



COVID 19 Associated Mucormycosis: Preventable Risk Factors Leading to a Better Prognosis: A Case Series

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Abstract India was severely affected by the second wave of coronavirus disease (COVID-19), leading to sudden expansive spread of Mucormycosis, presenting with sinusitis, blackish mucus secretions, discolouration of palate, facial pain, swelling and blurring of vision. Hyperglycemia, hypercoagulable state and elevated levels of serum ferritin were the major contributing factors in progression of the deadly disease. To highlight the correlation between Diabetes Mellitus, hyperferritinemia and elevated levels of D-Dimer with increased rate of incidence and poor prognosis of the disease. This study was undertaken in KLES Dr Prabhakar Kore Hospital & MRC, Belagavi, including 30 patients, between April to July 2021. Serum ferritin, HbA1C and D-Dimer were evaluated for patients on admission, along with the other routine blood investigations. The mean age was 50 years (49.99 ± 1.8), with a male predominance of 83.33% (25 Male patients). 93.33% patients had uncontrolled Diabetes Mellitus with a mean value of 10.12% (± 0.37) indicating Diabetes Mellitus to be the prime risk factor. The raised levels of serum ferritin with a mean of 662.01 ng/ml (± 129.18) and high levels of D-Dimer (Mean- 761.33 ± 151.8 ng/ml) also demonstrated their role as interlinked factors. Mucor epidemic was caused by convergence of interlinked risk factors. Awareness of red flag clinical features, prompt diagnosis, early initiation of treatment with amphotericin-B with aggressive surgical debridement are essential for successful outcome, to avoid high rate of mortality and morbidity rates in the mucormycosis patients.

Keywords COVID-19 · Serum ferritin · HbA1c · D-dimer · Mucormycosis · Diabetes

Introduction

Mucormycosis has emerged in the second wave of the COVID-19 pandemic as a challenge to otorhinolaryngologists primarily with its high invasive and fulminant progression of the disease leading to the most common type of presentation—*Rhino-Orbito-Cerebral-Mucormycosis*. It's a life-threatening infection caused by fungi belonging to the family Mucoraceae, specifically *Rhizopus oryzae*. With its high predilection towards invading sinuses, orbit, brain, palate causing necrotizing infection along with systemic spread especially when the immunity of the host is compromised. Patients with diabetic ketoacidosis have elevated levels of serum iron, likely due to release of iron from binding protein in presence of acidosis due to proton mediated displacement of iron from transferrin [1, 2]. Hyperglycaemic state favours rapid growth of fungal elements by impairing phagocytosis. Dissociation of iron sequestering proteins in the serum caused by acidosis promotes fungal multiplication and disease progression. Prior to the COVID-19 pandemic, D-dimer was not considered a useful biomarker for bacterial or viral pneumonia despite evidence. But post the pandemic, elevated D-dimer and thrombotic complications have been widely reported in COVID-19 patients [3]. Thus, amalgamation of monitoring of serum ferritin, blood sugar and D-Dimer levels is a promising therapeutic strategy in decelerating the rapid progression of this deadly disease.

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Materials and Methods

Patient Selection

This study was undertaken in the Department of Otorhinolaryngology & Head and Neck Surgery in KLES Dr Prabhakar Kore Hospital & MRC, Belagavi. The study included 30 patients who presented to our tertiary care hospital, between April 2021 to July 2021, with complaints of sinusitis-like features along with palatal and orbital involvement with a history of contracting COVID-19 infection (RT-PCR positive cases).

Method

Serum ferritin, HbA1c and D-Dimer was evaluated for patients on admission, along with the other routine blood investigations. All the patients underwent surgical debridement of the necrosed area (Fig. 1) based on MRI/CT findings, all the fungal debris was extensively removed (Fig. 2) and adjunctive anti-fungal therapy with liposomal Amphotericin-B was given.

Results

The patients involved in the study were monitored closely for HbA1 levels, Serum Ferritin and the D-Dimer levels as on the day of admission to the hospital was charted, as has been displayed in the Table 1.

