



Fulminating Fungal Infections Complicating Covid19 Recovery in India

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Abstract

The cases of mucor mycotic infections are on the rise in the wake of rise in Covid 19 cases and recovery since a month or so in India. As of end June 2021, India has recorded over 40845 cases across the country. Among all the opportunistic fungus worldwide Aspergillosis is the most common variety. Globally outbreaks of mucor mycosis have occurred due to contaminated products such as hospital linens, medications, and packaged foods. Three types of fungi colloquially called as Black, White, and yellow fungus have identified. While the black fungus infection is the most prevalent both as single and combined infections, the other 2 are reported along with the black fungus recently. Misuse of steroids in managing Covid 19 cases especially among diabetics is attributed playing a major role behind this infection. Other contributory factors being blamed are long stay in ICU, unclean water used is dehumidifiers of the Oxygen cylinders and ventilators, unclean masks and going in the dusty construction sites after recovery from the Covid 19 infection. The symptoms appeared on an average of 2-3 weeks after patients were discharged from hospital, shortest interval being as early as 5-6 days after testing positive for Covid 19. One eye care hospital in Mumbai that used to see about 5-6 cases in the entire year before the pandemic has reported more than 10 MM patients first two weeks of May 2021.

Diagnosis: A biopsy, usually from the nose, can confirm the diagnosis.

Treatment and Prognosis: Most patients with infection are admitted to hospitals and treated with Amphotericin B Injections and recover well if treated early. Some required surgery to debulk or reduce the fungal load. In some cases, ENT/Ophthalmic surgeon report removing parts of the eye or sinus system, leading to partial or complete vision or hearing loss. When the infection spreads all over the body, or to the brain patients usually succumb to death.

Due to sudden upsurge of cases India need of Amphotericin B injections has gone up to 1-1.5 million vials per month vials as against domestic production capacity of 800,000 vials per month. The national government has swung into quick action to import another 700,000 vials per month to fulfil the GOI and State governments commitment of free treatment for the illness.

Days after the GOI's prompting the State Governments of Maharashtra, Karnataka, Gujarat, Rajasthan, Telangana, and Uttar Pradesh etc. have classified mucor mycosis, as a notifiable disease under the epidemic diseases Act, 1897, that will give better data, management, and outcome information.

Methodology: This article has used the GOI, MOH&FW and State Health departments (NHM) periodical bulletins and press releases, TV, social media, and print media reports and a few published articles.

Keywords: Mucor Mycosis; Black Fungus; White Fungus; Yellow Fungus; Uncontrolled Diabetes; Corticosteroids; Ophthalmologist; ENT Specialist; Brain Invasion; GI Tract Infection

Background

Medical mycology

Among under 1.5 million described species of fungi, a little over 400 are known to cause disease in animals, and much fewer specifically cause disease in people. Majority of the fungi affecting human being superficial types cause a cosmetic concern than a health problem. Only a few species of fungi are pathogenic to humans in normal circumstances. But when the human immunity gets compromised as in cases of cancers, Chemotherapy for cancers, HIV/AIDs, long standing chronic illnesses being put on cortisones, Diabetics on cortisone for more than 10 days for any infection/inflammation of multiple organs are likely to be getting affected. When fungi enter human brain invariably there will be deaths.

Most of the human pathogenic fungi are saprophytes that feeds on non-living organic matter and are generally in the soil around us, but given a thriving condition such as, an open wound, fungus enters our system, or when our immunity is compromised like in HIV/AIDs, Corona, Cancers etc. they will attack people aggressively. Speller and MacIver, 1970 showed that *Coprinus cinereus*, a common mushroom causes endocarditis. Similarly, Lacaz., *et al.* 1996 demonstrated that *Ustilago maydis*, a corn smut causing skin lesions and Kern and Uecker, 1986 reported a wood decomposing fungus- *Schizophyllum commune* causing meningitis and lung disorder.

Some Fungal Human Pathogens: 1. Dermatophyte (Superficial infections), fungi attack the skin or nails, and hair that we recognise as infection of ringworms, jock-itch, and athlete's foot. 2. Systemic infections: Saprotrophic fungi, spores growing in the soil, are either inhaled or enter through open wounds anywhere in our bodies and either through our blood circulation reach and infect any other internal organ. 3. A third, Intermediate infection, that occurs below the skin, but will remain localized [1].

