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Review Article

COVID-19 associated mucormycosis – An emerging threat

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Abstract Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly become a global threaten since its emergence in the end of 2019. Moreover, SARS-CoV-2 infection could also present with co-infection or secondary infection by other virus, bacteria, or fungi. Among them, mucormycosis is a rare but aggressive fungal disease and it mainly affects patients particularly with poorly controlled diabetes mellitus with diabetic ketoacidosis (DKA). We here did a comprehensive review of literature reporting COVID-19 associated with mucormycosis (CAM) cases, which have been reported worldwide. The prevalence is higher in India, Iran, and Egypt than other countries, particularly highest in the states of Gujarat and Maharashtra in India. Poor diabetic control and the administration of systemic corticosteroids are the common precipitating factors causing mucormycosis in the severe and critical COVID-19 patients. In addition, COVID-19 itself may affect the immune system resulting in vulnerability of the patients to mucormycosis. Appropriate treatments of CAM include strict glycemic control, extensive surgical debridement, and antifungal therapy with amphotericin B formulations.

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Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly become a global threaten since its emergence in the end of 2019.¹ As of November 20, 2021, more than 255 million confirmed cases have been identified worldwide and more than 5 million deaths have been reported.¹ SARS-CoV-2 infection could present as asymptomatic, mild symptom, severe pneumonia, and acute respiratory distress syndrome (ARDS).^{1–3} Although respiratory tract symptoms and fever were the most common clinical presentations among symptomatic patients, extra-pulmonary involvements by COVID-19 include cardiac, gastrointestinal, hepatic, renal, neurological, olfactory, gustatory, ocular, cutaneous and hematological symptoms.⁴ Moreover, SARS-CoV-2 infections could also present with co-infections or secondary infections by bacteria, such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*; viruses such as influenza, coronavirus, rhinovirus/enterovirus, parainfluenza, metapneumovirus, and human immunodeficiency virus, and fungi, such as *Aspergillus* spp.^{5–10} In addition to these co-pathogens, many cases of mucormycosis among COVID-19 patients have been reported recently.^{11–18} Mucormycosis is a rare but aggressive fungal disease and it mainly affects patients with poorly controlled diabetes mellitus and severely immunocompromised patients.¹⁹ In contrast to aspergillosis, mucormycosis was rarely reported following viral infection.^{20–22} At present, the studies and knowledge about COVID-19 associated with mucormycosis (CAM) have been limited. Therefore, we did a comprehensive review of literature reporting mucormycosis in patients with COVID-19 to provide updated information.

Epidemiology

Since the outbreak of COVID-19, more and more cases of CAM have been reported.^{23–27} In UK, the post-mortem study of 10 several fatal COVID-19 cases in the early pandemic (between March 1 and April 30, 2020) showed one patient who had unexpected disseminated mucormycosis involving the lungs and brain.²³ In US, Placik et al. reported a fatal case of mucormycosis with necrotizing pulmonary infections and a bronchopleural fistula following COVID-19 in Arizona.²⁵ In India, Mehta et al. demonstrated a diabetic patient of rhino-orbital mucormycosis associated with COVID-19.²⁶ In Brazil, Monte Junio et al. showed an unusual case of gastric mucormycosis in an elderly patient with COVID-19.²⁴ In Italy, Paserol et al. reported one COVID-19 case who developed a pulmonary mucormycosis with extensive cavitory lesions.²⁷ Thereafter, more and more CAM cases have been reported in Egypt, the Netherlands, Iran, Japan, Spain, Mexico, and Austria.^{28–36} In contrast to other countries, India reported the most cases with a rapid increasing incidence.³⁷ As of May 28, 2021, at least 14, 872 cases of CAM have been found in India, in which the state of Gujarat had the highest incidence, with at least 3726 cases, followed by the state of Maharashtra.³⁷ The similar trend was reported in another large retrospective study of 2826 patients with COVID-19 associated rhino-orbital-cerebral

mucormycosis, in which the states of Gujarat (22%) and Maharashtra (21%) had the highest cases.³⁸ At the same time, the number of acute invasive fungal rhinosinusitis in a single center in Egypt was much higher in 2020 ($n = 29$) than 2017 ($n = 9$), 2018 ($n = 8$), and 2019 ($n = 10$).³⁹ A multicenter study in India showed that the prevalence of CAM was 0.27% among hospitalized COVID-19 patients, in which the prevalence was higher in COVID-19 managed in intensive care unit (ICU) than in general ward (25/1579 versus 28/10,517).¹³ Till now, almost 90% of the CAM cases were reported from India (Table 1),^{13,14,26,38,40–53} which may be attributed the following causes: (1) India has the second largest diabetic population and about 70% of them were not under control⁵⁴ and (2) the environmental factors in India - tropical and sub-tropical humid climate and high environmental temperature.⁵⁴

