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Increasing Incidence of Mucormycosis: A Systemic Review of Case Reports

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Abstract

There are increasing in reports of mucormycosis in the post COVID-19 patients especially in India. Diabetes mellitus plays a vital role in both severe COVID-19 and mucormycosis. Our aim is to review a literature to find out the patient's characteristics having mucormycosis and COVID-19 with the source of electronic database of Google Scholar and PubMed for the search of review. We have analyzed the data and characteristics of post COVID patients with mucormycosis. Overall, we have collected 288 cases from 50 articles and analyzed. We additionally reviewed why this mucormycosis majorly affects India and mentioned what are all the causes that affect in post-COVID patients. The post-COVID patients with uncontrolled diabetes must be altered and aware with disease mucormycosis.

Keywords: Diabetes mellitus; Mucormycosis; Post-COVID patients; Electronic database

Introduction

Mucormycosis is a rare type of fungal infection that occurs through exposure to fungi called mucormycetes. These groups of fungi are commonly occurring in the environment, particularly in all plant surfaces, soil, compost and animal dung. The infection caused by fungi belonging to the order Mucorales. Mucormycetes can enter the body through breathing, inhaling and exposed wounds in the skin. Fungi that most commonly cause mucormycosis are *Rhizopus sp*, *Mucor sp*, *Rhizomucor sp*, *Syncephalastrum sp*, *Cunninghamella Bertholletia*, *Apophysomyces sp* and *Lichtheimia sp*. There are five types of mucormycosis, such as rhinocerebral (sinus and brain) infection in the sinuses that can spread to the brain. This is most common in people with uncontrolled diabetes and in people who have had a kidney transplant, pulmonary (lung) infection is the most common type of mucormycosis in people with cancer and in people who have had an organ transplant or a stem cell transplant, gastrointestinal mucormycosis is more common among young children than adults, especially premature and low birth weight infants less than 1 month of age, who had antibiotics, surgery or medications that lower the body's ability to fight germs and sickness, cutaneous (skin) mucormycosis occurs after the fungi enter the body through a break in the skin (after surgery, a burn, or other type of skin trauma). This is the most common form of mucormycosis among people who do not have weakened immune systems and disseminated mucormycosis occurs when the infection spreads through the bloodstream to affect other part of the body. The infection most commonly affects the brain, but also can affect other organs such as the spleen, heart and skin. For mucormycosis, precautions are debatable with respect to their efficacy in preventing these infections. But the main goal is prevention, which will require ensuring a good immune system, especially in those who are post-COVID-19. However strict monitoring of diabetes and avoiding dead/decaying organic matter will helps [1].

The major risk factors for mucormycosis include uncontrolled diabetes mellitus in ketoacidosis, other forms of metabolic acidosis, treatment with corticosteroids, organ or bone marrow transplantation, neutropenia, trauma and burns, malignant hematologic disorders, and deferoxamine therapy in patients receiving hemodialysis [2]. Higher rates of mucormycosis cases in India are due to a combination of COVID-19 and diabetes mellitus. For instance, more than 30 million people in India have a diabetes diagnosis. While the country is still dealing with COVID-19 pandemic, cases of black fungus or mucormycosis are on the rise in the country. Meanwhile, cases of white fungus and yellow fungus have also been reported from some parts of the country [3].

However steroids reduce inflammation in the lungs for COVID-19 and appear to help stop some of the damage that can happen when the body's immune system goes into overdrive to fight

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off coronavirus. But they also reduce immunity and push up blood sugar levels in both diabetics and non-diabetic COVID-19 patients. It's thought that this drop in immunity could be triggering these cases of mucormycosis. Unchecked level of blood sugar, abuse of steroids during COVID treatment is being considered as the reasons for this outbreak. Fighting the coronavirus can leave people's immune systems compromised or weakened, which means they may have a higher chance of developing mucormycosis [4].

