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Review Article

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Coronavirus Diseases (covid -19) and Mucormycosis: A Mini-Review

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ABSTRACT

Introduction: Mucormycosis is an opportunistic infection emerging as a major public health problem during COVID-19 pandemic. Predisposing factors such as Diabetes mellitus (DM) as well as use of corticosteroids in COVID-19 patients act as a key role for the surge of the disease. However, the epidemiological factors, site of the infections, demographic details, morbidity and mortality of the patients were not well documented, so we under took the study to review the published original articles, case series and case report on mucormycosis associated with COVID-19 with predisposing factors such as DM and the use of corticosteroids,

Methods: On analysis of 30 articles from India as well as from other countries.

Results: After analysis of the available data, it was found that mucormycosis predominantly seen in male in the age of 50±5. The common site of the infection was rhino-orbital mucormycosis followed by rhino orbital cerebral. Pre-existing DM was the most significant risk factors followed by corticosteroid treatment along with hospitals supplied oxygen to patients. Hospital environment also play a significant role for the sudden rise of the disease.

Conclusion: To overcome this severe situation in future, there is need to maintain optimal hyperglycemia in population, avoid overuse of corticosteroid and proper hospital infection control (HIC) program in order to reduce the burden of fatal mucormycosis.

Key Words: Mucormycosis, COVID-19, Diabetes Mellitus, Corticosteroid, HIC, Oxygen

INTRODUCTION

Severe acute respiratory syndrome Coronavirus -2 (SARS-CoV-2) Infections has been associated with wide range of opportunistic infection.[1] Bacterial as well as fungal infections were reported in patients with corona viral diseases. Mucormycosis one such opportunistic infection which shows sudden rise in covid 19 second wave in India.[2] There are several mechanism that appears to be facilitating Mucorales spores to germinate in people with COVID-19 is an environment of low oxygen (hypoxia), diabetes high glucose (diabetes, metabolic acidosis, diabetic keto-acidosis [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 co morbidities) along with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators. [3]

It has been found that the prevalence of mucormycosis is nearly 80 times higher in India in compare with other developed country in COVID 19 era this might be due to the presence of highest number of diabetic patients in Indian population with this long-term use of corticosteroids were also considered as important risk factor for the sudden spike of mucormycosis in Indian population.[3,4,5,6]

These findings need to be re-look in the context of COVID19 pandemic hence we conduct a systemic review of published case report/ case series of mucormycosis in people with COVID19 who have DM and treated with corticosteroids.

METHODS

A systematic literature search of Medline, PubMed, and Google Scholar was done using the term “COVID 19 and Mucormycosis, SARS COV-2 and Mucormycosis, Zygomycosis, Phycomycosis, Mucorales, COVID-19 and Diabetes mellitus. On the basis of title and available abstract, articles were including for the selected topics. For the study only those articles have included their abstract in English. Of the published articles, 38 original articles and 12 reviewed were

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excluded in which studies were mainly focused on COVID 19 and mucormycosis.

Overall 30 original articles / case report was found in Medline, PubMed, and Google Scholar. Of the total of 30articles 14 were from India where overall 75 mucormycosis cases were documented.

Diabetic mellitus and corticosteroid as risk factors:

Sharma et al. studied mucormycosis cases in COVID 19 patients where they found 21 patients were diabetic and all the patients were under Steroid treatment, on analysis of the prognosis they have found all of them were recovered from COVID 19 as well as mucormycosis.[7]

Yet in another study by Moorthy et al. from Bangalore of 17 COVID 19 patients with mucormucosis had found 15 patients were diabetic and also under steroid treatment. The mortality rate was 40% which were high in compare to other studies.[8]

Another study in Iran by Pakdel F et al. was reported fifteen cases of rhino-orbital mucormycosis in COVID-19 patients. The median age of patients was 52 years (range 14-71) and 66% were male. The median interval time between COVID-19 disease and diagnosis of mucormycosis was seven (range: 1-37) days. Among all, 13 patients (86%) had diabetes mellitus, while 7 patients (46.6%) previously received intravenous corticosteroid therapy. Five patients (33%) underwent orbital exenteration, while seven (47%) patients died from mucormycosis. Six patients (40%) received combined anti-fungal therapy and none that received combined anti-fungal therapy died.[9]

Another study in USA by Dallalzadeh et al. reported one confirm cases of mucormycosis in COVID 19 patients with DM and Steroid were act as an important risk factor. [10]

There were many other case studies/ series from India reported that Diabetic mellitus and Steroid treatment were two important risk factors of mucormycosis in COVID 19 infected patients which all are summarize in table 1.

On analysis of the pooled data from all the studies showed mucormycosis was predominantly seen in males and mean age were 50±5years, the common site of the infection was rhino- orbital mucormycosis followed by rhino orbito cerebral. Pre-existing DM was the most significant risk factors followed by corticosteroid treatment. While considering the mortality rate the pooled data shows about one in three patients were expired due to mucormycosis.

