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Review Article

COVID-Associated Mucormycosis: Review of Cases Reported Worldwide and in India

Rohini R Nair[1], Anjan Kumar Sahoo[2], Anukampa Sharma[1]

[1]Senior Resident, [2]Associate Professor, Department of ENT and Head and Neck Surgery, All India Institute of Medical Sciences, Bhopal, India.

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I N F O

Corresponding Author:
Anjan Kumar Sahoo, Department of ENT and Head and Neck Surgery, All India Institute of Medical Sciences, Bhopal, India.
E-mail Id:
anjan.ent@aiimsbhopal.edu.in
Orcid Id:
https://orcid.org/0000-0002-8073-6549

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A B S T R A C T

Objective: The aim of this review literature is to collate and analyse various case reports and series reporting mucormycosis in COVID and post-COVID patients in India and worldwide.

Methods: A systematic literature search was conducted from December 2019 to June 2021 using keywords. Details of all the case reports/ series that reported rhino-orbital-cerebral mucormycosis in COVID and post-COVID settings were retrieved and analysed.

Results: In this systematic review, 33 articles were included and a total of 181 cases of mucormycosis in COVID and post-COVID patients were reported. Mucormycosis was predominantly seen in males (71.2%) as compared to females (28.7%). History of steroid use was present in 113 patients (62.4%). Type 2 diabetes mellitus was the most common independent risk factor, present in 138 patients (76%). Sino-nasal involvement was seen in 27 patients (14.9%), rhino-orbital involvement in 114 patients (62.9%), andrhino-orbital-cerebral involvement was observed in 40 patients (22%). Improvement in clinical status was observed in 106 patients (58.5%) while 38 patients (21%) expired.

Conclusions: A rapid rise in cases of mucormycosis had been reported in the COVID era. Unwarranted use of steroids coupled with uncontrolled hyperglycemia, unregulated activation of inflammatory mediators and overactivation of entry-point receptors inflicted by the Coronavirus cause a state of immune dysregulation, leading to opportunistic invasive fungal infections. A delay in diagnosis can result in disfigurement, functional loss, or even death. Multidisciplinary management with prompt reversal of risk factors is recommended.

Keywords: Mucormycosis, Post-COVID, COVID-Associated Mucormycosis, Invasive fungal Sinusitis, Sinonasal Mucormycosis

Introduction

The novel coronavirus SARS-CoV-2 (Coronavirus disease 2019; previously 2019-nCoV) outbreak, which began in the Hubei Province of the People's Republic of China, has spread to a number of other countries. The WHO Emergency Committee declared it a global health emergency on January 30, 2020, based on increasing case notification rates in China and other international locations.[1]

Mucormycosis is a rare opportunistic fungal disease which has been seen on the rise post-COVID, especially in India. Although, it was more common in India even before the COVID-19 pandemic, with an incidence 70 times higher than the global average.[2]

Dubbed as the "black fungus" in popular media, mucormycosis is caused by ubiquitous environmental moulds with a global distribution. Its incidence has risen more rapidly during the second wave of COVID as compared to the first wave of COVID-19 in India with at least 14, 872 cases as of May 28, 2021.[3]

The reason for this sharp rise in cases is not clearly known; however, factors like widespread and unwarranted use of steroids, the masked burden of undiagnosed diabetes mellitus, poorly controlled diabetes combined with the microthrombi and mucosal injury caused by coronavirus can be attributed as the plausible causes.

Given the enigmatic aetiology, poor prognosis, time liability and high fatality rate, this disease has prompted us to conduct a systematic review of published case reports/ case series to establish a temporal relationship with comorbidities, the severity of COVID, steroid usage, and patient outcome.

Methodology

A systematic literature search was conducted in the electronic database of PubMed and Google Scholar from December 2019 until June 2021 using the keywords "COVID-19", "SARS-CoV-2" and "Mucormycosis", "Mucorales", "Zygomycosis". Details of all the case reports/ series that reported rhino - orbital-cerebral mucormycosis (suspected and confirmed) in post-COVID settings were retrieved and tabulated in an Excel sheet. Further, we manually searched references of relevant articles. SPSS software was used to analyse the data. Two authors independently checked the veracity of the data.

Inclusion Criteria: Included confirmed cases of sino-nasal or rhino-orbital or rhino-orbital-cerebral mucormycosis after COVID-19 infection.

Exclusion Criteria: Included mucormycosis without a history of COVID-19 and systemic involvement other than sino-nasal, orbit or brain.

