Original research article

CROSS SECTIONAL STUDY OF EAR, NOSE AND THROAT MANIFESTATIONS OF POST COVID-19 MUCORMYCOSIS PATIENTS IN A TERTIARY CARE HOSPITAL

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Abstract

Background: COVID-19 has been one of the worst pandemics that hit the humans. Mucormycosis in people with COVID-19 have been increasingly reported world-wide, in particular from India. Rhino-Orbito-Cerebral Mucormycosis is the most common form of it. Intracranial involvement of mucormycosis increased the fatality rate to as high as 90%.

Aim and Objectives: To assess the clinical manifestations of the patients with post COVID-19 mucormycosis and to study steroids and oxygen usage in such patients.

Materials and Method: This retrospective cross-sectional study was carried out in the Department of Ear, Nose and Throat, Grant medical college and Sir JJ Group of Hospitals, Mumbai, from Oct 2020 to September 2022.

Observation and Results: This study included 163 patients among which 115 were male (71%) and 48 females (29%) and also it was observed that maximum patients were in the age group of 41-60yrs (60%). 55% presented with symptoms in less than 10 days of COVID-19 infection. 71% had history of diabetes. 63% had received steroids treatment, while 41% required oxygen during COVID-19. 80% patients had nose related complaints, while 36% had throat related complaints and in other complaints 39% and 22% of the patients had facial pain and proptosis observed in major.

Conclusion: COVID-19 infection are more susceptible to mucormycosis and to ascertain the relationships between the present treatment protocol, prospective co-morbidities, and environmental variables and mucormycosis infection, more study is needed.

Keywords: COVID-19, Mucormycosis, Rhino-Orbito-Cerebral, Protopsis, Facial Pain

Introduction

COVID-19 has been one of the worst pandemics that hit the humans. It is associated with broad spectrum of otorhinolaryngological manifestations are commonly seen in this disease [1,2]. Secondary infections were reportedly common in hospitalized, severely ill COVID-19

patients, encompassing between 10 and 30% of cases, fungal being 10 times more common [3]. Both *Aspergill us* and *Candida* have been reported as the main fungal pathogens for co-infection in people with COVID-19 [4]. Recently, several cases of mucormycosis in people with COVID-19 have been increasingly reported world-wide, in particular from India. A total of 20,908 cases of mucormycosis with 1,376 confirmed deaths have been reported from India so far as July 31, 2021 as per the reports of Ministry of Health and Family Welfare. The active cases were more than 28,000 and were declared as "black fungus epidemic" [5].

The primary reason that appears to be facilitating Mucorales spores to germinate in people with COVID-19 is an ideal environment of low oxygen (hypoxia), high glucose (diabetes, new-onset hyperglycemia, steroid-induced hyperglycemia), acidic medium (metabolic acidosis, diabetic ketoacidosis [DKA]), high iron levels (increased ferritins) and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression (SARS-CoV-2 mediated, steroid-mediated or background comorbidities) coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators [6].

The two most important types of Mucormycosis in this scenario are rhino-orbital-cerebral and pulmonary. Rhino-Orbito-Cerebral Mucormycosis is the most common form, and it is usually seen in diabetic ketoacidosis or poorly controlled diabetes mellitus [7]. The clinical hallmark of invasive mucormycosis is necrosis of tissue due to angioinvasion and subsequent thrombosis. The early symptoms of Rhino-Orbito-Cerebral Mucormycosis are similar to sinusitis and periorbital cellulitis and may report eye and/or facial pain and numbness followed by blurred vision. Signs and symptoms suggestive of Mucormycosis in susceptible individuals includes multiple cranial nerve palsies, unilateral periorbital facial pain, edema of eyelids, orbital inflammation, blepharoptosis, proptosis, acute ocular motility changes, internal or external ophthalmoplegia, headache, and acute vision loss [8]. The development of black lesions or discharge on the nasal bridge or upper inside part of the mouth that may quickly progress and become more severe.