Pathogenetic roles of ketoacidosis and unbound iron

The patients developing diabetic ketoacidosis (DKA) are susceptible to mucormycosis. In a study testing the *in-vitro* growth of *Rhizopus oryzae*, a common etiologic agent of mucormycosis, in DKA serum, the acidotic conditions (pH 7.3–6.6) of serum would reduce the capacity of transferrin to bind iron, thus offering the unbound iron in the DKA serum to support the profuse growth of *R. oryzae*. DKA sera did not support fungal growth at two conditions of either iron-deficient status or at a serum pH greater than or equal to 7.4.⁵⁵ Clinical and animal model data have demonstrated that the presence of elevated available serum iron predisposes the host to mucormycosis due to the critical role of the ability of *Mucorales* to acquire host iron as a virulence factor.^{56,57} *Rhizopus* invades the epithelium via fungal spore coat proteins (CoH) binding to the host receptor of glucose-regulated protein 78 (GRP78) on the nasal and alveolar epithelial cells.^{58,59} The hallmark features of DKA including β -hydroxy butyrate (BHB), glucose, and iron components in DKA sera can increase surface expression of GRP78 in epithelial cells and fungal CoH expression. BHB also indirectly compromised the ability of transferrin to bind iron, thus increasing the available serum iron. Together with use of corticosteroid in a standard care of COVID-19 patients can further upregulate CoH3 and nasal GRP78,⁶⁰ thereby trapping the fungal cells within the rhino-orbital epithelium, leading to subsequent invasive diseases. These BHB-developed acidotic serum conditions extremely predispose to mucormycosis, but not to aspergillosis.^{60–62}

Interactions between COVID-19 and mucormycosis

Most cases of mucormycosis are temporally linked to COVID-19.⁶³ The surge in the number of cases of CAM is relevant to environmental characteristics and universal glucocorticoid use for severe COVID-19 cases, in addition to a previous well-known demographic factor of poor control for diabetes mellitus especially with DKA. The systemic use of corticosteroids is a double-edged sword in the therapy for cytokine storm and triggering for mucormycosis in the COVID-19

Table 1 Summary of reported COVID-19 associated mucormycosis from different geographic areas.

Geographic areas	Case no.	Age (yr)	Gender	Underlying condition	Lesion	Mortality	Author
United Kingdom	1					1 (100%)	
London	1	22	M	Obesity, hypothyroidism	Disseminated	Yes	Hanley et al. ²³
South America	2					2 (100%)	
São Paulo, Brazil	1	86	M	Corticosteroid use	Stomach	Yes	Monte Junior et al. ²⁴
Mexico City, Mexico	1	24	F	Obesity	Rhino-orbital	Yes	Waizel-Haiat et al. ³⁵
United States	9					7 (78%)	
New York	1	68	M	Heart transplant, DM	Cutaneous	Yes	Khatri et al. ¹⁶
New York	1	33	F	DM	Rhino-orbital-cerebral	Yes	Werthman-Ehrenreich et al. ³⁴
San Francisco, California	1	60	M	DM	Rhino-orbital	Yes	Mekonnen et al. ¹⁷
Riverside, California	1	79	M	Corticosteroid use	Pulmonary	no	Johnson et al. ⁷³
San Diego, California	2	NA	NA	DM (2), corticosteroid use (2)	Rhino-orbital-cerebral (2)	2/2	Dallalzadeh et al. ⁶⁹
Dover, Delaware	1	41	M	DM	Rhino-cerebral	no	Alekseyev et al. ³⁶
Lewes, Delaware	1	56	M	ESRD, corticosteroid use	Lung	Yes	Kanwar et al. ⁶⁸
Yuma, Arizona	1	49	M	Corticosteroid use	Lung	Yes	Placik et al. ²⁵
European Union	9					6 (67%)	
Multisite, the Netherlands	4	50–70	M (4)	DM (2), corticosteroid use (1), obesity (1)	Lung (3), orbital (1)	3/4	Buil et al. ¹¹
Barcelona, Spain	2	62, 48	M (2)	Kidney transplant (2), DM (1), corticosteroid use (2)	Rhinosinusal (1), Musculoskeletal (1)	0/2	Arana et al. ³¹
Besançon, France	1	55	M	Lymphoma	Lung	Yes	Bellanger et al. ⁷²
Sassari, Italy	1	66	M	Hypertension	Lung	Yes	Pasero et al. ²⁷
Graz, Austria	1	53	M	Acute myeloid leukemia	Lung	Yes	Zurl et al. ³³
Egypt	7					3 (42.8%)	
Cairo	7	41–67	M (4) F (3)	DM (6)	Rhino-orbital-cerebral (7)	3/7	Ashour et al. ²⁹
Middle East	29					15 (52%)	
Tehran, Iran	1	61	M	Corticosteroid use	Rhino-orbito-cerebral	no	Karimi-Galougahi et al. ¹⁵
Tehran, Iran	2	40, 54	M (1) F (1)	Corticosteroid use (2)	Rhino-orbital (1), rhino-orbital-cerebral (1)	1/2	Veisi et al. ³²
Tehran, Iran	15	14–71	M (9) F (6)	DM (13), corticosteroid use (7)	Rhino-orbital (15)	7/15	Pakdel et al. ¹²
Kayseri, Turkey	11	61–88	M (9) F (2)	DM (8), corticosteroid use (11)	Sino-orbital (11)	7/11	Bayram et al. ³⁰
India	3129					412/3106 (13%)	
Chandigarh	1	55	M	DM, ESRD, corticosteroid use	Lung	no	Garg et al. ⁴⁰
Mangalore, Karnataka	1	32	F	DM	Rhino-orbital-cerebral	no	Saldanha et al. ⁴⁵
Mangalore, Karnataka	1	NA	F	DM	Rhino-orbital-cerebral	no	Revannavar et al. ⁴³