Results

In this systematic review, 33 articles were included from the database of PubMed and Google Scholar. Out of these, 20 articles were from India and the remaining 13 were from the rest of the world (Table 1). A total of 181 cases of COVID-associated as well as post - COVID mucormycosis were retrieved. Most of the cases i.e. 153 (84.5%) were reported from India, 20 cases (11%) from Iran, 3 cases (1.6%) from the USA, and 1 case (0.5%) each from Brazil, Mexico, Spain, Turkey, and Iraq.

Pooled data from this study showed that mucormycosis was predominantly seen in males (71.2%) as compared to females (28.7%) with a male-to-female ratio of 2.5:1. The mean age of the affected patients was 52.4 years.

On average, mucormycosis occurred within 28 days after the appearance of COVID symptoms in India, while it presented within 9 days from the onset of COVID symptoms in the rest of the world population, bringing the overall average to 18.5 days. Only two of these cases were found to be COVID-positive incidentally and only 3 studies reported the presentation of mucormycosis more than 2 months post-COVID.

The severity of mucormycosis was mild in 20 patients (11%), moderate in 60 patients (33%), severe in 17 patients (9.3%), and asymptomatic in only 1 patient (0.5%). However, it is to be noted that the severity of the disease wasn't unanimously defined in any of these studies and data on the severity of ARI in 83 patients were missing. History of steroid usage for the treatment of COVID was present in 113 patients (62.4%) while the data of 35 patients (19.3%) were missing.

Amongst the predisposing comorbidities, a history of type 2 diabetes mellitus or newly diagnosed type 2 diabetes mellitus was predominant and was present in 138 patients constituting 76% of the total patients. Other comorbidities included hypertension, chronic kidney disease, coronary heart disease, post-transplant status, haematological malignancy etc.

Mucormycosis involving only nose/ paranasal sinus, orbit, and brain were included in the review study. Sino-nasal involvement was seen in 26 patients (14.3%), rhino-orbital involvement in 114 patients (62.9%), and rhino-orbital-cerebral involvement was observed in 40 patients (22%). Only one patient had an isolated palatal lesion without any sino-nasal component. Surgical intervention was done in 153 patients (84.5%) and data was unavailable for 4 patients (2.2%). Endoscopic debridement was the most frequent surgical intervention performed; however, the extent of debridement wasn't defined in most of these studies and hence couldn't be commented upon. Antifungal therapy in the form of injection amphotericin B (plain/ liposomal) was administered to all patients except one, i.e. 180 patients (99.4%). 13 patients received posaconazole either as adjuvant therapy with amphotericin or as a step-down therapy. Voriconazole was used in patients with mixed aetiology. Injection caspofungin was used in 1 patient. Broad, aseptate ribbon-like hyphae with right-angled branching were isolated in 48 patients (26.5%), aspergillus was isolated in 1 patient (0.5%) while mixed

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microbiota was seen in 2 patients (1%). Improvement in clinical status was observed in 106 patients (58.5%) while 38 patients (21%) expired. The data on patient outcome was unavailable for 35 patients (19.3%) and 2 patients (1.1%) were lost to follow-up.

Table 1.Tabulation of Case Reports/Series of COVID-Associated Mucormycosis in India and Worldwide

S. No.	Study/ Case Report	Age (Mean in Years)	Presentation Time from ARI	H/O T2DM	Severity of ARI	Steroid/ Immunosuppressant	Type of Clinical Presentation			Patient Outcome	Isolated Organism
							Sinonasal	Orbital	Cerebral		
1.	Saldanha et al.[4]	32	Incidental	Yes	Mild	No	√	√	-	Improved	NA
2.	Sharma et al.[5]	NA	NA	21/23	NA	Yes	23	12	2	Improved	NA
3.	Dronamraju et al.[6]	50	NA	NA	NA	NA	√	√	√	Expired	Rhizopus sp
4.	Sebastian et al.[7]	59	7 days	Yes	Severe	Yes	√	√	-	Expired	Aspergillus fumigatus/ rhizopus
		60	10 days	Yes	Severe	Yes	√	√	√	Expired	Aseptateribbon like hyphae
		64	9 days	Yes	Severe	Yes	√	√	-	Expired	Broadaseptate branching hyphae
5.	Revannavar et al.[8]	NA	Incidental	Yes	Mild	No	√	√	-	Improved	Rhizopus sp
6.	Sarkar et al.[9]	45.5	NA	10/ 10	Severe (9/10)	Yes	10	9	1	Improved (6/10)	Rhizopus-4/10 mucor-2/10 negative-4/10
7.	Shirke et al.[10]	51.5	NA	2/ 4	NA	NA	√	√	-	NA	Rhizopus sp in 1/ 4
8.	Mehta et al.[11]	60	13 days	Yes	Severe	Yes	√	√	-	Expired	Broad aseptate filamentous fungal hyphae
9.	Sen et al.[12]	60.5	15.6 days	Yes	Moderate severe	5/ 6	6	6	5	Improved	Fungal-mucor S/0 mucor in 4/ 6
10.	Patil et al.[13]	55.75	NA	3/ 4	NA	NA	√	√	-	NA	NA