There was a steep rise in case reports/series of mucormycosis in people with COVID-19 especially from India. Similarly, many cases were being reported from other parts of globe. Several anecdotal cases are also being reported in grey literature such as the print and electronic media. These finding were unprecedented and carry an immense public health importance, primarily because fatality rate with mucormycosis is pretty high. Especially the intracranial involvement of mucormycosis increased the fatality rate to as high as 90% [9]. Moreover, rapidity of dissemination of mucormycosis is an extraordinary phenomenon and even a delay of 12 h in the diagnosis could be fatal, the reason 50% of cases of mucormycosis have been historically diagnosed only in the post-mortem autopsy series [10]. This prompted us to conduct a retrospective study with an aim to assess the clinical manifestations of the patients with post COVID-19 mucormycosis and to study steroids and oxygen usage in such patients.

METHODOLOGY

This retrospective cross-sectional study was carried out in the Department of Ear, Nose and Throat, Grant medical college and Sir JJ Group of Hospitals, Mumbai, from Oct 2020 to September 2022. Ethical approval was taken from Institutional Ethics Committee prior to start the study (Ref. IEC/637/Oct/2021). A written informed consent was obtained from all the patients/guardians after explaining the objectives of the study. Precautions were taken throughout the study to safeguard the rights and welfare of all the participants.

Clinically and microbiologically proven cases of mucormycosis with past history of COVID-19 infection were included in the study. The demographic and clinical data was collected with the consent of the patients.

RESULTS

In present study we included 163 patients diagnosed with mucormycosis post COVID-19 infection. Among them 115 were male (71%) and 48 females (29%). These patients were further distributed based on age groups and it was observed that maximum patients were in the age group of 41-60yrs (60%) (Fig 1).

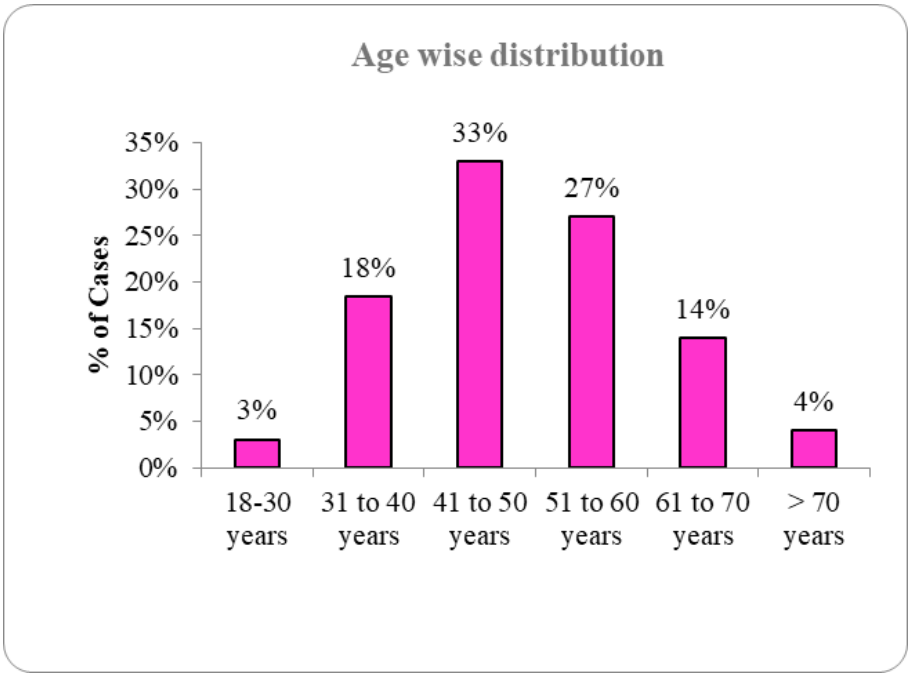

Fig 1: Distribution of patients according to age

Clinical history of all patients was recorded and it was observed that 115 patients (71%) had history of diabetes. We also observed that 84 patients (63%) had received steroids treatment, while 67 patients (41%) required oxygen during COVID-19 infection (Table 1).

