MUCORMYCOSIS: A SCAVENGER FOR PATIENTS WITH COVID-19 INFECTION WITH HYPERGLYCAEMIA

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ABSTRACT

Introduction: The study aims to find the incidence of diabetes in post-COVID-19 patients with mucormycosis as there was a significant rise in cases of mucormycosis in India due to the use of steroids and India being the diabetic capital of the world. Materials and methods: This prospective cross-sectional study was conducted with 50 mucormycosis patients who had a history positive for COVID 19 in the recent past and had been treated for the same and were admitted to the mucor ward in Dr D.Y.Patil medical college and were positive for mucormycosis on fungal culture. Their HbA1C, fasting blood sugars, and urine ketone was evaluated on admission. Results: All the 50 (100%) patients had diabetes, out of which 23 (46%) were newly diagnosed while 27 (54%) were known diabetic. Males were more affected than females almost three times. About 88% of patients had deranged fasting blood sugars, and 5 patients had diabetic ketoacidosis. Conclusion: Post-COVID patients who received corticosteroids and are known diabetic must be warned about the above alarming symptoms and counselled to monitor their blood sugars and HbA1C levels regularly.

KEYWORDS Mucormycosis, HbA1C, COVID-19, Diabetic, hyperglycaemia

Introduction

Mucorales are fast-growing thermotolerant fungi that are ubiquitous in the environment. They have a worldwide distribution and are commonly found in decaying organic material or agricultural and forest soils. Mucorales infections are emerging as a matter of concern in COVID-19, as poorly controlled diabetes mellitus (DM) and other co-morbidities are risk factors for severe COVID-19 and mucormycosis, and the use of corticosteroids to treat severe/critical COVID-19 is a well-known risk factor for mucormycosis. The infection has a high incidence in diabetic patients due to the greater availability of glucose to the pathogen, the lower response of T-cells, reduced serum inhibitory activity against the Rhizopus at lower pH and increased expression of some host receptors that mediate the invasion of human epithelial cells through microorganism. Infection of SARS-CoV-2 in those with diabetes possibly triggers higher stress conditions, with the greater release of hyperglycemic hormones, e.g., glucocorticoids and catecholamines, leading to increased blood glucose levels and abnormal glucose variability. In India, for example, uncontrolled DM was the most commonly found predisposing factor in 74%. Type-2 diabetes and diabetic ketoacidosis were significantly associated with rhino-orbito-cerebral involvement. The use of high doses of corticosteroids in COVID-19 patients has led to a flare-up of mucormycosis cases during the 2nd COVID-19 wave. These reasons have contributed to the rise in mucormycosis cases in post-COVID diabetic patients.

Hyperglycemia directly contributes to the risk of mucormycosis by at least four likely mechanisms: (1) hyperglycation of iron-sequestering proteins, disrupting normal iron sequestration; (2) upregulation of a mammalian cell receptor (GRP78) that binds to Mucorales, enabling tissue penetration (due to both a direct effect of hyperglycemia and increasing levels of free iron, which independently enhances GRP78 expression); (3) induction of poorly characterized defects in phagocytic function; and (4) enhanced expression of CotH, a Mucorales-specific protein that mediates host cell invasion by binding to GRP78 (due to hyperglycemia and the resulting free iron).
### Table 1
Mean HbA1C and distribution of newly diagnosed and known diabetics according to age groups.

| Age group | 21 – 40 | 41 - 60 | 61 - 80 | >81 | Total no of patients |
|-----------|---------|---------|---------|-----|---------------------|
| Mean HbA1C | 9.1 | 9.6 | 9.1 | 11.4 |                    |
| Known DM  | 2 | 16 | 7 | 2 | 27 |
| Newly diagnosed DM | 6 | 13 | 4 | 0 | 23 |
| Total no of patients | 8 | 29 | 11 | 2 | 50 |

### Table 2
Range of HbA1c levels of mucormycosis patients.

| HbA1c | No of patients | % of patients |
|-------|----------------|---------------|
| 6.1 - 7 | 12 | 24 |
| 7.1 - 8 | 6 | 12 |
| 8.1 – 9 | 7 | 14 |
| 9.1 – 10 | 5 | 10 |
| >10 | 20 | 40 |
| Total | 50 | 100 |

### Materials and Methods
This prospective cross-sectional study was conducted with 50 patients who had a history positive for COVID-19 in the recent past and had been treated for the same. Now they were admitted to Dr. D. Y. Patil Medical College and Research Centre Pimpri, Pune; between March 2021 to August 2021 and were positive for mucorale species on fungal culture. HbA1c, fasting blood sugars, and urine ketones were sent on admission day as a part of a routine investigation.

### Results
Out of 50 mucormycosis patients admitted to our hospital between March 2021 to August 2021, males were more commonly affected than females. The distribution of patients according to their sex is shown in fig.1.

![Sex Distribution](image)

Figure 1 Shows sex distribution of mucor cases.

All 50 patients had a recent history of COVID-19 infection. 28 (56%) patients were positive for COVID 19 at admission, whereas 22 (44%) patients had a recent history of COVID 19 infection. In addition, 38 (76%) patients were given steroid therapy. The presentation duration of mucormycosis from the recent COVID-19 infection was about 4 weeks.

The patients ranged from 27 years to 83 years old. Most of the patients belonged to the fourth, fifth and sixth decades of life. All the 50 (100%) patients had diabetes, out of which 23 (46%) were newly diagnosed while 27 (54%) were known diabetic. 6 (12%) patients had their fasting blood sugar levels under control, rest 44 (88%) patients had deranged random blood sugar levels, out of which 7 (14%) patients had random sugars >400 mg/dl, and 5 (10%) patients out these 7 had urine ketone bodies and therefore had diabetic ketoacidosis. Out of the 27 newly diagnosed diabetic patients, 15 had a recent history of COVID-19 infection, and all had been administered with injectable corticosteroids.