Black fungus is Mucor fungus occurs, when the immunocompromised patient comes in contact with the Mucor fungus, which spreads to the eyes, nose, lungs and skull cavity. Though non-contiguous, it can be deadly if not treated on time. It mainly affects lungs, respiratory system and digestive tract. White fungus is Candida fungus which begins from the tongue or private parts, it makes the patchy tongue white, and then it spreads to other parts like the lungs, brain and food pipes. It also affects face, nose, and eye orbit and skull tissue. The yellow fungus starts internally, causes pus leakage and leads to slow healing of wounds. In severe cases, it could further lead to organ failure and serious necrosis [5]. The primary reason that appears to be facilitating Mucorales spores to germinate in people with COVID-19 is an ideal environment of low oxygen, high glucose, acidic medium, high iron levels and decreased phagocytic activity of white blood cells 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. Globally, the prevalence of mucormycosis varied from 0.005 to 1.7 per million populations, while its prevalence is nearly 80 times higher (0.14 per 1000) in India compared to other developing countries, in a recent estimate of year 2019 to 2020. In other words, India has highest cases of the mucormycosis in the world [6]. These prompted us to conduct a systematic review of published case reports of mucormycosis in people with COVID-19, to know overall characteristics of patients with its outcome. We additionally reported why this cause largely in India.

Diabetes Mellitus Impact on Mucormycosis

The lethal combination of high COVID-19 caseload in a country with around 70 million diabetes patients in India and when as part of dealing with COVID-19 steroids are administered. India is already having second largest population with diabetes mellitus and was the diabetes capital of the world, until recently. The probable reasons include a delay in diagnosis and the high cost of managing mucormycosis. Importantly, diabetes mellitus has been the most common risk factor linked with mucormycosis in India, with an overall mortality of 46% [6]. The reason we are seeing such large number of mucormycosis than in any other country is because of the high number of diabetic patients, that too with uncontrolled diabetes, record number of COVID cases, large doses of steroids being administered for too long bordering onto indiscriminate use of steroids. To cause infection, these fungal spores will typically enter the respiratory tract through inhalation; however, they can also enter host cells through the skin as a result of trauma or through accidental ingestion. As previously mentioned, patients with diabetes mellitus are at the highest risk of developing mucormycosis [3].

More specifically, the most frequent presentation of this fungal infection in patients with diabetes mellitus is rhino-orbital-cerebral mucormycosis. First and foremost, patients with diabetes mellitus often exhibit impaired innate and adaptive immunity, which increases their susceptibility to any type of infection, particularly mucormycosis, as this infection is rarely seen in non-immunocompromised hosts. Upon exposure to Mucorales spores, a competent immune system will send macrophages to engulf spores and prevent their germination. Comparatively, diabetes mellitus patients often have altered phagocytic pathways, thus rendering macrophages unable to phagocytize these spores. As a result, the free spores swell and form buds throughout the blood vessels of the respiratory tract. Although polymorph nuclear cells are recruited to these areas, these cells often exhibit an impaired function in diabetes mellitus patients, which limits their ability to prevent the proliferation of Mucorales. As a result, the fungal spores are able to extensively invade tissues and large blood vessels. In addition to the altered immune system in diabetes mellitus patients that allows for the proliferation of Mucorales fungi, both the iron and pH levels of diabetes mellitus patients can also contribute to the development of mucormycosis. When the pH of human serum is reduced, which often occurs in ketoacidosis, mucorales can disrupt the iron-binding capacity of transferrin. This disrupted function in transferrin, therefore, allows for free iron to be released into the serum, which can be readily used by the Mucorales spore to thrive in these environments [7].