The data collected was analysed. The mean age of the 30 patients was 50 years (49.99 ± 1.8), with a male predominance of 83.33% (25 Male patients) and Male:Female ratio as 5:1 as depicted in Fig. 3

The mean value of HbA1c was 10.12% (± 0.37) as depicted in Fig. 4 indicating Diabetes Mellitus to be one

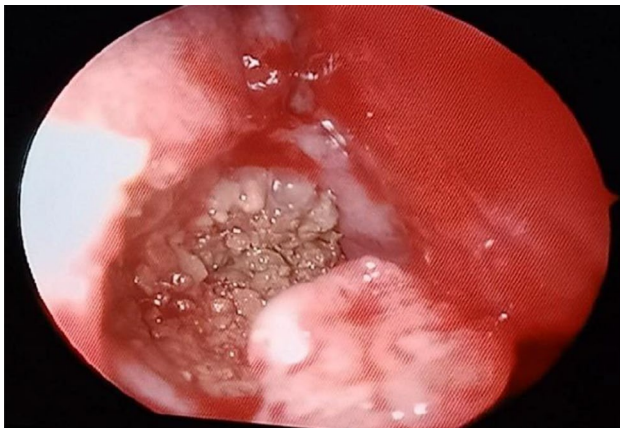


Fig. 1 Surgical debridement of the necrotic area

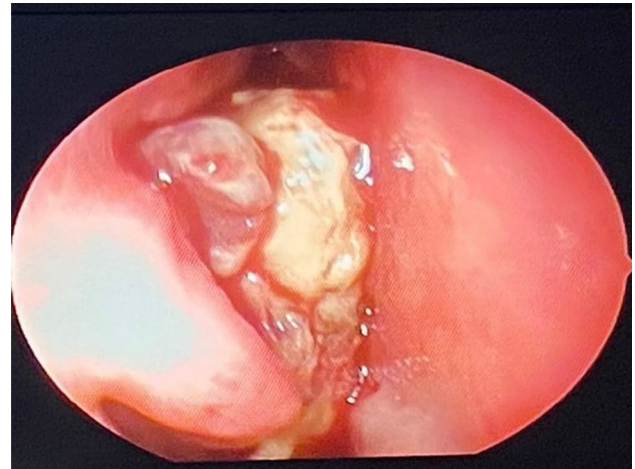


Fig. 2 Fungal debris material in the right middle meatal region

Table 1 Patient details with HbA1c, serum ferritin, D-dimer levels

Patient	Age	Sex	HbA1c levels (%)	Sr. Ferritin (ng/ml)	D-Dimer levels (ng/ml)
1	51	M	14.1	9.1	339
2	48	M	12.7	4120	1000
3	42	M	11.8	452.50	221
4	40	F	12.3	227.20	354
5	60	M	9.7	986.50	714
6	31	M	8.2	261.60	377
7	31	M	10.0	360.70	562
8	52	M	9.8	560.80	> 5000
9	43	M	4.9	367	452
10	30	M	6.2	908.70	564
11	65	M	10.2	782	891
12	52	M	11.0	602.50	408
13	68	F	11.1	593.70	701
14	50	M	8.2	232	503
15	45	M	10.6	489	631
16	52	M	11.9	984.50	1019
17	48	F	9.2	218	576
18	60	M	13.5	746.20	895
19	60	F	8.0	372.40	271
20	46	M	10.2	702	881
21	59	M	9.8	578.20	298
22	65	M	11.2	332	681
23	38	M	8.5	203	487
24	48	F	10.8	936.40	635
25	54	M	12.1	471	782
26	42	M	7.9	902.30	561
27	62	M	9.4	567	824
28	51	M	10.1	884	927
29	47	M	8.5	781	826
30	58	M	11.7	229	472