Table 1: Distribution of patients based on demographic and clinical history

Total patients diagnosed with mucormycosis infection	**N= 163**	
Gender	Male	Female
	115/163 (71%)	48/163 (29%)
History of diabetes	Yes	No
	124/163 (76%)	39/163 (24%)
Steroids treatment during COVID-19	Yes	No
	84/163 (52%)	79/163 (48%
Oxygen requirement during COVID-19	Yes	No
	67/163 (41%)	96/163 (59%)

Further, it was observed that maximum number of patients (55%) presented with symptoms in less than 10 days of COVID-19 infection, while 29% had symptoms within 11-20 days of infection. The duration of presenting symptoms was less than 10 days in 56% of patients, it

was 11-20 days in 29% patients, 21-30 days in 14% patients and it was more than 30 days in 10% patients (Table 2).

In this study we mainly took in to consideration about the ENT symptoms among which 80% patients had nose related complaints, while 36% had throat related complaints, none of the patient had any eye related complaint.

Table 2: Distribution of patients based on complaints/presenting symptoms post COVID-19 infection

S, No.	Symptoms/Complaints	Frequency
1.	**Gap between COVID-19 infection and presentation of symptoms**	
	< 10 days	55%
	11 to 20 days	29%
	21 to 30 days	9%
	> 30 days	7%
2.	**Duration of presenting symptom**	
	< 10 days	56%
	11 to 20 days	29%
	21 to 30 days	14%
	> 30 days	10%
3.	**Post COVID-19 ENT manifestations**	
	Nose complaints	80%
	Throat complaints	36%
	Other complaints	100%
4.	**Other Complaints**	
	Facial Pain	39%
	Proptosis	22%
	Facial Swelling	31%
	Loss of Vision	9%

We further observed that among the throat related complications, loosening of tooth/dental pain was most common complication (23%), followed by perforation (6%), swelling over hard palate (4%) and discoloration of hard palate (2%). Among the nose related complaints, nasal blockage was most common (36%), followed by headache (26%), hyposmia/anosmia (9%), rhinitis (5%) and epistaxis (5%) (Fig 2).

