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COVID-19 AND MUCORMYCOSIS SUPERIMPOSITION: A DEADLY SQUALL

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ABSTRACT

Background: The recent emergence of the Coronavirus Disease (COVID-19) disease had been associated with reports of fungal infections such as aspergillosis and mucormycosis especially among critically ill patients treated with steroids. The recent surge in cases of COVID-19 in India during the second wave of the pandemic had been associated with increased reporting of invasive mucormycosis post COVID-19. There are multiple case reports and case series describing mucormycosis in COVID-19.

Purpose: In this review, we included most recent reported case reports and case-series of mucormycosis among patients with COVID-19 and describe the clinical features and outcome.

Results: Many of the mucormycosis reports were reported from India, especially in COVID-19 patients who were treated and recovered patients. The most commonly reported infection sites were rhino-orbital/rhino-cerebral mucormycosis. Those patients were diabetic and had corticosteroids therapy for controlling the severity of COVID-19, leading to a higher fatality in such cases and complicating the pandemic scenario. The triad of severe acute respiratory

syndrome coronavirus 2 (SARSCoV- 2), corticosteroid use and uncontrolled diabetes mellitus have been evident for significant increase in the incidence of angioinvasive maxillofacial mucormycosis. In addition, the presence of spores and other factors might play a role as well.

Conclusion: With the ongoing COVID-19 pandemic and increasing number of critically ill patients infected with SARSCoV-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 corticosteroids and immunosuppressive agents in patients with cancer and transplants.

Keywords: SARS-CoV-2, COVID-19, Mucormycosis

INTRODUCTION

The current Severe Acute Respiratory Syndrome Corona- virus 2 (SARS-CoV-2) infection is associated with a wide clinical spectrum of Coronavirus Disease 2019 (COVID-
19) that ranges from being asymptomatic to severe disease requiring intensive care unit (ICU) admission [1–7]. The rate of admission to ICU is about 5% of all COVID-19 patients [8, 9]. Severe COVID-19 pneumonia is associated with immune dysregulation and cytokine syndrome leading to the increased use of immunomodulators [10, 11]. Emerging fungal infections such as aspergillosis were described in critically ill patients treated with steroids [12]. The mortality rate of SARS-CoV-2 infection in critically ill patients co- infected with aspergillosis was high [13].

Since the emergence of the COVID-19 pandemic, it has been suspected that mucormycosis might cause significant morbidity to infected patients. This was based on a retrospective analysis of SARS and influenza cases as suggested by Song *et al*. [14]. The more vulnerable individuals are those requiring hospitalization and intensive care, which represent advanced stage of their disease [15]. The recent surge in cases of COVID-19 in India during the second wave of the pan- demic had been associated with increased reporting of invasive mucormycosis post COVID-19, of up to 9000 cases and are continuously being reported to be rising, popularly known as black fungal infection [16–18]. In this review, we describe the important risk factors, clinical presentation and outcome of mucormycosis in patients infected with SARS-CoV-2.

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 [19]. 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 [21]. Given the large number of diabetic patients in India of almost 62 million, mucormycosis has caused large public health burden in India [20]. In one study, diabetes mellitus was the underlying disease in 54–76% of mucormycosis cases with 8–22% presenting with diabetic ketoacidosis [22]. 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 [23]. The true incidence of rhino-orbital mucormycosis in COVID-19 patients is not known. However, there are multiple case reports describing mucormycosis in COVID-19 and most of these case reports are presently from India, especially in COVID-19 treated and recovered patients those were diabetic and corticosteroids were administered injudiciously for controlling severity of COVID-19, leading to a higher fatality in such cases and complicating the pandemic scenario [17, 18, 24–37].