(continued on next page)

Table 1 (continued)

Geographic areas	Case no.	Age (yr)	Gender	Underlying condition	Lesion	Mortality	Author
Mysuru, Karnataka	2	34, 50	M (2)	Nil	Rhino-orbital (2)	0/2	Sai Krishna et al. ⁴⁴
Bangalore, Karnataka	1	66	M	DM, corticosteroid use	Rhino-orbital	no	Rao et al. ⁴²
Bangalore, Karnataka	17	35–73	M (14) F (3)	DM (16), corticosteroid use (16)	Rhino-orbito-cerebral (17)	6/17	Moorthy et al. ⁴¹
Puducherry	10	23–67	M (8) F (2)	DM (5), corticosteroid use (10)	Orbital (10)	4/10	Sarkar et al. ⁴⁶
Ahmedabad, Gujarat	1	42	M	DM, corticosteroid use	Rhino-orbital	no	Selarka et al. ¹⁴
Ahmedabad, Gujarat	2	25, 47	M (2)	Kidney transplant (2), DM (2)	Rhino-orbital (1), lung (1)	2/2	Meshram et al. ⁴⁷
Ahmedabad, Gujarat	19	NA	NA	DM (19), corticosteroid use (19)	Rhino-orbital (19)	3/19	Ravani et al. ⁴⁹
Bikaner, Rajasthan	5	52–70	M (1) F (4)	DM (5)	Rhino-orbital (5)	2/5	Nehara et al. ⁴⁸
Jaipur, Rajasthan	23	NA	NA	NA	Rhino-orbital-cerebral (23)	NA	Sharma et al. ⁵⁰
Hyderabad, Telangana; Mumbai, Maharashtra	6	46–74	M (6)	DM (6), corticosteroid use (5)	Rhino-orbital (6)	0/6	Sen et al. ⁵³
Mumbai, Maharashtra	1	60	M	DM	Rhino-orbital	Yes	Mehta et al. ²⁶
Mumbai, Maharashtra	1	38	M	Corticosteroid use	Rhino-orbital-cerebral	no	Maini et al. ⁵²
Mumbai, Maharashtra	25	NA	NA	DM (22), HIV (2), corticosteroid use (25)	Rhino-orbital-cerebral (25)	14/25	Joshi et al. ⁵¹
Multicenter	187	57 ^a	M (150) F (37)	DM (113), corticosteroid use (146), kidney transplant (3)	Rhino-orbital (117), rhino-orbital-cerebral (44), lung (16), kidney (1), disseminated (4), others (5)	75/170	Patel et al. ¹³
102 centers	2826	12–88	M (1993) F (833)	DM (2194), hypertension (690), renal failure (88)	Rhino-orbital-cerebral (2826)	305/2218	Sen et al. ³⁸

^a Mean \pm SD, 56.9 \pm 12.5.