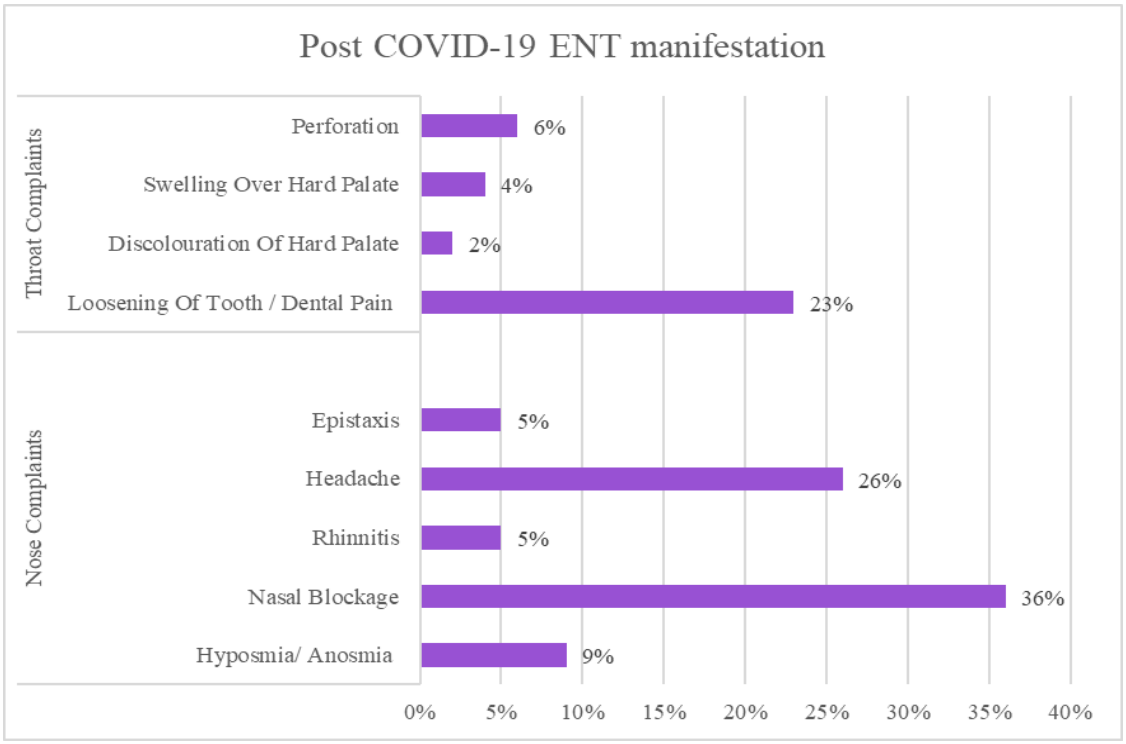

Fig 2: ENT manifestation in post COVID-19 patients infected with mucormycosis

Apart from ENT, other common complaints were facial pain (39%), facial swelling (31%), proptosis (22%) and loss of vision in 9% patients (Table 2).

DISCUSSION

Although COVID-19 secondary infections were frequently documented, an increase in mucormycosis infections in COVID-19 patients was unexpected during the second wave worldwide, particularly in India. Among COVID-19 patients, mucormycosis cases were most recorded [6], along with other fungi illnesses such aspergillosis [11]. Despite not being a recent illness, mucormycosis causes a significant amount of morbidity and mortality in individuals with SARS-CoV-2 infection. It is still unclear what the complication's whole aetiology is. Therefore, a thorough examination of the potential causes for COVID-19-associated mucormycosis (CAM) is required.

Although mucormycosis is relatively rare in healthy people, it is more common in people with immunosuppressed diseases. Included are uncontrolled diabetes mellitus (DM) with or without diabetic ketoacidosis, haematological and other cancers, organ transplantation, protracted neutropenia, immunosuppressive medications, and corticosteroid treatment. [12]. Diabetes was found to be a common factor across many studies. In present study also we identified that 75% patients had diabetes. Similarly, case report study by John *et al*, of 41 COVID-19-associated mucormycosis patients, observed that 94% of the patients had diabetes [13]. Hoenigl M et al, did a review of CAM cases from 18 countries and observed that diabetes was the most prevalent condition overall (83%), with type 2 diabetes being more common than type 1 diabetes (89% vs 9%) [14]. These findings are consistent with findings of Singh et al, ,where 80% cases had DM.

Steroids were widely used for the treatment of COVID-19 patients, however, they cause immunosuppression by inhibiting the transcription of the cytokine genes, especially IL1 and

6 and sequestration of CD4+ lymphocytes [15]. In the background of an immunosuppressive state like COVID-19 and diabetes, steroids have increased the risk of mucormycosis. Singh *et al*. [6] have done a systematic analysis on 101 reported cases of COVID-19 and mucormycosis worldwide. Among the 101 cases reported, 76.3% of the patients were on steroid. Similar results were observed in our study, wherein, 52% patients had steroids during COVID-19 treatment. Collectively, these findings suggest a familiar connection of mucormycosis, diabetes and steroid, in people with COVID-19.

One of the reasons of mucormycosis is said to be the substitution of industrial oxygen for medical oxygen as a result of the rising need for oxygen cylinders in the treatment of COVID-19. Medical oxygen is very different from industrial oxygen, and there is a significant risk that the oxygen's quality and hygienic standards will be lowered. It's possible that the water used to humidify the oxygen is also where the fungus spores come from that enter the lungs through inhalation. Hyperbaric oxygen therapy is a complementary treatment for mucor infection [16]. We observed that 41% of the patients infected with mucormycosis in present study had oxygen requirement during COVID-19 infection.

The manifestations of mucormycosis symptoms include facial pain, headache, inflammation, swelling of periorbital and nasal region, bad odor, proptosis, eyelid drooping and edema, external and internal ophthalmoplegia, exophthalmos, nasal bleeding, facial paralysis accompanied by loss of vision, and nasal discharge consisting of some amount of reddish-black nasal turbinate. In present study facial pain, swelling and proptosis were common complaints.