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11.	Deshmukh et al.[14]	39	NA	Yes	Asymp tom-atic	No	√	-	-	Improved	NA
		43	30 days	Yes	NA	Yes	√	-	-	Improved	NA
		50	60 days	Yes	NA	Yes	√	√	-	Improved	NA
12.	Moo-rthy et al.[15]	54.6	NA	16/ 18	NA	15/ 18	18	15	9	Improved: 11/18 expired: 6/18 lost to F/U: 1/18	Mucor-16/18, aspergillus-1/18 mixed: 1/18
13.	Maini et al.[16]	38	18 days	No	Mild	Yes	√	√	-	Improved	Rhizopus oryzae
14.	Satish et al.[17]	NA	NA	NA	Mode-rate severe	NA	25	18	6	NA	NA
15.	Mishra et al.[18]	55.8	NA	8/10	Mild	6/10	√	√	-	Improved: 5/10 lost to F/U: 1/10 expired: 4/10	NA
16.	Mes-hram et al.[19]	47	7 days	Yes	Mild	No	√	√	-	Expired	NA
17.	Ravani et al.[20]	56.3	60 days	30/31	Vari-able	19/31	31	31	7	Improv-ement: 28/31 expired: 3/31	NA
18.	Nehara et al.[21]	62.2	12 days	Yes	Mode-rate severe	Yes	5	5	3	Expired: 2/5 improved: 3/5	Rhizopu-sarrhizus
19.	Shah et al.[22]	55	109 days	2/4	Mode-rate severe	Yes	4	3	-	Improved	NA
20.	Rao et al.[23]	66	15 days	Yes	Mild	Yes	√	√	-	NA	S/O mucor
21.	Mekonnen et al.[24]	60	8 days	Yes	Severe	Yes	√	√	-	Expired	Rhiz-opus sp
22.	Werthman-Ehrenreich[25]	33	2 days	Yes	Mode-rate	NA	√	√	√	Expired	Extensiv-ehyphae, yeast, staph aureus
23.	Waizel-Haiat et al.[26]	24	NA	Yes	Severe	Yes	√	√	-	Expired	Lichteimia (Absidia) spp

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24.	Paul et al.[27]	50	8 days	Yes	Mild	No	√ (Palate)	-	-	Improved	Nonseptatehyphae with RT angle branching
25.	Tabarshi et al.[28]	50	5 days	Yes	Moderate	Yes	√	√	-	Improved	Rhizopus oryzae
26.	Karimi-Galougahi et al.[29]	61	17 days	No	Moderate	Yes	√	√	√	NA	NA
27.	Ahmadikia et al.[30]	44	20 days	Yes	Mild	Yes	√	-	-	Improved	Rhizopus oryzae
28.	Veisi et al.[31]	40	8 days	No	Moderate	Yes	√	√	√	Expired	Mucor
		54	7 days	Yes	Severe	Yes	√	√	-	Improved	Nonseptatehyphae with branching
29.	Alekseyev et al.[32]	41	7 days	yes	Mild	Yes	√	√	√	Improved	NA
30.	Sargin et al.[33]	56	7 days	Yes	Moderate	Yes	√	√	√	Expired	NA
31.	Arana et al.[34]	62	14 days	Yes	Severe	Yes	√	√	-	Improved	Rhizopus oryzae
32.	Pakdel et al.[35]	51.7	12.2 days	13/15	Moderate severe	7/15	√	√	-	Improved: 8/15 Expired: 7/15	NA
33.	Farid et al.[36]	53	2 days	Yes	Mild	Yes	√	√	-	Expired	NA

Discussion

The term 'mucormycosis' was coined by American pathologist RD Baker, describing the disease caused by fungi belonging to the phylum glomeromycota and subphylum mucoromycotina according to the newer taxonomy of fungi (2007).[37] The first case in humans was first reported by German pathologist Paltauf in 1885, while the first case of rhino-orbital cerebral mucormycosis was described by JL Gregory in 1943. However, it wasn't until 1955, the first known survivor was reported by Harris.[38]

Mucormycosis is caused by a group of thermoresistant, filamentous fungi of the order mucorales that are ubiquitous in the environment, often growing in soil and decaying organic matter. It morphologically appears as broad, aseptate or sparsely septate ribbon-like hyphae with right-angled branching. It may be acquired through inhalation of fungal spores (10-20 micrometres in diameter), traumatic inoculation or through the percutaneous route.