Note. M: man; F: female; DM, diabetes mellitus; ESRD, end stage renal disease; HIV, human immunodeficiency virus; NA, not applicable.

patients that requires critical care.⁶⁴ The combination of steroid therapy and diabetes mellitus can augment immunosuppression and hyperglycemia, increasing the risk of mucormycosis.⁶⁴ Most cases were reported from India in the literature.⁴¹ Even though a rather high regional prevalence in India, a 2.1-fold rise in mucormycosis during the COVID-19 pandemic than previous year was noted.¹³ The median time interval between COVID-19 diagnosis and the first evidence of a mucormycosis infection was 7–15 days.^{38,63}

Cases of mucormycosis may occur in COVID-19 patients without diabetes mellitus and only with mild-to-moderate diseases outside intensive care units, as reported in the Netherlands.¹¹ Although severe or critical COVID-19 in poorly controlled diabetic patients is the most perfect storm for mucormycosis,⁶⁵ receiving corticosteroids might contribute to the emergence of mucormycosis in COVID-19 patients even without critical severity and a risk comorbidity.¹¹

High counts of *Mucorales* spores in both the indoor and outdoor environments are possible additional predisposing factors. The environmental factors might contribute to the “hot-spot” regions of CAM in the world, such as the cities of Bangalore, Ahmedabad, Jaipur, and Mumbai in India (Table 1). *Mucorales* were isolated from the soil samples of different geographical locations in India, including the most common isolate of *Rhizopus arrhizus* (24.6%), followed by *Lichtheimia* spp. (23.2%), *Cunninghamella* spp. (21.7%), *Rhizopus microsporus* (14%) and *Apophysomyces* spp. (4.5%).⁶⁶ However, there are very few data concerning correlation of the environmental levels of zygomycete sporangiospores with zygomycosis, particularly in geographical areas where zygomycosis is highly prevalent.⁶⁷

Furthermore, severe COVID-19 disease is associated with an increase in pro-inflammatory markers, such as interleukin (IL)-1, IL-6, and therapy with IL-6 receptor antagonist might be at a higher risk for fungal infections.⁶⁸ COVID-19 may affect the immune system leading to lymphopenia, dysregulation of CD4 interferon-gamma expression, and reduced numbers of T lymphocytes, CD4+T cells, and CD8+T cells, altering the innate immunity.³⁹

Clinical manifestations

Uncontrolled diabetes mellitus was the most common underlying conditions contributed to CAM.^{13,37,38} Additionally, other immunocompromised conditions, including neutropenia, end-stage kidney disease, hematologic malignancy, solid organ transplant recipients and the use of corticosteroid have been reported.^{11–13,16,31–33,40} In one large series of COVID-19 associated rhino-orbital-cerebral mucormycosis, diabetes mellitus was presented in 78% of 2826 patients, and 87% had been treated with corticosteroid.³⁸ Another study of 187 CAM cases showed the similar thing that 78.1% of patients had received corticosteroid and 60.4% of patients had diabetes mellitus.¹³ However, COVID-19 could be the only underlying disease in 32.6% of CAM patients.¹³ The most common involved site of CAM was rhino-orbital cerebral, but lung, kidney, cutaneous, stomach, mediastinal lymph node, heart, pericardium, kidney, musculoskeletal and disseminated infections have been reported (Table 1).^{13,38,69,70} For patients with rhino-orbital-cerebral sinusitis, orbital/facial pain and orbital/facial

edema were the most common symptoms, followed by loss of vision, ptosis and nasal block.³⁸ Additionally, these patients could have the presentation of fever, eyelid edema, conjunctival chemosis, deteriorating visual acuity, proptosis, ophthalmoplegia, diplopia, periorbital pain, orbital/facial discoloration, cranial nerve palsy, headache, nasal blockage, ear pain, black nasal crusts, nasal discharge, periocular hypoesthesia, palatal ulcer/eschar, toothache, loose teeth, epistaxis, and facial deviation/palsy.^{12,29,38,42} CT or MRI can show sinusitis, oroantral fistula, erosions of the nasal septum, hard palate, and sinus wall, air within bony sinus structures, focal mucosal nonenhancement, panophthalmitis, orbital infiltration involving the optic nerve, skull base involvement, cerebral sinus thrombosis with secondary vasculitis, watershed acute cerebral infarctions and meningeal enhancement.^{29,51} For patient with pulmonary involvement, fever, cough, dyspnea, and hypoxia could be the presenting signs and symptoms, and the radiographic manifestations included consolidations, cavitary lung lesions and bronchopleural fistula formations with empyema.^{13,25,40,66} Although the diagnosis of CAM based on the identification of organisms in tissue by histopathology with culture confirmation, it should also require clinicians' high index of suspicion, recognition of host factors, prompt assessment of clinical manifestations and further image investigations using CT or MRI.

