How to Cite:
Melvindominic, M., Senthil, M., Sudhan, C. H. H., Syed, A. S., & Chanjal, K. S. (2022). Incidence and outcome of mucormycosis in diabetic patients with COVID-19. *International Journal of Health Sciences*, *6*(S5), 11898–11905.
https://doi.org/10.53730/ijhs.v6nS5.11480

Incidence and outcome of mucormycosis in diabetic patients with COVID-19

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***Abstract*---**Aims and objectives: Diabetes Mellitus predisposes patients to invasive fungal infections. Aim of this study is to find out the incidence and outcome of Mucormycosis in diabetic patients with COVID-19. Materials and Methodology: A Retrospective study of 150 patients with COVID-19 who were admitted in VMKVMCH COVID-19 Ward, Salem from May 2021 to July 2021 was included in the study. Results: Among 150 hospitalized patients with COVID 19 infection, 32 patients had CAM with an incidence of 3.36%. In patients with CAM, 87.5% had Diabetes Mellitus as the most common co-morbidity. The majority of the patients had poor glycemic control with a mean HbA1c of 9.06%. Out of the total study population, 93% had prior exposure to high dose corticosteroids. During the study period,

12.5% patients of CAM did not survive. Conclusion: Mucormycosis is an angioinvasive fungal infection with high mortality. The disease has surged in COVID 19 pandemic due to uncontrolled diabetes and improper corticosteroid use.

Keywords---mucormycosis, diabetes, COVID-19, fungal infection.

Introduction

The current outbreak of viral pneumonia, caused by novel coronavirus SARS-CoV-2, is the focus of worldwide attention. The WHO declared the COVID-19 outbreak a pandemic event on Mar 12, 2020, and the number of confirmed cases is still on the rise worldwide. While most infected individuals only experience mild symptoms or may even be asymptomatic, some patients rapidly progress to severe acute respiratory failure.

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with a wide range of opportunistic bacterial and fungal infections. Mucormycosis is a rare and opportunistic fungal infection that mainly affects diabetic and immunocompromised patients.[1] Both *Aspergill us* and *Candida* have been reported as the main fungal pathogens for co-infection in people with COVID-19 .Recently, several cases of mucormycosis in people with COVID-19 have been increasingly reported world-wide, in particular from India. 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. Increase in mucormycosis in Indian context appears to be an unholy intersection of trinity of diabetes (high prevalence genetically), rampant use of corticosteroid (increases blood glucose and opportunistic fungal infection) and COVID-19 (cytokine storm, lymphopenia, endothelial damage).[2] Any case of documented non-bacteriological sinusitis in diabetic patients, even without ketoacidosis, should prompt suspicion of a mucormycosis diagnosis.[3]

Phycomycosis or zygomycosis was first described in 1885 by Paltauf and later coined as Mucormycosis in 1957 by Baker an American pathologist for an aggressive infection caused by *Rhizopus*. Mucormycosis is an uncommon but a fatal fungal infection that usually affects patients with altered immunity. Mucormycosis is an angioinvasive disease caused by mold fungi of the genus *Rhizopus*, *Mucor*, *Rhizomucor, Cunninghamella* and *Absidia* of Order-Mucorales, Class- Zygomycetes. The *Rhizopus Oryzae* is most common type and responsible for nearly 60% of mucormycosis cases in humans and also accounts for 90% of the Rhino-orbital-cerebral (ROCM) form. Mode of contamination occurs through the inhalation of fungal spores.

Globally, the prevalence of mucormycosis varied from 0.005 to 1.7 per million population, while its prevalence is nearly 80 times higher (0.14 per 1000) in India compared to developed countries, in a recent estimate of year 2019–2020 . In other words, India has highest cases of the mucormycosis in the world. Notwithstanding, India is already having second largest population with diabetes mellitus (DM) and was the diabetes capital of the world.