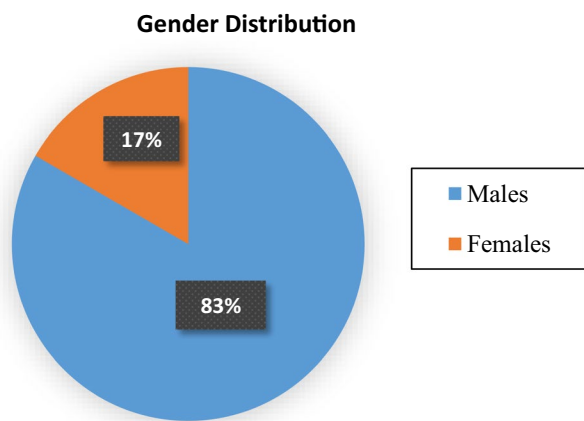


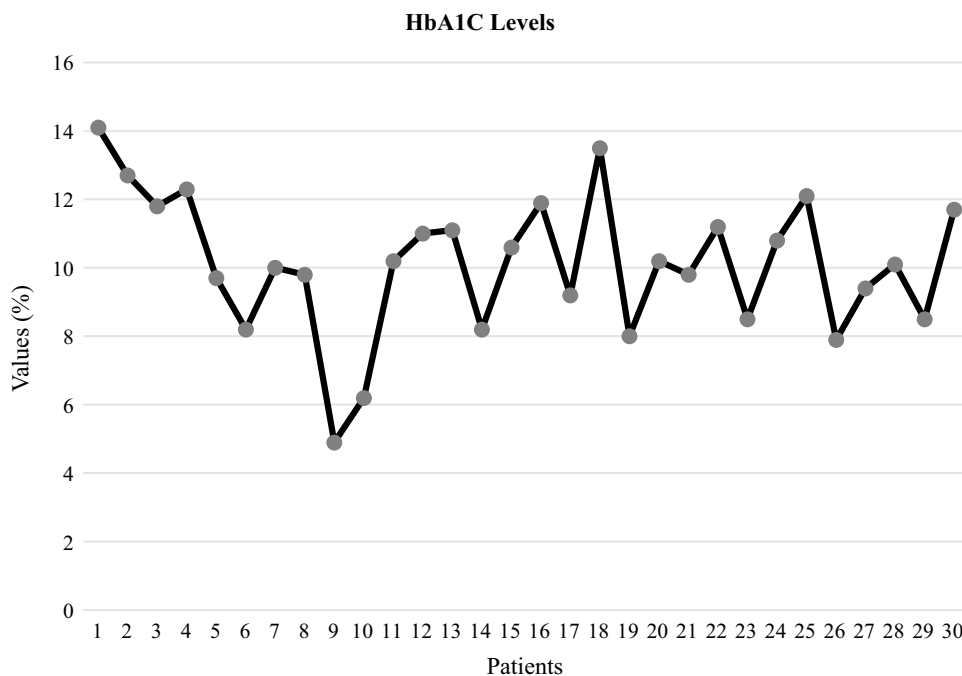
Fig. 3 Pie chart for gender wise distribution of patients

of the most common underlying predisposing factor to contribute to mucormycosis. Apart from 2 patients, all patients had increased value of HbA1c > 6.5% representing Uncontrolled Diabetes Mellitus. Out of these 28 patients, 15 were newly diagnosed on admission.

The raised levels of serum ferritin with a mean of 662.01 ng/ml (± 129.18) as depicted in Fig. 5 showed that hyperferritinemia was one of the major contributing factors in pathophysiology of mucormycosis.

Highly elevated levels of D-Dimer (Mean- 761.33 ± 151.8 ng/ml) as depicted in Fig. 6 substantiated their role as additional risk factors.

Fig. 4 Line graph depicting HbA1C levels of the study group



So, in almost all the patients, hyperferritinemia, elevated D-Dimer and hyperglycemia was seen.