Microbiologic distribution

Previously, the most common reported saprophytic environmental fungi causing mucormycosis was *Rhizopus* species and other pathogens including *Mucor*, *Cunninghamella*, *Aposphysomyces*, *Lichtheimia* (formerly *Absidia*) *Saksenaea*, *Syncephalastrum*, *Bertholletia*, and *Rhizomucor* species have been reported.⁷¹ During COVID-19 pandemic, several fungi including *R. oryzae*, *R. microsporus*, *Rhizopus azygosporus*, *Lichtheimia mucor*, and *Lichtheimia ramosa* have been identified as causative pathogens.^{11,16,31,33,39,40,52,68} Rarely, CAM can have concomitant infections with *Aspergillus* species.^{41,72,73}

Treatment

First-line treatment with high-dose liposomal amphotericin B but not slow escalation is strongly recommended. Liposomal amphotericin B (5 mg/kg/day), dilute in 200 cc 5% dextrose over 2–3 h infusion, is the preferred regimen; and higher dose of 10 mg/kg/day may be given in orbital-cerebral involvement. Amphotericin B deoxycholate (1 mg/kg/day) as substantial toxicity is used only if cost and availability of liposomal amphotericin B is an issue. Patients who are intolerant to amphotericin B, alternative agents are posaconazole or isavuconazole. Both triazoles are also strongly recommended salvage treatments.^{74,75} Posaconazole or isavuconazole is often combined with liposomal amphotericin B with refractory mycosis.^{53,76} Anti-fungal therapy may be initiated with liposomal amphotericin B and posaconazole, followed by isavuconazole as salvage therapy.⁷⁷ Several case reports have shown isavuconazole to be effective as the salvage therapy for mucormycosis.^{78–80} A total of 72 clinical isolates of *Mucorales* were evaluated,

more isolates were found to be potentially susceptible to isavuconazole when compared to posaconazole.⁸¹ Successful treatment of fungal meningitis with isavuconazole in limited case reports supports brain penetration in humans.⁸² In addition to appropriate antifungal agents, the management of mucormycosis is multimodal, including reversal of underlying risk factors, such as glycemic control, and extensive or repeated surgical debridement.⁷² Surgery according to the extent of CAM involvement is important in rhino-orbitocerebral infection and in soft tissue infection and surgery intervention should be very aggressive.⁸³

Outcomes

The morbidity and mortality of CAM remain high.²³ Buil et al. reported that three of 4 CAM cases developed in the ICU and three deaths occurred in the Netherlands.¹¹ In a series of 187 CAM cases in India, the reported overall mortality was 37.4% (70/187) and 44.1% (75/170) within 6 and 12 weeks respectively.¹³ The mortality rates were substantially higher in non-prevalent regions (>50%–100% in United States and the European countries) than prevalent regions (about 40%–50% in the middle East and Egypt) and lowest (13%) in India (Table 1). However, the prognosis of mucormycosis could vary according to the site of involvement.¹³ The largest study of 2826 patients with COVID-19 associated rhino-orbital-cerebral mucormycosis in India reported the all-cause mortality was 14% ($n = 305$) of 2128 patients with available outcome data.³⁸ Although the patients with disease stage >3b (defining stage 3c: central retinal or ophthalmic artery occlusion or superior ophthalmic vein thrombosis; involvement of superior orbital fissure, inferior orbital fissure, orbital apex, loss of vision; stage 3d: bilateral orbital involvement; and stage 4) had poorer prognosis in this study, paranasal sinus debridement and orbital exenteration could significantly help reduce the mortality rate in patients with stage 4 of intracranial extension (52% versus 39%, $p < 0.05$).³⁸

Conclusion

During COVID-19 pandemic, the emergence of CAM has become a serious concern, particularly in India. Uncontrolled diabetes mellitus with DKA and the use of corticosteroid are the most common conditions among patients with CAMs. Rhino-orbital-cerebral is the most common site of involvement, but CAM can also involve pulmonary, skin and stomach. Highly suspicion and early diagnosis are the key of successful management of patients with CAM. Although the prognosis of CAM is poor, first-line high-dose liposomal amphotericin B and appropriate surgical intervention can help improve the outcome.

Ethical

Not relevant. We declare that reporting of the study was in line with the Declaration of Helsinki, as revised in 2013.

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None declare.

Author contributions

Concept and design: C.-M.C., C.-C.L. and W.-L.Y. Drafting of the manuscript: C.-M.C. and C.-C.L. Critical revision of the manuscript: C.-C.L. and W.-L.Y.

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