Although rare, gastrointestinal mucormycosis is caused by ingestion of food items contaminated by mucorales spores.[38,39] However, the entry of these spores in healthy individuals results in phagocytosis by polymorphonuclear phagocytes and thereby clearance of infection. But conditions like hyperglycemia and acidosis affect chemotaxis and phagocytic killing by immune cells, thus facilitating the growth of the hyphal form of these saprophytic fungi in the tissues.

The true incidence as well as, the prevalence of the global burden of mucormycosis is undetermined, as many of these cases pose a diagnostic challenge. According to a Leading International Fungal Education (LIFE) portal in the pre-COVID era, the annual prevalence of mucormycosis could be around 10,000 cases. With the inclusion of Indian data, the global estimate of mucormycosis rose to 910,000 cases.[39]

The principal risk factors for mucormycosis in immunocompromised host include diabetes mellitus with

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or without ketoacidosis, haematological malignancies, solid organ/ stem cell transplant, chronic kidney or liver disease, immunological disorders, and prolonged corticosteroid therapy. However, in immunocompetent patients, major trauma, use of contaminated materials during surgery, prolonged ICU stay, intravenous drug use and desferrioxamine therapy constitute the major risk factors.[40,41] In contrast to haematological-malignancy patients and solid organ transplant recipients in developed countries, uncontrolled diabetes mellitus is the most common underlying disease associated with mucormycosis in India.

A recent multicentre study from India reported that 77% of rhino-orbital cerebral mucormycosis cases were in the diabetic population.[42]

Pathogenesis of post-COVID mucormycosis can be categorised based on local and systemic factors. Local factors include nasal mucosal breach and endotheliitis induced by the coronavirus, which provide a portal of entry for the fungi. Delayed mucociliary clearance due to viral activity can also aid in the festering of the fungus in the nasal mucosa. Systemic factors include uncontrolled hyperglycaemia and iron dysregulation.[43] The role of glucose receptor protein, GRP78 has also been elucidated in the pathogenesis of COVID-associated mucormycosis.[44]

The unmasked burden of diabetes mellitus in the population has unlocked a secret portal of susceptible immunocompromised individuals. This has greatly contributed to the huge number of cases seen in the Indian subcontinent. Hyperglycaemia and associated ketoacidosis create an acidic environment, which serves as a fertile medium for the growth of mucor spores. Furthermore, the use of corticosteroids reduces polymorphonuclear cell phagocytic activity, impairing bronchoalveolar macrophage migration, ingestion, and phagolysosome fusion, making a diabetic patient particularly vulnerable to mucormycosis.

Free serum iron is an ideal resource for the growth of mucormycosis. Hyperglycaemia causes glycosylation of transferrin and ferritin thereby reducing their iron binding capacity. High cytokine levels in patients with COVID-19 increase ferritin levels. These factors lead to an overall increase in free serum iron levels.[45]

High glucose, low pH, free iron and ketones in presence of decreased phagocytic activity of WBC facilitate the growth of mucor. Additionally, it increases the production of glucose-regulator protein 78 (GRP-78) in endothelial cells, which promotes tissue necrosis, haematogenous spread, and angiogenic invasion.[46]

This propensity for angioinvasion manifests in immunocompromised hosts as an acute, necrotic, rapidly progressive disease that may prove fatal if not intervened quickly.[40] The clinical presentations of mucormycosis are classified as Rhino-Orbital-Cerebral (ROC), pulmonary, gastrointestinal, cutaneous, renal and disseminated. In India, ROC mucormycosis is the most common clinical presentation followed by pulmonary and cutaneous types.[42]

In a meta-analysis by Roden et al., 929 reported cases of mucormycosis since 1885 were analysed. It was observed that sinus infection was the most common presentation (39%), followed by pulmonary (24%) and cutaneous (19%) infections. Dissemination was reported in 23% of cases.[47]

Clinical presentation from sino-nasal involvement includes low-grade fever, headache, unilateral brownish, thick, purulent nasal discharge, hypoesthesia of maxillary region and facial swelling. The subsequent involvement of contiguous skin surrounding the nose results in ulceration with blackish discolouration of the skin. Palatal involvement presents as blackish necrotic ulceration of the hard palate respecting the midline associated with the loosening of teeth of the affected side of the arch. Discolouration or soft boggy swelling in the palate can also be seen in the early stages.

