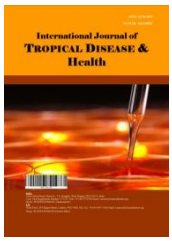

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A Prospective Study of COVID-19 Associated Mucormycosis at Tertiary Care Hospital

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Mucormycosis is an emerging aggressive angioinvasive fungal infection due to non-septate fungi which belongs to order Mucorales. It is associated with covid-19 patients mainly with risk factors like diabetes mellitus use of steroids etc.
Materials and Methods: The present study was carried out in 30 cases with a history of covid-19 infections and had acquired mucormycosis after recovery from SARS CoV-2 infection. These patients with history of mucormycosis were studied prospectively concerning the site involved, associated disease, evolution and diagnosis, therapy, and end result of the disease. Diagnosis was confirmed by histopatholgy with broad non-septate hyphae, ribbon-like with 90 degree-angled branching showing in specimen of tissue submitted.
Result: Out of 30, 22 patients with maxillary sinusitis, seven cases of rhino-orbital mucormycosis, and one case with the rhino-orbital-cerebral mucormycosis. Twenty-five (83.3%) were males and mean age was 51 years. 25(83.3%) cases had diabetes Mellitus. HbA1C ranges from 5.4-10.9 and mean were 8.3. Out of 25 patients of diabetes mallitus, 16(64%) had uncontrolled Diabetes Mellitus

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on admission. Four (4/25, 16%) patients had Diabetes Mellitus of new onset. Out of the sixteen cases of uncontrolled Diabetes Mellitus 9(30%) had diabetic ketoacidosis. Out of 30 cases, 6 patients had no risk factors except steroids given as a part of therapy for covid-19 infection.Amid of 30 cases with COVID-19 eighteen (18/30,60 %) patients had severe COVID-19 disease, required ICU mechanical ventilation. 9(30%) had CKD out of which8(26.6%) cases. Mucormycosis were identified in all 30(100%) patients on H&E, PAS, and GMS.

Conclusion: Mucormycosis is an aggressive angioinvasive disease with high morbidity and mortality. The disease has risen drastically in the recent times due to COVID 19 pandemic together with diabetes, inappropriate corticosteroid use and immunosuppression due to mechanical ventilation, prolonged hospitalization setting the perfect stormfor mucormycosis.

Keywords: COVID-19; diabetes mellitus; steroids; mucormycosis.

1. INTRODUCTION

The Covid-19 virus caused by severe acute respiratory syndrome corona virus has been associated with opportunistic infections by bacteria and fungi [1]. The main fungal pathogens are aspergillosis and candida but nowadays many cases of mucormycosis in patient with Covid-19 has been reported worldwide and particularly from India [2]. Mucormycosis is caused by fungi that belongs to the Mucorales [3]. The Rhizopus oryzae is the most prevalent cause of 60% of cases of mucormycosis cases in humans [4-6]. According to a current estimate of the year, 2019-2020 the wide spread presence of mucormycosis varies from 0.005 to 1.7 per million populations, and in India, it is 0.14 per 1000 population which is highest compared to another world [7-9].

The etiological factors that caused life-threatening infection in patients of COVID-19 are hypoxia, hyperglycemia (both due to steroid and diabetes Mellitus), metabolic acidosis, high ferritins levels and immunosuppressant caused by multiple confounding factors which include SARS-CoV-2 infection, steroid therapy along with co morbidities like diabetes, prolong hospitalization use of mechanical ventilators, etc. along with many risk factors which include prolong stay in hospital with the requirement of mechanical ventilation [10]. Fungal hyphae invade blood vessels from any route of infection like ingestion, or direct skin leads to tissue infarction and necrosis [11].

This prospective study was being done to identify various risk factors and to treat the patient appropriately which should result in increased patient survival.

2. MATERIALS AND METHODS

The study was conducted at SGT medical college and research institute, Gurugram, India during period of march-August 2021 on patients with a previous history of covid-19 infections and acquired mucormycosis after recovery from SARS CoV-2 infection. Patients with mucormycosis were studied prospectively for the site involved, associated disease, evolution of disease and diagnosis, therapy, and prognosis. Diagnosis was confirmed by histopatholgy which shows broad non-septate hyphae, ribbon-like with 90 degree-angled branching showing in specimen of tissue submitted.

2.1 Sample Processing

The biopsy specimen from clinically suspected mucormycosis was collected in sterile containers, with 10% formalin, and tissue processingdone in the Pathology department. For microscopic study tissue sections were stained with Hematoxylin and eosin (H&E), Periodic acid Schiff stain (PAS), and Grocott's methenamine silver stain (GMS) (Figs. 1,2,3) The sections were seen microscopically for the presence or absence of specific fungi [3–15].

