The risk of developing a secondary infection is inevitably high for such patients.[12] The patients that presented to us were well managed on oral hypoglycaemic agents prior to COVID infection and reported a shift to subcutaneous insulin during admission for moderate to severe COVID infection. The steroid, immunomodulators and antibiotics used for the COVID treatment are major causes in exacerbating the underlying diabetes. The complex interplay of decreased immunity, hyperglycaemia, susceptibility to secondary infections is providing a fertile ground for mucormycosis.

We at our centre witnessed that after recovery and post discharge, 19 out of 23 patients reported that they did not continue the subcutaneous insulin upon discharge or monitored sugar levels at home. The rural patient population visiting our hospital is non complaint to post discharge advice due to many factors such as lack of financial support, lack of awareness and access to tertiary care eventually leading to poor follow up rates. A delay of even six days in initiating the treatment doubles the 30-day mortality from 35% to 66%.[13-16] Almost all the patients presented very late to us when the vision loss had already set in. In such scenario prompt diagnosis and high index of suspicion is necessary based on the clinical signs and history. The early surgical debridement and initiation of Amphotericin ln an urgent basis after a positive KOH report has been life-saving. Although the morbidity remains high, our purpose is to salvage while we can. The current treatment protocol we are following at present is a sandwich therapy of immediately initiating Intravenous Amphotericin followed by surgical debridement and continuing titrated dose of amphotericin for a total of 21 days with rigorous monitoring of renal function and serum electrolytes. The observation which was made during the surgical debridement is most commonly maxillary artery and its distal peripheral branches is proving to be the seat of the disease. The resultant thrombosed arterial branches cut off the blood supply causing necrosis of the mucosa. The Modified Denker's approach endoscopically is utilised for removing the

medial and posterior wall of involved maxillary sinus. Debridement of pterygopalatine fossa is done along with its extension to orbit if present and other necrosed areas like septum, palate, turbinates and other paranasal sinuses are debrided extensively for complete clearance. The post operative continuation of Amphotericin is mandatory. It is of utmost importance that we ensure post operative nasal douching with saline and anti-fungal solution along with bi weekly nasal endoscopy to remove the crusting and cleaning of the cavity and identify any residual disease.

Our battle with COVID-19 disease is long over, the least that can be done to decrease the load on already strained health infrastructure is to judiciously manage the steroid / immunomodulator therapy. Strict monitoring of sugars cannot be over emphasized along with extensive counselling and routine follow up of high-risk patients. The warning signs of developing mucor needs to be explained to the patients along with instructions to monitor blood sugars at home and immediately report if any of the suggestive symptoms or deranged sugar levels occur. Upon follow up, the attending physician should redirect the patient to the otolaryngology immediately for detailed ENT examination. Early intervention can significantly reduce the spread and morbidity of the disease. The management from physicians, ophthalmologist and otolaryngologists is vital to a comprehensive management of the patients. Uniform treatment protocols should be established at institutional level and stress should be laid on performing a routine Diagnostic Nasal Endoscopy for all Post COVID-19 recovered patients in order to pick up subtle evolution of the disease early and this helps to optimise the time needed for initiating early management. The visual outcome remains poor but can decrease the mortality significantly. Thus, it is necessary to counter this upcoming lethal disease which can further complicate the existing COVID crisis.

The pressing questions we are facing is to determine if the current rise of mucormycosis can be attributed to the current virulent strain of corona virus or proportional increase in risk of mucormycosis with duration of stay in the hospital especially Intensive Care Unit setups. Largely considered to be community acquired, should mucormycosis be considered as a nosocomial infection is a question of debate. Further detailed study is needed to determine the optimum steroid treatment and dosage combined with early detection policy. Should Prophylactic anti-fungal therapy be started in high risk group keeping in mind the risk versus benefit should be considered in future studies along with mandatory ENT examination and visual assessments in all high risk groups of COVID patients.

CONCLUSION

COVID-19 is commonly associated with a significant incidence of secondary infections, both bacterial and fungal probably due to immune alterations/cytokine storm landing the patients in immunocompromised state. Additionally, the widespread use of steroids/monoclonal antibodies / broad-spectrum antibiotics as part of treatment protocol against COVID-19 may lead to the development / exacerbation of diabetes mellitus and eventually fungal diseases like mucor. It is necessary to raise awareness of the possibility of invasive secondary fungal infections in patients with history of COVID-19 infection especially in patients with pre-existing risk factors. The use of therapeutic agents should be judicious at the lowest dose and shortest durations. Strict sugar control and educating the patients about the same along with warning signs can be the initial step which will eventually lead to early presentation and management.

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