



Case Series

Mucormycosis in this COVID times- A case series

Manisha Parida¹, Alaka Sahu¹, Radhamohan Ghare¹, Sagarika Panda^{1,*}¹Dept. of Pathology, Veer Surendra Sai Institute of Medical Sciences and Research, Burla, Odisha, India

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ABSTRACT

Mucorales are fast-growing thermophilic fungi that are ubiquitous in environment. Most common form is rhino-orbito-cerebral mucormycosis. It is the third most common cause of invasive fungal infections following aspergillosis and candidiasis. Their incidence has increased in recent times, especially in the 2nd wave of COVID-19 in India. COVID-19 is caused by non-segmented negative sense RNA virus, which causes profound lymphopenia. Glucocorticoid has emerged as main treatment of choice for COVID-19 patients with severe symptoms. The patients of COVID-19 are increasingly affected with mucormycosis because of decreased immunity, impaired defense mechanisms, dysfunctional lymphocytes and neutrophils, and injudicious use of glucocorticoids. Diabetes mellitus is an independent risk factor for both mucormycosis and severe COVID-19. Hyperglycemia due to diabetes and glucocorticoid increases the incidence of infection due to greater availability of glucose to the pathogen, lower response of T cells, and acidic pH. This fungus has predilection to invade blood vessels leading to extensive necrosis (black eschar). The overall mortality rate is 56%. Mortality depends upon underlying health condition of patient and the part of the body affected.

In this retrospective study, we present an interesting case series of 15 patients with mucormycosis. Association with diabetes, with uncontrolled glycemic index was found in all the cases. COVID-19 associated mucormycosis was seen in 10 patients.

Excessive use of corticosteroid in a patient with COVID-19 has aggravated the scenario. An early foresight about the condition and judicious use of steroids is useful. So, an early diagnosis and prompt treatment of mucormycosis can decrease the fatality and morbidity in patients.

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1. Introduction

Mucormycosis is emerging as angioinvasive infection, associated with high mortality rate. It is caused by Mucorales (Zygomycetes).¹ Studies till now, estimated that the world wide prevalence of mucormycosis varies from 0.005 to 1.7 per million populations, while its prevalence is nearly 80 times higher (0.14 per 100) in India as compared to other developed countries, in a recent estimate of year 2019-2020.² Diabetes mellitus has arisen as a single most important risk factor for mucormycosis in (36-38%) cases.

* Corresponding author.

E-mail address: pandadsagarika@gmail.com (S. Panda).

India has the highest burden of mucormycosis in the world, as India being the 2nd largest population with diabetes mellitus.³ Mucormycosis has been-emerging as a matter of concern in the ongoing COVID-19 pandemic affecting worldwide. COVID-19 is caused by single stranded RNA virus SARS-COV-2.

Mucormycosis is an uncommon disease in healthy individuals, but recently emerged as a fatal fungal opportunistic infection in persons owing to decreased immunity. Normally the inhaled spores do not germinate in healthy individuals, but they tend to germinate in a case of COVID-19 due to low oxygen(hypoxia),

high glucose (diabetes, new onset diabetes, steroid induced hyperglycaemia), acidic environment (Diabetic ketoacidosis), high iron levels (increased ferritin) and decreased phagocytic activity of WBC owing to both COVID-19 and steroid induced immunosuppression.⁴

In COVID-19, glucocorticoids have emerged as a mainstay of treatment. Injudicious use of glucocorticoids is being pointed out as the major cause of mucormycosis, owing to its immunomodulatory effects.⁵ A dose of prednisolone more than 600mg with a course of 5-14 days predisposes the immunocompromised patients to mucormycosis.⁶ The poor prognosis is related to delay in diagnosis, and inherited resistant to mucorales to most anti-fungals. The purpose of this article is to discuss 15 cases of mucormycosis diagnosed in a very short period, which were found to have some similarities.