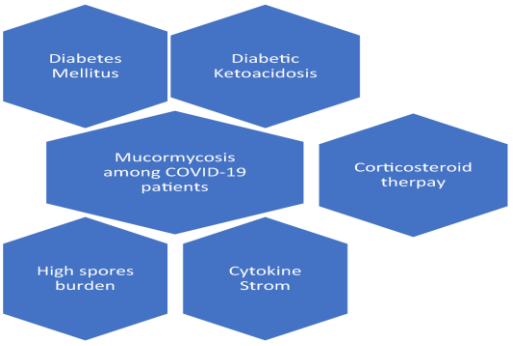
Incidence and prevalence

The occurrence of mucormycosis, a rare disease, in the general population was previously cited as 0.005 to 1.7 per million population [4]. However, the incidence of mucormycosis in India was reported to be 0.14/1000 diabetic patients which is 80 times higher than that reported in other parts of the world[20] and more than that in the general population based on computational-modeling.[5] Given the large number of diabetic patients in India of almost 62 million, mucormycosis has caused large public health burden in India [6]. In one study, diabetes mellitus was the underlying disease in 54–76% of mucormycosis cases with 8–22% presenting with diabetic ketoacidosis [7]. In addition, there had been geographic difference in the rate of diabetes mellitus among patients with mucormycosis in India. Even prior to COVID-19, the prevalence of diabetes mellitus was a major risk factor with regional differences ranging from 67% in North India to 22% among patients from the South of India [8]. The true incidence of rhino-orbital mucormycosis in COVID-19 patients is not known.

Risk factors

In patients with CAM, 28/32 (87.5%) had diabetes as the most frequent co-morbidity. In patient with diabetes, mean blood glucose was 242.63 (±84.81) g/dl with mean glycated haemoglobin (HbA1c) of 9.06% (±2.19) at admission. There were no patients with diabetic ketoacidosis in our study. The majority of the patients, 30/32 (93%) had history of steroid exposure in form of either dexamethasone and methylprednisolone. The duration and amount of exposure could not be determined as it varied due to physician preference and intake of OTC (over the counter) steroid by the patients. None of our patients received anti- IL6 therapy or monoclonal antibodies. There were no cases of malignancy, organ transplant or HIV/AIDS with Mucormycosis in our study.

Fig. 1 COVID-19 and mucormycosis superinfection: the perfect storm



Clinical presentation

In Patients with CAM 30/32 (93.8%) had headache, 20/32 (62.5%) had nasal symptoms in form of rhinorrhoea & nasal stuffiness and 19/32 (59.4%) had eyes symptoms in form of redness or eye pain. On admission, 18/32 (56.2%) patients had history or presented with Severe COVID-19 pneumonia. At the time of diagnosis of CAM, 22/32 (68.8%) had hypoxemia and required supplemental oxygen. The mean duration from onset of COVID-19 to diagnosis of CAM was 17.28 (±11.76) days. In patients with CAM, none of them were fully vaccinated against COVID-19. Two patients had received a single dose of ChAdOx1- Oxford–AstraZeneca (Covishield) COVID-19 vaccine. Both the patients are still admitted at our centre and are on antifungal therapy.

Laboratory evaluation & diagnosis

At admission, 17/32 (53.3%) patients with CAM had a mean leucocyte count: 11478.13 (±3693.83)/mm^3. Leucocytosis was significantly higher in non-survivors with mean leucocyte count of 15775.0 (±7650.4)

Outcomes and prognosis

Before the COVID-19 era, mucormycosis is known for its poor prognosis, especially with delayed management may lead to a high mortality rate. There was no difference in the mortality between solid organ transplants and diabetes mellitus with a mortality of about 28%, (2/7 (28.57%) vs 5/18 (27.78%); $p = 0.66$ in patients with solid organ transplant and diabetes mellitus, respectively) [9]. However, another study showed higher mortality of 49% among diabetes mellitus patients compared to 30% among non-diabetic patients[9]. Morbidity and mortality were linked to the invasive nature of the underlying disease. However, even with COVID-19, early intravenous anti-fungal treatment and surgical debridement were associated with favorable outcomes[10].