3. RESULTS

We identified 30 such patients and proved mucormycosis on histopathology (Table 1) Out of 30, 22 patients with maxillary sinusitis, seven cases of rhino-orbital mucormycosis, and one case with the rhino-orbital-cerebral mucormycosis. Twenty-five (83.3%) were males and mean age was 51 years. 25(83.3%) cases had diabetes Mellitus. HbA1C ranges from 5.4-10.9 and mean were 8.3. Out of 25, 16(64%) had uncontrolled Diabetes Mellitus on admission. Four (4/25, 16%) cases had Diabetes Mellitus of new onset. Out of the sixteen cases of Diabetes Mellitus 9 (30%) had diabetic ketoacidosis. Out of 30 cases, 6 patients had no risk factors except steroids given as a part of therapy for covid-19 infection. Amid of 30 cases with COVID-19 eighteen (18/30,60 %) patients had severe

COVID-19 disease, required ICU mechanical ventilation. 9(30%) had CKD out of which 8(26.6%) cases. Mucormycosis were identified in all 30(100%) patients on H&E, PAS, and GMS. All patients were treated medically with antifungal amphotericin B and surgically with debridement and excision of infected parts, out of 30 patients 3(10%) died during treatment due to severity with respiratory distress or multiorgan failure due to complications.

4. DISCUSSION

Mucormycosis is unusual in normal healthy individuals, but few immune system related diseases predispose fungal infections. These include uncontrolled diabetes mellitus, hematological malignancies, organ transplantation, immunosuppressive and corticosteroid treatment burns, in malnourished individuals, drug users, an acquired immunodeficiency syndrome (AIDS) [16]. Mucormycosis involves various sites like the nose, all sinuses, orbital cavity, brain, gastrointestinal tract, skin, lung, jawbones, joints, heart, but rhino-orbital is the most common site observed by physicians worldwide [9]. Granuloma with giant cell formation, thrombo-embolism and tissue necrosis is the main pathology found in mucormycosis.

Table 1. Epidemiological profile

Total patient	30
Sex	Male- 25(83.3%) Female- 5 (16.6%)
Age	Range-24-72 mean 49.5
Presence of risk factor	25(83.3%)
Diabetes mellitus	25(83.3%)
Hb1Ac	Range 5.4-10.9 mean 8.3
Presence of DKA	9(30%)
Chronic kidney disease	9(30%)
Renal failure	8(26.6%)
ICU admission	18(60%)
Systemic corticosteroids(risk factor other then diabetes)	30(100%)
Rhino-orbital-cerebral	1 (3.3%)
Rhino-orbital	7(23.3%)
Maxillary sinusitis alone	22(73.3%)
H&E-Broad non septate fungal hyphae-Mucormycosis	30(100%)
PAS Stain- Magenta color mucormycosis	30(100%)
GMS Stain- Black oulines of fungal hyphae seen	30(100%)
Treatment given	30(100%)
Mortality	3 (10%)