The spread of the infection to the eye is common and carries a poor prognosis. Orbital pain, diminution of vision, restricted eye movements, diplopia, lid oedema, proptosis, chemosis, corneal ulceration or total blindness can result, depending upon the extent of involvement. A fundoscopic examination may reveal occlusion of central retinal vessels. The fungus has a predilection for blood vessels and nerves rather than muscles leading to infarction of the invaded area. An intracranial extension can occur through the cavernous sinus, olfactory cleft, or anterior or lateral skull base leading to loss of cranial nerve function, obtundation of cerebral function and contralateral hemiplegia. Lethargy, seizures and coma are usual complications of brain involvement.[40]

Because of the dreadful prognosis, even a minute suspicion of the disease should prompt the clinician to investigate the patient for mucormycosis to avoid any further delay in diagnosis and treatment. A diagnostic nasal endoscopy should be performed on the first visit and tissue samples should be obtained for direct microscopic examination and fungal (KOH) stain with culture. Radiological imaging helps in assessing the extent of disease and identification of complications and is indispensable for surgical planning. In contrast, enhanced MRI images, T2W signal as well as enhancement patterns are variable with around 20% of patients showing hyperintense T2 signal and thus are not reliable markers of invasive fungal infections. Careful attention to extra sinus extension in the form of fat stranding in the premaxillary, retroantral fat, orbital fat and altered intensities in pterygopalatine fossa is more important to suggest the diagnosis of invasive fungal sinusitis.[48] Gamba

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et al. reported that bone destruction was unusual and seen late even with spread beyond the paranasal sinuses.[49]

The four cornerstones in the management of mucormycosis include:

a) Early recognition and diagnosis of infection
b) Prompt initiation of antifungal therapy (Amphotericin B/ Posaconazole/ Isavuconazole)
c) Surgical debridement of the necrotic tissue
d) Rapid reversal of underlying risk factors

Surgery includes resection of infarcted tissues, radical debridement and adequate drainage of all the paranasal sinuses. Revision debridement may be required in cases with extensive involvement and the patient should be kept under vigilant post-debridement care for early detection of recurrence.

The first line of anti-fungal therapy includes liposomal amphotericin B 5-10 mg/ kg/ day. The dose is tapered as necessary, if renal toxicity occurs. The calculated daily dose should be initiated from the first day itself rather than gradually increasing the dose. Amphotericin B lipid complex 5 mg/ kg/ day can be used for patients without CNS involvement. The use of deoxycholate salt is discouraged whenever alternatives are available due to substantial toxicity. Isavuconazole is strongly supported as a salvage treatment. Apart from it, posaconazole either in oral suspension or sustained release tablet form is used as a step-down therapy for 3-6 months.[50,51] The exact dose and duration of drugs needed are not defined. An optimal treatment takes at least 8-10 weeks until the resolution of symptoms. The usual total dose is 2-4 g.[40]

The review article by Roden et al. mentions that the survival rate is 61-67% with antifungal therapy, 57% with surgery, and 70% with combination therapy of surgery and antifungal treatment. With the use of modern antifungals and surgical procedures, mortality has dropped from around 100% in the 1940s to about 40% in the most recent research.[47]

Conclusions

A rapid rise in the cases of mucormycosis in COVID/ post-COVID status all over the globe has imposed a great medical, social and economic burden on the patient, all the while adding to the already overstretched capacity of healthcare infrastructure worldwide. Unwarranted use of steroids coupled with unchecked steroid-induced hyperglycaemia along with endothelial damage, lymphopenia, unregulated activation of inflammatory mediators and overactivation of entry-point receptors, inflicted by the novel Coronavirus cause a state of immune dysregulation leading to opportunistic invasive fungal infections. Delay in diagnosis/ treatment can cost a huge price to the patients in the form of disfigurement, functional loss or even death. Hence, controlled use of steroids with the maintenance of a normoglycemic state can significantly decrease the risk of acquiring this deadly fungus. Also, a high index of suspicion and low threshold for investigations can lead to early diagnosis and prompt initiation of treatment for mucormycosis by the treating physician resulting in better clinical outcomes. Multidisciplinary management involving otolaryngologists, ophthalmologists, neurologists, and endocrinologists is thus recommended.

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