Treatment and outcome

Patients at our centre were started on liposomal amphotericin B with glycemic control on clinical suspicion of Mucormycosis followed by endoscopic debridement. In 30/32 (93.3%) patients, endoscopic debridement of sinuses was done. One patient died before surgery while another denied surgery. During the entire duration of study 4/32 (12.5%) patients did not survive, 5 (15.6%) were discharged and the rest are in hospital on parenteral antifungals.

Inclusion criteria

Patients who were admitted with RT-PCR positive or CT thorax - CORADS 4 and above (CORADS - COVID-19 Reporting and Data System) with CT severity > 40%.

1) Age > 18 years
2) Clinical signs of Mucormycosis

Exclusion criteria

1) Age less than 18 years
2) Contra indication for Inj.Amphotericin B

Discussion

The etiologic agent of mucormycosis are ubiquitous in nature and thus may easily be acquired, and its global epidemiology has been studied by several investigators, and may pose a threat during ongoing pandemic as has been observed in India [11] Due to the steep rise in cases of mucormycosis (black fungus infection) amid the second COVID-19 pandemic wave and its association with severe complications and associated higher fatality rate in post COVID-19 patients, this rare disease is now a notifiable disease in India. It is postulated that the use of non-sterile medical supplies might be associated with spore contamination and higher exposure of patients to mucormycosis [12]. As summarized in Tables 1 and 2, most patients had severe COVID-19 pneumonia requiring intensive care, intubation and ventilation. In addition, most patients had underlying diabetes mellitus and received steroids .The presence of diabetes mellitus is a major predisposing factor for mucormycosis as described in a meta-analysis among 600 (70%) of 851 patients with rhino-orbital–cerebral mucormycosis . The presence of diabetes mellitus among patients with COVID-19 was estimated to be 17% in one study [13] and 9% in another study .However, the presence of diabetes mellitus might be higher in other populations and may be more than 50% [4,5,6]. One meta-analysis showed that diabetes mellitus was associated with an odds ratio (OR) of 2.40 (95% CI 1.98–2.91) for severe disease , OR of 1.64 (95% CI 2.30–1.08) in a second meta-analysis , and an OR of 2.04, 95% CI 1.67–2.50 in a third meta-analysis [13]. Corticosteroid are currently the only medication that had shown conclusively to be effective in the treatment of COVID-19 in clinical trials therapy .The RECOVERY trial utilized dexamethasone at a dose of 6 mg intravenous or oral once a day for treatment of COVID-19. Systemic steroids could further exaggerate the underlying glycemic control as well as impede the body's immune system. The use of high dose corticosteroid had been used in patients with COVID-19 disease and the use of such medications required assessment [14]. One study showed that adherence to the use of low dose corticosteroid and good glycemic control were important in having no mucormycosis among 1027 ICU patients despite the use of corticosteroids in 89% and that 40% had diabetes mellitus. The presence of these pre-disposing factors in association with high fungal spore burden in certain localities and communities may set the perfect storm for the development of mucormycosis in patients with COVID-19 patients.

The outcome was favorable for patients who had surgical debridement in three case series.[15]With the ongoing COVID-19 pandemic and increasing number of critically ill patients infected with SARS-CoV-2, it is important to develop a risk-based approach for patients at risk of mucormycosis based on the epidemiological burden of mucormycosis, prevalence of diabetes mellitus, COVID-19 disease severity and use of immune modulating agents including the combined use of steroids and immunosuppressive agents in patients with cancer and transplants. A suggested approach for aspergillosis in COVID-19 was developed [16] and a

similar approach is needed for mucormycosis in SARS-CoV-2 infected patients. Whether a mold prophylaxis is required in high-risk patients need further studies. Early diagnosis of cases of mucormycosis, timely treatment with prescribed drugs and surgical operations, checking glycemic levels and judicious use of corticosteroids in patients with COVID-19 along with adopting appropriate hygienic and sanitization measures would aid in limiting the rising cases of this fungal infection. In-depth studies are required to investigate how COVID-19 is triggering mucormycosis infections in patients and why mainly most cases are being reported from India as compared to other countries amidst second wave of ongoing pandemic.