Risk factors

There are multiple possible contributing factors for the development of mucormycosis among patients with COVID-19 and these include diabetes mellitus, obesity, use of corticosteroid, and the development of cytokine storms. The triad of SARS-CoV-2, steroid and uncontrolled diabetes mellitus have contributed towards a significant increase in the incidence of angioinvasive maxillofacial mucormycosis [30]. However, the presence of spores and other factors might play a role as well [38]. The contribution of diabetes mellitus per se to the development of rhino-orbital-cerebral mucormycosis was the most common underlying comorbidity in 340 of 851 (40%) patients who were included in a meta-analysis, with an odds ratio (OR) of 2.49 (95% CI 1.77–3.54) com- pared to the next possible factor of having hematological malignancies with an OR of 0.76 (0.44–1.26) [19]. The role of Interleukin 6 blockers as a risk factor for mucormycosis is not clear [39]. Whether the combined use of steroids and

interleukin 6 blockers will increase the risk of mucormycosis compared to the use of steroids alone needs more studies.

Clinical features and management

Literature review identified 30 publications of case reports and case series of mucormycosis among COVID- 19 patients [24–26, 30, 31, 33–37, 40–55]. Of all the reports, 11 publications were from India [24–26, 30–37]. The most commonly reported infection sites were rhino-orbital/rhino-cerebral mucormycosis[24–26, 30, 32–37,40, 42, 45, 47, 52–54]. Other presentations included pulmonary [31, 41, 43, 44, 49, 51, 55], cutaneous [46], disseminated [56] and gastrointestinal [48] diseases. The reported organisms were *Rhizopus* spp. [24, 31, 36, 41–44, 47, 49, 51, 55] and the others were reported as unspecified Mucorale [25, 26, 30, 33–35, 37, 40, 45, 48,50, 52, 54]. The management of mucormycosis is usu- ally difficult and requires urgent medical and surgical debridement while the choice of drug to treat mucormy- cosis is Amphotericin B [23, 57] and Amphotericin was used in 23 of the included studies [24–26, 30–37, 40–44,46, 47, 49–54] and surgical debridement was reported in 20 of the included studies [24–26, 30, 32–37, 40, 44–47, 50–54]. The majority of the included patients in this review underwent surgical resection/debridement [24–26, 30, 32–37, 40, 44–47, 50–54].

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 trans- plant and diabetes mellitus, respectively) [58]. However, another study showed higher mortality of 49% among diabetes mellitus patients compared to 30% among non- diabetic patients [58]. Morbidity and mortality were linked to the invasive nature of the underlying disease [59]. How- ever, even with COVID-19, early intravenous anti-fungal treatment and surgical debridement were associated with favorable outcomes [26].

Table 1: Summary of therapy and outcome of mucormycosis among SARS-CoV-2 infected patients

Author, year, study location	Time between diagnosis of SARS-CoV-2 and mucormycosis (days)	Surgical debridement made	Antifungal treatment	Treatment outcome
Alekseyev *et al* . (2021), United States [40]	NA	Yes	Amphotericin B	Survived
Bellanger *et al* . (2021), France [41]		15	NA	Amphotericin B Died
Dallalzadeh *et al* . (2021), United States [42]	6	No	Amphotericin B, isavuconazole	Died (*n* = 2)
Garg *et al* . (2021), India [31]	17	Scheduled for right upper lobectomy	Amphotericin B	Survived
Hanley *et al* . (2020), United King- dom [56]	NA	No	No	Died
	NA	NA	Amphotericin B, voriconazole	Discharged
Johnson *et al* . (2021), United States [43]	16	Yes	Amphotericin B	Died
	21	Yes	Systemic antifungals (Unspecified)	Survived
Kanwar *et al* . (2021), United States [44]	90	Yes	Amphotericin B, posaconazole	Died
Karimi-Galougahi *et al* . (2021), Iran [45]				
Khatri *et al* . (2021), United States [46]				
Maini *et al* . (2021), India [32]	18	Yes	Amphotericin B, fluconazole	Survived
Mehta *et al* . (2020), India [33]	10	Yes	Amphotericin B	Died
Mekonnen *et al* . (2021), United States [47]	7	Yes	Amphotericin B, caspofungin, posaconazole;	Died
Monte Junior *et al* . (2020), Brazil [48]	5	No	No	Died
Moorthy *et al* . (2021), India [30]	NA	Yes (*n* = 7)	Amphotericin B	Survived (*n* = 11),died (*n* = 6) and lost to follow-up (*n* = 1)
Pasero *et al* . (2020), Italy [49]	17	No	Amphotericin B, isavuconazole	Died
Pauli *et al* . (2021), Brazil [50]	8	Yes	Amphotericin B	Survived
Placik *et al* . (2020), United States [51]	14	Yes	Amphotericin B	Died
Rao *et al* . (2021), India [34]	NA	Yes	Amphotericin B	Survived
Ravani *et al* . (2021), India [35]	NA	Yes (*n* = 19)	Amphotericin B (*n* = 19)	Survived (*n* = 18), died (*n* = 1)
Revannavar *et al* . (2021), India [36]	NA	Yes	Amphotericin B	Survived
Saldanha *et al* . (2021), India [37]	NA	Yes	Amphotericin B	Survived
Sarkar *et al* . (2021), India [24]	NA	Yes	Amphotericin B	Improved (*n* = 1), died (*n* = 4), unchanged (*n* = 4), exenteration (*n* = 1)