Discussion

Mucormycosis is a rare but aggressive opportunistic fungal infection, which has shown increased incidence in the recent COVID-19 pandemic. The affected COVID-19 patients are more susceptible to infections due to their immunocompromised state as seen in diabetic ketoacidosis, neutropenia, organ or stem cell transplantation, trauma and burns, hematological disorders, metabolic acidosis, intravenous drug usage, renal insufficiency, broad-spectrum antibiotics, increase in iron in the system and malnutrition [4]. These conditions in addition to the heavy use of steroids have played a major role in the progression of the disease.

Acidosis temporarily disrupts the capacity of transferrin to bind iron. Therefore, the increased susceptibility of patients with diabetic ketoacidosis to mucormycosis is likely due, at least in part, to an elevation in available serum iron during diabetic ketoacidosis due to proton-mediated dissociation of iron from transferrin. Patients with elevated levels of serum iron are susceptible to infection with *R. oryzae* and other zygomycetes [2]. Siderophores secreted by the fungi provided the cell with much needed iron by chelating these ferric ions. In our study, the mean Sr. Ferritin level was 662.01 ng/ml (± 129.18), and a state of hyperferritinemia was seen in the patients.

D-dimer is a fibrin degradation product, widely used as a biomarker for thrombotic disorders [3]. A study in India

Fig. 5 Line graph depicting serum ferritin levels of the study group

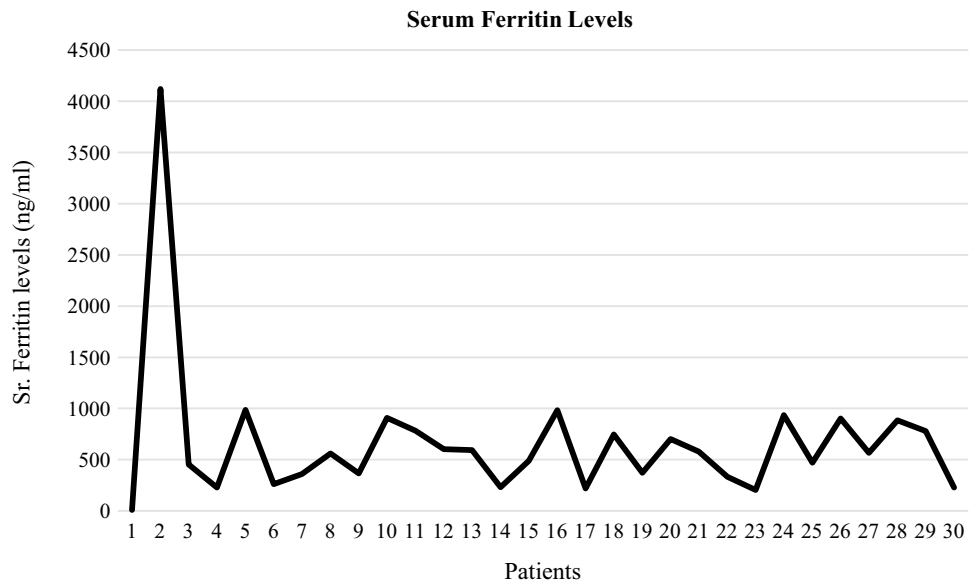
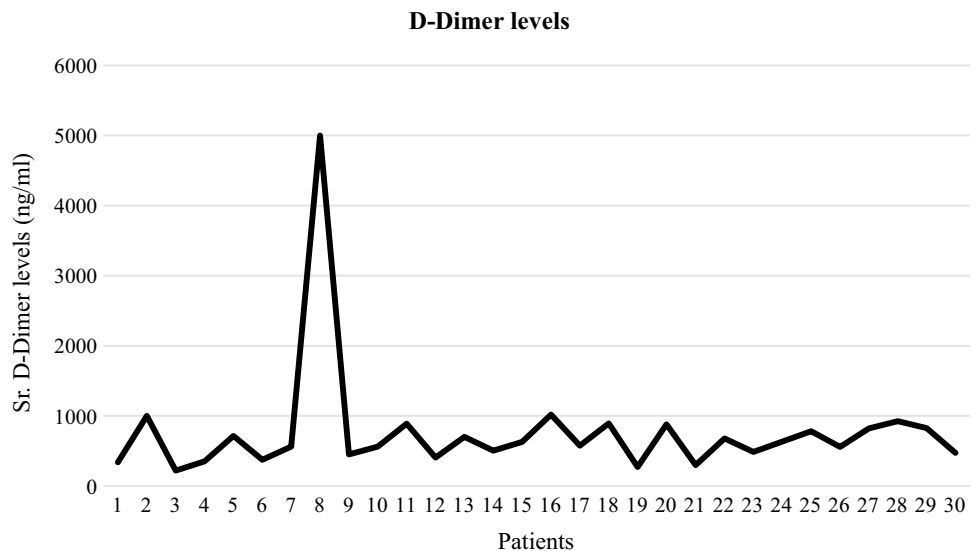