In addition, oxygen support for people with severe COVID-19 can cause drying of the nasal cavity and further increase the risk of infection. The lack of immunity allows the fungus to spread, invade and destroy tissue. The recent pandemic of COVID-19 infection has led to a large number of people suffering severe illness, which has left them to have the following issues prolonged ICU stay, high blood sugars and prolonged oxygen use. Previously the patients were getting inflicted with these diseases. Amongst the diabetic patients, poorly controlled type II diabetes mellitus is the most common risk factor for mucormycosis, mainly from north to south India, with nearly half of them exhibiting ketoacidosis. It should be noted, however, that as confounding factors, renal failure and alcoholism related chronic liver disease have also been detected in patients along with diabetes in India. The probable reasons include a delay in diagnosis and the high cost of managing mucormycosis. Post coved patients with uncontrolled diabetes must be altered and aware with disease mucormycosis [4].

Methods

A systematic literature survey was conducted through electronic database of Google Scholar and PubMed until November 19th, 2021 using keyword COVID-19, and Mucormycosis, Zygomycosis, Mucorales, Mucor and Rhizopus. Details of all the cases that reported mucormycosis in people with COVID-19 so far were retrieved. Characteristics of each patient was collected on excel sheet and analyzed [6].

Results

Overall, we have collected 38 articles from the database of PubMed (30/50) and Google Scholar (20/50). A total of 288 cases of mucormycosis in people with confirmed COVID-19 were retrieved. Largely, 172 cases (59.72%) of mucormycosis in patients with COVID-19 were reported from India, followed by 52 cases (18.05%) from USA and 22 cases (7.63%) from Iran. Only 37 (12.84%) cases were reported from other parts of the world as shown in Table 1. Data from this study showed mucormycosis was predominantly seen in 209 male cases (72.56%), and in female 79 cases (27.43%). Majority of the cases were recorder with diabetes mellitus and hypertension.

Table 1: Mucormycosis and COVID-19 cases reported in selected countries.

S. No	Countries	No. of Cases	Percentage of cases (%)
1	India	172	59.72
2	USA	52	18.05
3	Iran	22	7.63
4	Egypt	16	5.55
5	Turkey	12	4.16
6	Europe	4	1.38
7	Spain	4	1.38
8	Pakistan	1	0.34

History of diabetes mellitus and intake of steroid for COVID-19 are the major reason for mucormycosis [51-58]. Number of mortality was reported as 73 cases (25.34%) and case reports were shown in Table 2.

Discussion

The epidemiology of mucormycosis in India is intriguing, and varies significantly from the developed countries. The estimated number of cases in India seems to be alarmingly high, with uncontrolled diabetes being the most important risk factor. The risk factors for mucormycosis differ significantly amongst the developed and developing countries. Nearly 60% of the mucormycosis cases reported from India are in patients with uncontrolled diabetes, with or without Ketoacidosis. The distribution of risk factors varies across geographical regions, as uncontrolled diabetes is the most common underlying disease found in India studies. Mortality associated with mucormycosis in India is considerably high due to delays in seeking medical attention and diagnosing the disease, and challenges in managing the advanced stage of infection. The diagnosis is thus often delayed, which result in poor outcomes despite the availability of better diagnostic and therapeutic tools. Multidisciplinary approach is essential for prompt diagnosis and management of mucormycosis. It is necessary to study the role of newer antifungal agents such in the treatment of mucormycosis.

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Table 2: Details of mucormycosis reported cases up to August 19th, 2021.