All the 50 patients had their HbA1C levels above 6.5 except one, but he was a known diabetic and had deranged fasting blood sugars. The mean HbA1C value was 7.4. Only 12 patients (24%) had their HbA1C levels below 7, while 13 (26%) patients had HbA1C levels between 7 and 10. 20 (40%) patients had their HbA1C levels more than 10, which is significantly high and 13 out of these 20 patients were newly diagnosed diabetics.

### Discussion
Mucormycosis is found predominantly in patients with poorly controlled diabetes mellitus and diabetic ketoacidosis. Diabetic ketoacidosis impairs neutrophils' chemotactic and phagocytic activity and increases available serum iron, respectively.

In our attempt to find out a correlation between mucormycosis and covid 19, we found out that the infection of COVID-19 in those with diabetes possibly triggers higher stress conditions, with the greater release of hyperglycemic hormones, e.g., glucocorticoids and catecholamines, leading to increased blood glucose levels and abnormal glucose variability. Glucocorticoids have been widely used in syndromes closely related to Covid-19. Hyperglycemia and insulin resistance promotes the increased synthesis of glycosylation end products (AGEs) and proinflammatory cytokines, and oxidative stress, in addition to stimulating the production of adhesion molecules that mediate tissue inflammation. This inflammatory process may compose the underlying mechanism that leads to a higher propensity to infections, with worse outcomes in patients with diabetes. The prognosis depends on the extent of infection, underlying disease...
and the establishment of early treatment.

In our study, the male was more commonly affected than females, where males accounted for 74% of the patients, nearly similar to the study conducted by Devang P et al., where the male population was 67%.

The average age group affected in our study was 50 to 60 years, similar to the study done by Balai et al.12 All the patients in our study had diabetes, which is similar to the study done by Nezafati et al., who found diabetes in 90% of patients with mucormycosis and thus is the most common risk factor for rhinocerebral mucormycosis13. The mean HbA1C was 9.3, which is near a study done by Teny M Johan et al. It was found to be 10.14.

CONCLUSION

In the COVID-19 pandemic, there was injudicious use of corticosteroids, which led to deranged blood sugars and exposed poorly controlled and borderline diabetics to mucormycosis, causing an epidemic in the pandemic. Therefore there must be high suspicion in post-COVID patients or known diabetics presenting to otolaryngologists and ophthalmologists with facial pain or nasal discharge or obstruction or dimension of vision. Post-COVID patients who received corticosteroids and are known diabetic must be warned about the above alarming symptoms and regularly counselled to monitor their blood sugars and HbA1C.

References

1. Petrikos G, Skiada A, Lortholary O, et al. Epidemiology and clinical manifestation of mucormycosis. Clin Infect Dis. 2012;54:S23–S34.
2. Garg, D.; Muthu, V.; Sehgal, I.S.; Ramachandran, R.; Kaur, H.; Bhalla, A.; Puri, G.D.; Chakrabarti, A.; Agarwal, R. Coronavirus Disease (Covid-19) Associated Mucormycosis (CAM): Case Report and Systematic Review of Literature. Mycopathologia 2021, 1–10.
3. Lionakis, M.S.; Kontoyiannis, D.P. Glucocorticoids and invasive fungal infections. Lancet 2003, 362, 1828–1838.
4. Mohammadi R, Meidani M, Mostafavizadeh K, Iraj B, Hamedani P, Sayedain SM, Mokhtari M (2015) Case series of rhinocerebral mucormycosis occurring in diabetic patients. Caspian J Intern Med 6(4):243–246.
5. Aihong W, Zhao Weibo Xu, Jianwen ZG (2020) Timely blood glucose management for the outbreak of 2019 novel coronavirus disease (COVID-19) is urgently needed. Diabetes Res Clin Pract 162:108118.
6. Chakrabarti A, Das A, Mandal J, Shivaprakash MR, George VK, Tarai B, et al. The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus. Med Mycol 2006;44:335–42.
7. Devang P. Gupta, et al. Clinical Study of Surge of Mucormycosis in COVID-19 Pandemic: A Tertiary Care Center Study. Indian J Otolaryngol Head Neck Surg https://doi.org/10.1007/s12070-021-02784-6.
8. Spellberg B, Edwards J, Ibrahim A (2005) Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev 18(3):556–569.
9. Kim J-G, Park HJ, Park JH, Baek J, Kim HJ, Cha I-H, Nam W (2013) Importance of immediate surgical intervention and antifungal treatment for rhinocerebral mucormycosis. J Korean Assoc Oral Maxillofac Surg 39:246–250.
10. Aihong W, Zhao Weibo Xu, Jianwen ZG (2020) Timely blood glucose management for the outbreak of 2019 novel coronavirus disease (COVID-19) is urgently needed. Diabetes Res Clin Pract 162:108118.
11. Recovery Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19—Preliminary report. N Engl J Med. 2020.
12. Balai E, Mumadi S, Jolly K, Darr A, Aldeerawi H (2020) Rhinocerebral Mucormycosis: a Ten-Year Single Centre Case Series. Cureus.
13. Nezafati S, Kazemi A, Asgari K et al. (2018) Rhinocerebral mucormycosis, risk factors and the type of oral manifestations in patients referred to a university hospital in Tabriz, Iran 2007–2017. Mycoses 61:764–769.
14. John, T.M.; Jacob, C.N.; Kontoyiannis, D.P. When Uncontrolled Diabetes Mellitus and Severe COVID-19 Converge: The Perfect Storm for Mucormycosis. J. Fungi 2021, 7, 298.