2. Case Series

This is a retrospective observational study conducted in the department of pathology, VIMSAR, Burla over a period of one month from MAY 31st 2021 to JUNE 30th 2021. 15 cases of mucormycosis, which were histologically proven were studied. The demographic features, along with clinical presentation and other relevant history such as previous history of diabetes mellitus or other co morbidities, infection with COVID 19 or treatment with steroid is obtained from clinical records. The relevant MRI findings were also obtained from the patient. Biopsy tissue which was received by the department, was processed and the sections were then, stained with hematoxylin and eosin and periodic acid Schiff (for better visualisation of fungal hyphal structures and confirmation of diagnosis) were reviewed in our department and the results were compiled. Lastly KOH mount and culture reports were obtained from the department of microbiology and compiled. Out of the 15 cases, 11 were males (73.33%) and, 4 were females (26.66%) with the age ranging from 35- 70 years (median age 51yrs). Predisposing comorbidities like uncontrolled diabetes mellitus was identified on all 15 cases, while 10 patients (66.66%) were detected to be COVID-19 positive by RAT (Rapid antigen test), while remaining were negative on RAT test. All the cases presented with similar complaints of headache, retro-orbital pain, lacrimation and decreased vision of the affected eye, except for the case number 11 ie. (54yr male) who also complained of fever, cough, chest pain. From the total 15 cases, 13 cases seems to respond well with debridement of necrotic tissue and IV injection of amphotericin B and while there was death of 2 cases. Of the total 15 cases only 3 cases were reported to have prior steroid use. All the 15 patients were associated with deranged glycemic index.

Imaging and histopathological analysis of biopsy specimen are used to confirm the clinical diagnosis. Cases showed normal X-ray features with no lung involvement,

while HRCT, and X-ray of one patient (case number 11) revealed extensive well defined thick walled oval lesion with areas of opacity interspersed with air and irregular intersecting areas of stranding lined (bird nest sign) noted in the upper lobe of left lung, suggestive of pulmonary mucormycosis. Furthermore, the MRI findings of all the 15 cases were almost same. MRI finding were mild to moderate mucosal thickening in bilateral maxillary, ethmoid, frontal sphenoid sinus with moderate heterogenous enhancement suggestive of invasive fungal sinusitis. Orbit and no intracranial involvement was detected in 14 cases, while 1 case ie case number 2 showed features of invasive fungal sinusitis along with invasion of right optic nerve and right extraocular muscle without intracranial involvement. In this case, to prevent further intracranial extension enucleation of the right eye was done which revealed fungal hyphae on histopathological examination.

On histopathological examination of the H and E stained slides, one case ie case number 11 revealed mixed population of fungal hyphae (Mucor and fruting conidial bodies of aspergillosis), while the remaining 14 cases showed only broad based fungal hyphae belonging to mucormycosis. Characteristics of hyphae help in differentiating different fungal infections. The key features associated with mucormycosis, were typically thick walled, retractile hyphae 6-15 microns in diameter, broad-based, ribbon - like, non-septate hyphae with wide angle branching (approximately 90 degrees).⁷ In contrast aspergillus hyphae is (3 – 12 microns) in diameter, septate and branch at acute angles.⁸

Similarly the KOH 11 samples were positive, while 4 cases being negative.

The detailed demographic, the clinical findings, associated comorbidities, histopathological findings are discussed in the Table 1.

3. Discussion

The coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). It is a positive strand RNA virus belonging to the family coronaviridae. COVID-19 has a varied range of signs and symptoms including common cold to pneumonia and acute respiratory distress syndrome. In September 2020, WHO recommended the use of corticosteroids to the patients with severe and critical COVID-19. People with diabetes and other comorbidities tend to develop more severe COVID-19 infection and in turn more likely to receive corticosteroids. So the combination of COVID-19, corticosteroid, and diabetes mellitus creates a perfect combination in which, mucormycosis takes advantage and thrives.

Mucormycosis earlier called Zycomycosis is mostly caused by *Rhizopus Oryzae*. Mucormycosis is the second most common mould infection and the third most common

Table 1: Diabetes mellitus, RBS – Random blood sugar, KOH mount – potassium hydroxide mount, Inflammation, Ang inv-angioinvasion