DISCUSSION

Mucormycosis which is extremely rear in healthy population but can be coupled with immunocompromised condition such as malignancies, organ transplantation prolonged neutropenia , immunosuppressive and corticosteroid therapy, iron overload, AIDS, even with malnutrition and uncontrolled DM. Mucormycosis can infects in nose, sinuses, orbit, central nervous system (CNS), lung (Upper &Lower respiratory Tract), gastrointestinal tract (GITract), skin, jaw bones, joints, heart, kidney and media stinum, but rhino-orbital- cerebral mucormycosis is the commonest variety seen in clinical practice worldwide. [11] Based on our literature study it's revealed that it appears by the intersection of two crises: one is the use of corticosteroid in COVID 19 patients and the other of poorly controlled DM in the settings of pandemic. In addition to this an alternation iron metabolism occurs in severe COVID 19 which lead to cause hyper ferritin emic syndrome, studies have shown that high ferritin levels lead to excess intracellular iron that generates reactive oxygen species resulting in tissue damage. Cytokines, especially IL-6, due to severe infection and DKA, stimulate ferritin synthesis and down regulate iron export resulting in intracellular iron overload, further exacerbating the process.[12] The resultant tissue damage leads to the release of free iron into the circulation.[13] Iron overload and excess free iron seen in academic states are one of the key and unique risk factors for MCR.[14] However more details study is required to conclude that high ferritin level is directly involved in mucormycosis or whether its act as a modulator of the diseases. [15]

It has been observed that in second wave of COVID 19 there were huge demands of 'industrial oxygen' to address the lack of oxygen supply chain for medical use. Hence, proper handling and sanitization of oxygen gas cylinders in hospital/ home use is of utmost importance. Hospital environment also play an vital role in mucormycosis as its found Fungal pathogens are present in bed bars and headers, taps, bedside table and other places of hospitals. This problem can be suppressed by proper hospital infection control measures adopting hand washing measures by healthcare workers and decontaminating high-contact hospital surfaces. There is another factor which may also played an important role such as reusable oxygen humidifiers in the transmission of potential nosocomial pathogens via the generation of aerosol particles, for they reach deep into the lung immediately after inhalation, care should be taken for appropriate maintenance of reusable ones. Besides, clean distilled water should be used in humidifiers during oxygen therapy in COVID-19 patients.[30]

People requiring oxygen support at home should ensure the use of clean distilled water in oxygen concentrators. Over use of steam inhalation, as well as non-humidified oxygen, can lead to damage of the respiratory mucosa, allowing easy penetration of the fungal spore in COVID-19 positive individuals. Continued use of facemasks would reduce the chances of re-infection with SARS-CoV-2 and minimize the risk of inhalation of fungal spores. However, reusing the same masks for 2–3 weeks may increase the risk of acquiring mucormycosis.

CONCLUSION

It is found that uncontrolled diabetes mellitus, inappropriate steroid therapy, self-medication and high lode of fungal spore in the hospital environment were responsible for mucormycosis in COVID 19 era. So, there are needed to make efforts to maintain hyperglycemia, proper use of corticosteroids in patients with COVID-19 and hospital sanitization in order to reduce the burden of fatal mucormycosis.

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Table 1: summary of the COVID-19 associated mucormycosis reported in the literature:

Author	Number of cases	Country	sex	age	Diabetic	Under Steroid treatment	Location of mucormycosis	Outcome
Mehta et al.[16]	1	India	M	60	DM	YES	Nasal, Orbit	Death
Garg et al.[17]	1	India	M	55	DM	YES	Lung	Recovered
Satish et al. [18]	11	India	NA	30-74	DM (N=8)	YES (N= 6)	Nasal/Sinus/Bone	Death (N=4) Recovered (N =5) Lost to follow up (N=1)
Saldanha et al.[19]	1	India	F	32	DM	NO	Nasal/sinus	Recovered
Singh SP et al. [20]	6	India	M=5, F=1	30-55	DM	YES (N= 4)	Rhino-orbital	Death (N =1) Recovered (N= 5)
Moorty A et al.[8]	17	India	M=15, F=2	35-73	DM (N=15)	YES (N =15),	Rhino-orbital(N=6) Rhino orbito cerebral (N= 5), Rhinocerebral(N=3), Rhino sinusal (N=3)	Death (N =6) Recovered (N=10) NA (N=1)
Nehara HR et al.[21]	5	India	M=1, F=4	52-70	DM (N=5)	YES (N=4)	Rhino-orbito cerebral (N=5)	Death (N=2) Recovered (N=3)
Sarkar S et al. [22]	10	India	M=8, F=2	23-67	DM (N=10)	YES (N=10)	Rhino-orbital (N= 10)	Death (N =4), Recovered (N=6)
Sharma S et al.[7]	23	India	M=15, F=8	NA	DM (N=21)	YES (N=23)	Rhino orbitocerebral (N=2), Rhino-orbital (N=8), Rhino sinusal (N=13)	Recovered (N=23)
Hanley et al.[23]	1	UK	M	22	NIL	NO	Lung	Death
Mekkonenet al.[24]	1	USA	M	60	DM	YES	Nasal/ Sinus	Death
Monte junior et.al[25]	1	Brazil	M	86	NIL	NO	GIT	Death
Bayram N et al.[26]	11	Turkey	M=9; F=2	61-88	DM (N=8)	YES (N=11)	Rhino-orbital	Death (N =7) Recovered (N=4)
Alekseyev K et al.[27]	1	USA	M	41	DM	YES	Rhino-cerebral	Recovered
Johnson AK et al. [28]	1	USA	M	79	DM	YES	Pulmonary	Recovered
Karimi Galougahi M et al. [29]	1	Iran	F	61	DM	YES	Rhino-orbital	Recovered