Table 1 :Summary of clinical characteristics of the included studies of SARS-CoV-2 and mucormycosis co-infections

SN.	Patient Age in years	Gender,Male/female	BMI	Date of COVID-19 positive test	Date of Admission	Date of Mucormycotic diagnosis	Affected organs, please list	Chronic Medical condition, **Diabe**	Chronic Medical condition, **Kidne**	Chronic Medical condition, **Histor**	Chronic Medical condition, **Histor**	**COVID-19 treatment, Steroid,** yes/n	**Mucormycosis Treatment, Amph**	**Mucormycosis Treatment, Posco**	**Surgical Treatment,** yes/no	Any other Treatments, (combination therap	Complication during hospitalization, please write, **organ failure, shock, Respiratory**	ICU admission, yes/no	Hospital death, Yes/no
1	52	male	28	1/6/2021	4/12/2021	4/12/2021	left maxilla	yes	no	no	no	YES	yes	no	yes	meropenam	no	no	no
2	52	male	24	5/24/2021	6/1/2021	6/1/2021	RIGHT MAXILLA	YES	no	no	no	yes	yes	yes	yes	NO	no	YES	no
3	38	Male	22	5/18/2021	6/6/2021	6/7/2021	B/L MAXILLA	no	no	no	no	yes	yes	yes	yes	no	no	YES	no
4	65	female	27	4/29/2021	6/8/2021	6/8/2021	left maxillary sinus	yes	no	no	no	YES	yes	yes	yes	meropenam-sulbactam	no	YES	no
5	52	male	30	5/12/2021	6/25/2021	6/26/2021	left maxilla	yes	no	no	no	yes	yes	yes	yes	metronidazole, piperacillin tazobactam	no	YES	no
6	37	male	24		6/26/2021	6/26/2021	B/L MAXILLA	yes	no	no	no	NO	YES	yes	yes	linezolide,, metronidazole, piperacillin tazobactam	no	YES	no
7	39	male	26	5/3/2021	6/29/2021	6/29/2021	right maxilla	yes	no	no	no	no	yes	yes	yes	Taxim, piperacillin tazobactam	no	yes	no
8	56	male	25	6/7/2021	7/6/2021	7/6/2021	maxillary sinus, ethmoid sinus, left	yes	no	no	no	yes	yes	yes	yes	metro gyl, piptaz	no	yes	no
9	52	male	22	5/25/2021	7/6/2021	7/6/2021	right maxilla	yes	no	no	no	yes	yes	yes	yes	metro gyl, piptaz, meropenam	no	YES	no
10	35	male	23		9/10/2021	9/10/2021	left maxilla	yes	no	no	no		no	no	yes	taxim	no	no	no
11	60	male	28	6/6/2021	6/11/2021	6/17/2021	orbital mucormysis,	yes	no	no	no	yes	yes	no	yes	piperacillin tazobactam	acute kidney injury	YES	no
12	53	male	24	6/18/2021	6/18/2021	6/21/2021	orbital mucormysis	yes	no	no	no	yes	yes	no	no	no	acute kidney injury	covid icu	yes
13	55	male	22	7/13/1905	6/21/2021			yes	no	no	no	yes	yes						
14	35	male	20		7/27/2021	7/27/2021	Sinonasal mucorycosis	no	no	no	no		yes	yes	yes	no	no	YES	no

Table 2: Summary of therapy and outcome of mucormycosis among SARS-CoV-2 infected patients (Please insert the table over here)

Conclusion

Mucormycosis is angioinvasive fungal disease with significant morbidity and mortality. The disease has risen dramatically due to interplay of COVID 19 pandemic, uncontrolled diabetes and in-appropriate corticosteroid use leading to pathogenic invasion and adverse outcomes. The treatment involves early detection, surgical debridement and antifungal drugs for better survival.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The Authors declare there is no conflict of interest.

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