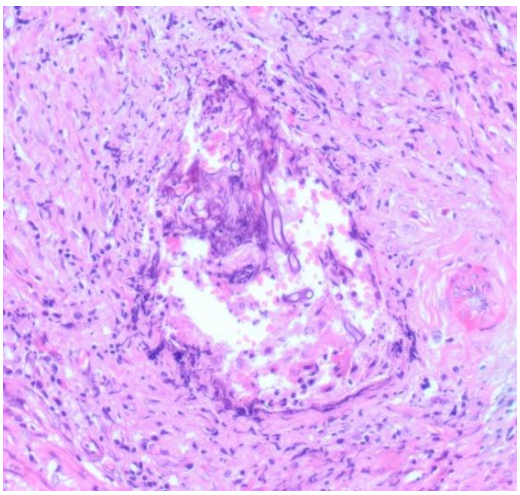

Fig. 1. H&E- 100X- Non septate broad fungal hyphae of mucormycosis

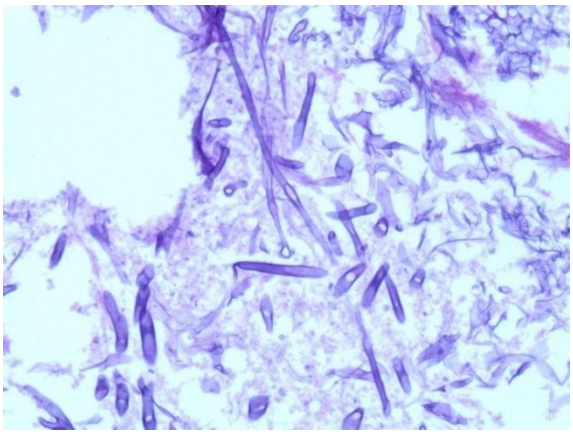

Fig. 2. PAS-400X- PAS positive fungal hyphae

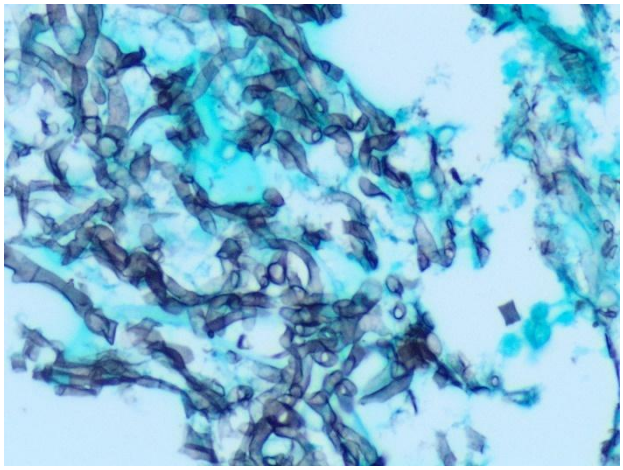

Fig. 3. GMS-400X- Silver stain positive Mucor mycosis

Although this study was done only in 30 cases of post covid 19 associated mucormycosis patients several observations were emerged. Mucormycosis in patient with corona virus is pathologically recorded disease(30/30) of the reported cases had both covid 19 infections followed by mucormycosis which contrasts with covid 19 associated aspergillosis seen in other countries. India has most suffered patients with mucormycosis in the world with an estimated prevalence of 140 cases per million population [16]. Apart from this, India has the 2nd largest number of cases with diabetes mellitus in the age group of 20-79 [17].

SARS-CoV-2 infects cells of the immune system mainly T cells (CD3, CD4, and CD8) leads to apoptosis of lymphocytes leading to decrease in lymphocyte count and immune dysregulation with deficient innate immunity causing cytokine storm [18]. Diabetes mellitus influence the adaptive immunity by hampering the intra-celular killing of pathogens, chemotaxic, phagocytosis process of neutrophils [18]. Consequently, Covid 19 infection with diabetes causes immune deregulation. Excessive use of steroids also causes immunosuppressant. Altogether, SARS-CoV-2, Diabetes, and steroid usage effectuate the risk of fungal invasion.

Covid 19 disease leads to endothelial dysfunction via direct invasion of virus and hosts immune response of inflammation causes endothelial cells apoptosis and pyroptosis [18]. Diabetes is known endothelial dysfunction due to chronic inflammatory disease [19]. Invasion of fungus occurs by endothelial adhesion and angio-invasion [19]. This is the reason, diabetic patients are at higher risk for invasion of mucormycosis with COVID-19 infection.

Overall, in patients with diabetes hyperglycemia and COVID-19 who are on steroids adding the risk of Mucormycosisvai following mechanisms:

a) defect in the neutrophil-macrophage phagocytic system; b) glucose regulated protein 78 (GRP78) receptor upregulation with increased expression. It is a member of HSP 70 protein family and functions as a major chaperone for protein folding which regulate calcium homeostasis c) Hyperglycation of iron leads toincreased iron delivery to Mucorales [20].

India has a high burden of Mucormycosis among patients with COVID-19 in the world [21]. The disease has drastically increases in the second wave of COVID-19 [22]. COVID 19 has been credit to B.1.617 variant of SARS-CoV-2, is called double mutated or the delta variant in the second wave [23]. This variant of Covid-19 is appraise as more virulent and highly infectious.

We faced many challenges in controlling mucormycosis in this study. There was a delay in pursuing treatment, less knowledge in health care providers a financial challenge. Patient with combined medical and surgical treatment had an extremely good outcome.

This study has various limitations. It is a one-center study with small cases of Mucormycosis with Covid-19 and cannot depict a clear picture of the disease and did not have enough data for more high-risk factors like an organ transplant, malignancy, HIV, neutropenia.

5. CONCLUSION

Mucormycosis is an aggressive angio-invasive disease with high morbidity and mortality. The disease has increased drastically due to intermixed COVID 19 disease associated with diabetes, and inappropriate steroid usage leading to invasion of mucormycosis with negative outcomes.

CONSENT

At the time of skin biopsy, consent will be taken from the patient for storage of specimen for further research. The specimens collected will be anonymited and coded so as to delink them with any identity of the source patient.(ICMR guideline, 2017, chapter- Informed consent process, page 54, 5.2 condition for granting waiver of consent).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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