S. No	No. of Cases	Age	Gender		Type of infection	Current Status	Reference
			M	F			
1	1	56	-	1	Rhino orbital mucormycosis	Expired	[8]
2	23	-	15	8	Sinusitis	Alive	[9]
3	25	30-74	22	3	12- Rhino orbital mucormycosis 6- Rhino orbito-cerebral-mucormycosis 7-pulmonary mucormycosis	2 Expired	
4	10	37-78	9	1	7- Rhino orbital mucormycosis 2- Pulmonary mucormycosis 1-Rhino orbito-cerebral-mucormycosis	4 Expired	[10]
5	1	55	1	-	Pulmonary mucormycosis	Alive	[3]
6	1	60	1	-	Rhino orbital mucormycosis	Expired	[11]
7	18	35-73	15	3	Rhino orbital mucormycosis	6 Expired	[12]
8	1	24	-	1	Rhino orbital mucormycosis	Alive	[13]
9	2	40-54	1	1	Rhino orbital mucormycosis	1 Expired	[14]
10	1	61	-	1	Rhino orbital mucormycosis	Alive	[15]
11	1	Middle age	-	1	Rhino orbital mucormycosis	Alive	[16]
12	1	60	1	-	Rhino orbital mucormycosis	1 Expired	[11]
13	12	16-69	6	6	Rhino orbito-cerebral-mucormycosis	6 Expired	[17]
14	1	56	1	-	Rhizopus azygosporus	Expired	[18]
15	1	66	1	-	Pulmonary Mucormycosis	Alive	[19]
16	1	38	1	-	Sino-orbital mucormycosis	Alive	[20]
17	1	33	-	1	Orbital compartment syndrome	Expired	[21]
18	1	49	1	-	Pulmonary mucormycosis	Alive	[22]
19	1	55	1	-	Not mentioned	Expired	[23]
20	1	44	-	1	Not mentioned	Alive	[24]
21	1	60	1	-	Rhino orbital mucormycosis	Expired	[25]
22	1	53	1	-	Pulmonary Mucormycosis	Expired	[26]
23	31	20-80	20	11	Rhino orbital mucormycosis	3 Expired	[27]
24	43	46-61	34	9	Rhino orbital cerebral mucormycosis, Rhino orbital mucormycosis, Sinusitis, Pneumonia	20 Expired	[28]

25	1	68	1	-	Cuteneous mucormycosis	Expired	[29]
26	1	79	1	-	Pulmonary mucormycosis	Alive	[30]
27	1	32	-	1	Orbital apex syndrome secondary to mucormycosis	Alive	[31]
28	4	50-70	4	-	Secondary mucormycosis	3 Expired	[32]
29	2	48-62	2	-	Rhinosinusal mucormycosis, Mucoskelatal.	Alive	[33]
30	1	44	-	1	Pulmonary mucormycosis	Expired	[34]
31	11	61-88	9	2	Rhino orbital mucormycosis	7 Expired	[35]
32	1	22	1	-	Mucormycosis	Expired	[36]
33	1	66	1	-	Rhino orbital mucormycosis	Alive	[37]
34	1	86	1	-	Mucormycosis	Expired	[38]
35	1	41	1	-	Rhinocerebral mucormycosis	Alive	[39]
36	5	52,70	1	4	Rhino orbital Mucormycosis and Sinusitis	1 Expired	[40]
37	2	48,62	1	1	Mucormycosis	Alive	[33]
38	1	28	1	-	Mucormycosis	Alive	[41]
39	15	14-71	10	5	Rhino orbital mucormycosis and rhino cerebral orbital mucormycosis	8 Alive and 7 Expired	
40	47	55 ± 12.8	35	12	Rhino orbital mucormycosis and rhino cerebral orbital mucormycosis	8 Expired and 39 Alive	
41	1	61	-	1	sinusitis mucormycosis	Expired	[42]
42	4	59-80	3	1	Rhino cerebral orbital mucormycosis	3 Alive 1 Expired	[43]
43	1	73	-	1	Mucormycosis in mouth	Alive	
44	1	48	1	-	Gastrointestinal Mucormycosis	Alive	[44]
45	1	67	1	-	Rhino orbital mucormycosis	Alive	[45]
46	1	57	-	1	Mucormycosis	Expired	[46]
47	1	32	1	-	Renal Mucormycosis	Alive	[47]
48	1	59	1	-	Mucormycosis	Alive	[48]
49	1	50	-	1	Sinusitis mucormycosis	Alive	[49]
50	1	94	1	-	Cutaneous Mucormycosis	Alive	[50]

M: Male; F: Female

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