CONCLUSION

There was a general perception that in post covid 19 patients hyposmia was the most common clinical manifestation in ENT, but in present study we concluded that in post covid 19 mucormycosis patient nasal blockage was most common ENT manifestation , overall. Apart from this, no otological manifestations were noted in these patients.A positive steroid association was documented in majority of patients.

It has been noticed that persons with diabetes who have recovered from COVID-19 infection are more susceptible to mucormycosis, albeit the exact explanation of its abrupt increase unexpectedly and in particular during the second wave is still under debate
Contrary to the consensus, there was no direct association of the use of industrial oxygen with post covid 19 sequelae. And more over there was no way to document if the patient was administered with medical oxygen or industrial oxygen during the active covid illness.

To ascertain the relationships between the present treatment protocol, prospective co-morbidities, and environmental variables and mucormycosis infection, more study is needed.

Acknowledgement :
Funding : None
Conflict of Interest : None to declare

REFERENCES

1. Krajewska J, Krajewski W, Zub K, Zatoński T. COVID-19 in otolaryngologist practice: A review of current knowledge. Eur Arch Otorhinolaryngol. 2020 Jul;277(7):1885-97.

2. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): A multicentre European study. Eur Arch Otorhinolaryngol. 2020 Aug;277(8):2251-61.
3. Superinfections and coinfections in COVID-19 MedPage Today. https://www.medpagetoday.com/infectiousdisease/covid19/86192.
4. Song G., Liang G., Liu W. Fungal Co-infections associated with global COVID-19 pandemic: a clinical and diagnostic perspective from China. *Mycopathologia.* 2020 Aug;185(4):599–606.
5. Dogra S, Arora A, Aggarwal A, Passi G, Sharma A, Singh G, et al. Mucormycosis Amid COVID-19 Crisis: Pathogenesis, Diagnosis, and Novel Treatment Strategies to Combat the Spread. *Front Microbiol*. 2022 Jan 4;12:794176
6. 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 Jul-Aug;15(4):102146
7. Spellberg, J. Edwards Jr., A. Ibrahim. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin. Microbiol. Rev., 18 (3) (2005), pp. 556-569
8. G. Petrikkos, A. Skiada, O. Lortholary, E. Roilides, T.J. Walsh, D.P. Kontoyiannis. Epidemiology and clinical manifestations of mucormycosis. Clin. Infect. Dis., 54 (Suppl 1) (2012), pp. S23-S34
9. Deutsch P.G., Whittaker J., Prasad S. Invasive and non-invasive fungal rhinosinusitis—a review and update of the evidence. *Medicina.* 2019;55:1–14.
10. Maartens G., Wood M.J. The clinical presentation and diagnosis of invasive fungal infections. *J Antimicrob Chemother.* 1991;28(13–22):17–44
11. White PL, Dhillon R, Cordey A, Hughes H, Faggian F, Soni S, et al. A National Strategy to Diagnose Coronavirus Disease 2019-Associated Invasive Fungal Disease in the Intensive Care Unit. Clin Infect Dis. 2021 Oct 5;73(7):e1634-e1644.
12. Sugar A.M. *Mucormycosis. Clin Infect Dis.* 1992;14:S126–S129
13. John TM, Jacob CN, Kontoyiannis DP When uncontrolled diabetes mellitus and severe COVID19-19 converge:The perfect storm for mucormycosis J Fungi 2021;7:298
14. Hoenigl M, Seidel D, Carvalho A, Rudramurthy SM, Arastehfar A, Gangneux JP, Nasir N, Bonifaz A, Araiza J, Klimko N, Serris A, Lagrou K, Meis JF, Cornely OA, Perfect JR, White PL, Chakrabarti A; ECMM and ISHAM collaborators. The emergence of COVID-19 associated mucormycosis: a review of cases from 18 countries. Lancet Microbe. 2022 Jul;3(7):e543-e552.
15. RECOVERY Collaborative Group Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with COVID19-19 N Engl J Med 2021; 384:693-704
16. Palanisamy, Priyadharsini R.; Elango, Dhivya. COVID19 associated mucormycosis: A review. Journal of Family Medicine and Primary Care 11(2):p 418-423, February 2022.