S.No.	Age	Sex	Place	DM	Other	Covid H/O	HbA1c/RBS	Steroid	KOH	Necrosis	Inflam	Ang. Inv.	Fungus
1	69yrs	M	Barpali	+	-	Negative	12.9%	-	+	+	+	-	Mucor
2	51yrs	M	Nuapada	+	-	Positive	143mg/dl	-	+	+	+	-	Mucor
3	35yrs	F	Kharsal	+	-	Positive	9.7%	+	+	+	+	-	Mucor
4	58yrs	M	Angul	+	HTN	Negative	250mg/dl	-	+	+	+	-	Mucor
5	68yrs	M	Bargarh	+	-	Positive	346mg/dl	-	+	+	+	-	Mucor
6	35yrs	F	Bamda	+	-	Negative	309mg/dl	-	-	+	+	-	Mucor
7	60yrs	M	Kalahandi	+	-	Negative	200mg/dl	-	+	+	+	-	Mucor
8	38yrs	M	Jharsuguda	+	-	Positive	500g/dl	+	+	+	+	-	Mucor
9	39yrs	M	Jharsuguda	+	-	Positive	473mg/dl	-	+	+	+	-	Mucor
10	65yrs	F	Sohala	+	-	Positive	15%	+	+	+	+	-	Mucor+aspergillus
11	54yrs	M	Barpalli	+	-	Positive	11.7%	-	+	+	+	-	Mucor
12	35yrs	M	Hirakud	+	-	Positive	400mg/dl	-	+	+	+	-	Mucor
13	52yrs	M	Angul	+	-	Negative	10.7%	-	-	+	+	-	Mucor
14	52yrs	F	Bargarh	+	-	Positive	12%	-	-	+	+	-	Mucor
15	60yrs	M	Boudh	+	-	Positive	300mg/dl	-	-	+	+	-	Mucor

invasive fungal infection in patients with hematological tumors and organ transplantation.⁹ It has emerged as one of the important infections in this ongoing pandemic. The incidence of mucormycosis in India has risen more rapidly during the 2nd wave, compared to the 1st wave. At least 28,200 cases of mucormycosis were diagnosed till 7th June 2021 in India.¹⁰ Mucormycosis is an aggressive fungal opportunistic infection of the immunocompromised and debilitated patients. It is a fast-growing thermostat fungus, present in agricultural soils. Mucormycosis is also known as the black fungus, is characterised by angio-invasion that results in vessel thrombosis and subsequent necrosis. This necrosis further prevents the delivery of leukocytes and antifungal agents to the foci of infection and also helps the organism to disseminate to target organs. We contact mucormycosis in three ways i.e by breathed spores, gulping spores in food, or when spores contaminate the wound. To purpose ailment, fungal spores need to germinate in the host. This can be done only when fungal spores can bypass the immune system. The main defense mechanisms which act against fungus are mononuclear cells and neutrophils. They act by the generation of oxidative and non-oxidative material. Rhino-orbito-cerebral mucormycosis is frequently observed in association with uncontrolled diabetes and diabetic ketoacidosis, whereas pulmonary involvement is seen in patients with neutropenia, bone marrow, and organ transplantation. The gastrointestinal tract gets involved in malnourished patients. The cutaneous form is due to direct inoculation of fungal spores in the skin. Overall mortality is 44% in diabetics while 66% in patients with malignancy and 35% in patients with no co-morbidities.¹¹

The factors like hyperglycemia, increase in serum iron, acidic PH increases the virulence of the fungus. Factors increasing the aggressiveness of mucor are (1) ability to take iron from the host, which being essential for growth and development of Mucorales, (2) mucormycosis causes angio-invasion leading to ischaemic necrosis of tissue, which further prevents entry of the immune cells and also anti-fungal agents.¹²

Steroid use reduces phagocytic activity of WBC, causes impairment of broncho-alveolar macrophage migration and phago-lysosome fusion. This also inhibits glucose uptake by muscle and fat, also causes pancreatic beta cell destruction. This cascade of events can lead to hyperglycemia.

Diabetes is the single most important risk factor predisposing to the alarming rise in mucormycosis in the present scenario. Type 1, type 2, and secondary diabetic mellitus are all risk factors for mucormycosis. Data from a study in a tertiary care in India shows 74% of patients with mucormycosis has uncontrolled diabetes, 43% of these cases are diagnosed for the first time.¹³ Hyperglycemia causes glycosylation of transferrin and ferritin, reducing the iron-binding capacity, allowing increased free serum iron level. Acidic PH also increases

serum iron by the same mechanism. Free iron is the ideal resource for mucormycosis. An early diagnosis, well-directed, multidisciplinary approach with prompt treatment has been vital for saving lots of life and sights of the patients.

Y. Mishra et al studied 953 COVID-19 patients, of which 32 got infected with mucormycosis. 87.5% of mucor infected patients were associated with diabetes mellitus, majority of them has poor glycemic index, with mean HbA1C of 9.06%. M.Banerjee et al also emphasised the combination of COVID-19, Diabetes and Mucormycosis. They suggested possible means of preventing COVID-19 associated mucormycosis. Apart from maintaining glycemic index and judicious use of glucocorticoid, they advocated for the avoidance of Voriconazole, broad spectrum antibiotics and use of iron, zinc supplements for management of COVID-19 patients.