Sharma *et al* . (2021), India [26] Survived (*n* = 23)	**NA**	**Yes**	**Amphotericin B**	
Veisi *et al* . (2021), Iran [52]	**8 (Case 1) and 7 (Case 2)**	**Yes (*n* = 2)**	**Amphotericin B (*n* = 2)**	**Died (Case 1) and discharged (Case 2)**
Waizel-Haiat *et al* . (2021), Mexico [53]	**6**	**Yes**	**Amphotericin B**	**Died**
	2	**Yes**	**Amphotericin B**	**Died**
Werthman-Ehrenreich *et al* . (2021), United States [54]				
Zurl *et al* . (2021), Austria [55]	**NA**	**No**	**None**	**Died**
Pakdel *et al* .; (2021), Iran [78]	**1–37**	**33%**	**6 (40%) combined antifungal**	**7 (47%) died**
Singh *et al* . (2021); India [79]	**19**	**Yes**	**Liposomal amphotericin B**	**Recovered**
Arjun *et al* . (2021); India [80]	**17.0 ± 3.6**	**Yes**	**Amphotericin B deoxycholate and isavuconazole**	**10% died**
Saidha *et al* . (2021); India [81]	**NA**	**Yes**	**Amphotericin**	**Recovered**
Jain *et al* . (2021); India [82]	**15**	**Yes**	**NA**	**Recovered**
Baskar *et al* . (2021); India [83]	**On diagnosis**	**Yes**	**Amphotericin**	**Recovered**
Joshi *et al* . (2021), India [84] died	**Not indicated**	**yes in 10 (45%)**	**Amphotericin**	**14 (63%)**
Sen *et al* . (2021); India [85]	**10–15**	**56% had functional endoscopic sinus surgery (FESS)/paranasal sinus (PNS) debridement, 15% orbital exenteration in 15%, 17% both FESS/PNS debridement and orbital exenteration**		

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 [17, 23, 27, 57, 60, 61]. 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 [62, 63]. 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 [28, 64, 65]. 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 [19]. The presence of diabetes mellitus among patients with COVID-19 was estimated to be 17% in one study [66] and 9% in another study [67]. However, the presence of diabetes mellitus might be higher in other populations and may be more than 50% [4–6]. 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 [68], OR of 1.64 (95% CI 2.30–1.08) in a second meta-analysis [69], and an OR of 2.04, 95% CI 1.67–2.50 in a third meta-analysis [66]. Corticosteroid are currently the only medication that had shown conclusively to be effective in the treatment of COVID-19 in clinical trials therapy [70–72]. The RECOVERY trial utilized dexamethasone at a dose of 6 mg intravenous or oral once a day for treatment of COVID-19 [73]. 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 [74] and the use of such medications required assessment [75]. 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 [76]. The presence of these pre-disposing factors in associa- tion 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 [25, 26, 35]. 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 [77] 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.

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