Fig. 6 Line graph depicting D-Dimer levels of the study group



found the optimal cutoff value for admission D-dimer to predict hospital mortality to be 1.44 $\mu\text{g/ml}$, whereas the optimal value for highest D-dimer measurement during hospital stay for predicting hospital mortality was 2.01 $\mu\text{g/ml}$ [5]. SARS-CoV-2-induced coagulation alterations and consequent micro- and macro- thrombotic events appeared to be an issue of primary importance [6]. The increased level of pro-inflammatory cytokines, activated coagulation cascade as well as hypoxia itself predisposes to thrombosis. Thus, the severe elevation of D-dimer levels has a strong association with the grave condition of critically ill COVID-19 patients. Treatment schemes with anticoagulant drugs, especially heparin and Low Molecular Weight Heparin(LMWH), based on monitoring the levels of

D-dimer and other coagulation factors, should be further addressed in order to define adequate timing (therapeutic and prophylactic) and efficacy, based on patients' characteristics, clinical presentations and coagulative function [6]. In our study, the mean levels for Serum D-Dimer were 761.33 ± 151.8 ng/ml, contributing for the poor prognosis for the mucormycosis patients.

India has a high burden of mucormycosis among patients with uncontrolled diabetes mellitus. It is also one of the countries which is worst affected by the COVID-19 pandemic [7]. In our study, almost all the patients had uncontrolled diabetes mellitus ($\text{HbA1c} > 6.5\%$) leading to decreased activity of the phagocytic action of macrophages and neutrophils. This corroborated Diabetes Mellitus as the

most common predisposing factor of the deadly Black Fungus infection.

Conclusion

India was majorly hit for COVID–Mucor during the second wave of the pandemic. The study showed that high blood sugar levels, iron overload, increased D-Dimer values have a critical contribution in the pathogenic mechanism. Serum Ferritin can help in monitoring the patient's prognosis, residual infection and aid in early diagnosis while the histopathology report is awaited, which may take about 7–10 days. D-Dimer shows hypercoagulable state. So, increased levels indicate the need of heparinization to prevent complications like pulmonary embolism and stroke. Excessive steroid usage even for milder cases also induces hyperglycaemia, ultimately predisposing the patient to opportunistic infection like mucormycosis.

Hence, prompt diagnosis, early identification and extensive investigations is extremely crucial in significantly reducing the severity of the disease and thus combat the high morbidity and mortality rates for the same.

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Dr. PN, Dr. IK, Dr. ADK, Dr. PB and Dr. RR. The first draft of manuscript was written by Dr. IK, Dr. ADK, Dr. PB and Dr. RR. Review and guidance were provided by Dr. ASH and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

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

Ethical Approval Institutional ethical committee approval was obtained for the conduction of this study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research commit-

tee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to Participate Informed consent was obtained from all individual participants in the study, after explaining the objectives and methodology clearly.

Consent to Publish Patients signed informed consent regarding publishing their data as per the guidelines of the institution and the journal prerequisites.

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