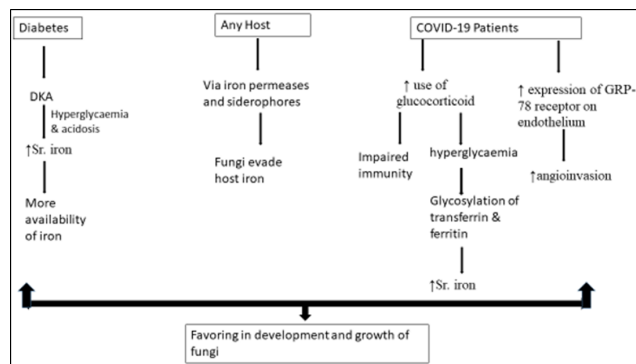


Fig. 1: Factors helping infection with mucor

4. Conclusion

Injudicious use of steroid consumption increases blood sugar levels and weakens the immune system, a condition favoring new fungal infections or aggravation of pre-existing fungal infections. So, we suggest steroids should be used judiciously to the COVID-19 patients with diabetes, and their glycaemic level should be regularly maintained to avoid complications.

5. Conflict of Interest

None.

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None.

References

- Nicolás F, Murcia L, Navarro E, Navarro-Mendoza M, Pérez-Arques C, Garre V, et al. Mucorales Species and Macrophages. *J Fungi (Basel)*. 2020;6(2):94. doi:10.3390/jof6020094.
- Singh A, Singh R, Joshi S, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. *Diabetes Metab Syndr*. 2021;15(4):102146. doi:10.1016/j.dsx.2021.05.019.
- International Diabetes Federation. Idf Diabetes Atlas. Available from: <https://diabetesatlas.org/en/resources>.
- Garg D, Muthu V, Sehgal I, Ramachandran R, Kaur H, Bhalla A, et al. Coronavirus Disease (Covid-19) Associated Mucormycosis (CAM): Case Report and Systematic Review of Literature. *Mycopathologia*. 2021;186(2):289–98.
- Ghosh A, Sarkar A, Paul P, Patel P. The rise in cases of mucormycosis, candidiasis and aspergillosis amidst COVID19. *Fungal Biol Rev*. 2021;38:67–91. doi:10.1016/j.fbr.2021.09.003.
- Mishra Y, Prashar M, Sharma D, Akash, Kumar V, Tilak T, et al. Diabetes, COVID 19 and mucormycosis: Clinical spectrum and outcome in a tertiary care medical center in Western India. *Diabetes Metab Syndr*. 2021;15(4):102196. doi:10.1016/j.dsx.2021.102196.
- Skiada A, Pavleas I, Drogari-Apiranthitou M. Epidemiology and Diagnosis of Mucormycosis: An Update. *J Fungi (Basel)*. 2020;6(4):265. doi:10.3390/jof6040265.
- Kung V, Chernock R, Burnham C. Diagnostic accuracy of fungal identification in histopathology and cytopathology specimens. *Eur J Clin Microbiol Infect Dis*. 2018;37(1):157–65.
- Petrikkos G, Tsioutis C. Recent Advances in the Pathogenesis of Mucormycoses. *Clinical Therapeutics*. 2018;40(6):894–902.
- Gambhir RS, Aggarwal A, Bhardwaj A, Kaur A, Sohi RK, Mehta S, et al. Covid-19 and mucormycosis (Black Fungus): An epidemic within the pandemic. *Rocz Panstw Zakl Hig*. 2021;72(3):239–44.
- Randle R, Ahmed S, Levine E, Fino N, Swett K, Stewart J, et al. Significance of diabetes on morbidity and mortality following cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. *J Surg Oncol*. 2015;111(6):740–5.
- Spellberg B, Edwards J, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. *Clin Microbiol Rev*. 2005;18(3):556–69.
- Goldman N, Fink D, Cai D, Lee YN, Davies Z. High prevalence of COVID-19 associated diabetic ketoacidosis in UK secondary care. *Diabetes Res Clin Pract*. 2020;166:108291. doi:10.1016/j.diabres.2020.108291.

Author biography

Manisha Parida, Post Graduate

Alaka Sahu, Associate Professor

Radhamohan Gharei, Assistant Professor

Sagarika Panda, Assistant Professor

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