Among the commonly known fungi like candida, aspergillosis, cryptococcus, histoplasmosis and coccidioidomycosis, Mucor mycosis, candida and aspergillosis are the ones that attack persons with low immunity. Mucor mycosis (MM) is not a new entity. In India case of MM has been reported following organ transplantation, uncontrolled diabetics given long term cortisone therapy for any infection, long term ICU stay, Comatose patients due to renal fail-

ure etc. In the current outbreak of mucor mycosis is being reported among Covid 19 patients discharged after hospital stay especially in ICU, among Comorbid with diabetes, cancer, HIV/AIDs, Organ transplanted patients. Cases are reported among prediabetics and non-diabetics recovered from Covid 19 and put on Cortisones exposed to dusty construction sites, handle soil, moss, or manure as a part of agricultural work, poor personal hygiene also. Steroids like dexamethasone, Prednisolone used indiscriminately (overuse, misuse and rampant) in Covid 19 management especially with oxygen over 90% (acts as culture media for fungal growth) rampantly repress immune system and the innocuous fungus becomes infective. Most doctors working in India agree that prescribing practices of higher doses for longer periods of time is a clear risk factor for invasive fungal infections [2].

Introduction

Many western countries have reported Aspergillosis, in patients with severe Covid-19 infections, or were in intensive care management and were on corticosteroids treatment. There are tests to rapidly diagnose unlike the case with mucor mycosis [3]. In the current outbreak an early diagnosis was based on observing key symptoms and signs like blurred vision, shortness of breath, discolouration over the nose, chest pain, cough, and coma when brain gets involved. The diagnosis was clinched by supporting CT scan of the face, head or any other part suspected to be affected. The standard treatment followed is giving antifungal injection Amphotericin for minimum (10-21 days some even extended to 4-6 weeks) course of intravenously [4]. The symptoms and signs based on the part of the body affected, can be summarized as.

Rhino-orbito-Cerebral mucor mycosis

These fungi attack eyes, ears, sinuses or nostrils and manifest as headache, pain in the eyes and orbit, blurring or double vision with pain, Nasal blockage/congestion, blackish patch over ears or cheeks, or bloody discharge. Sinus infection may result in Sinusitis, facial pain, numbness, swelling, oral infection in toothache, loosening of the tooth or jaw involvement, tingling sensation on the face, fever, and blackish lesions.

Pulmonary mucor mycosis

Infection of lungs usually manifest as cough, chest pain, blood in sputum after cough, worsening of existing respiratory symptoms and fever.

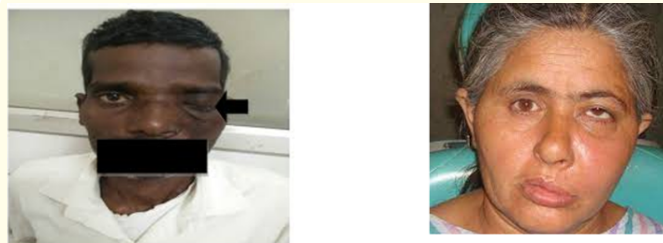


Figure a

Ophthalmic involvement

Overall 20 - 25% of cases in India have reported involvement one sided eye leading to enucleation and blindness Causing blindness.

One of the ways mucor mycosis travels is by invading the blood vessels and through circulation reaches to the distal organ, and thus produces necrosis that becomes black from which derives its name of "black fungus. If not controlled, not treated, case fatality is in the range of 20% to 50%" [3].

Treatment and cost

Antifungal medication is costly. One vial of amphotericin B of 50 mg costs around Rs 5000 to 8000. A minimum 5 mg per kg body weight is required for each dose Therefore, for an average Indian patient with a 50 kg weight needs 250 mg per day costing around Rs 40,000 per day. Other drugs used - Posaconazole and injectable Isavuconazole (isavuconazonium sulphate injection) cost Rs 4000 and Rs 12,000 per dose. Their schedule consists of on 3 injections on the first day followed by 2 injections per day for next 2 days.

Shortage of amphotericin injections

In June 2021 India needs about 15 Lakh vials Amphotericin per and 8 lakh vials will be produced in India, the remaining 7 lakh vials will be imported for treatment of black fungus to fulfil the GOI and State governments commitment of free treatment for the illness [9].

Review of fungal infections following Covid 19 infections

Global situation

World-wide apart from India very few countries have reported

mucor mycosis infections associated with Covid-19. Even before this pandemic, India had higher incidence of mucor mycosis at 14/100,000 people compared to 0.06 per 100,000 in Australia. Among the world-wide opportunistic fungus infections Aspergillosis is the commonest. Outbreaks of mucor mycosis are attributed to contaminated linens, medications, and packaged foods. The Indian widespread mucor mycosis outbreaks point to multiple contaminated sources. Presence of diabetes was seen among 40% of all mucor mycosis cases published in scientific journals globally between 2000 - 2017 [3]. Most western countries have seen increased Aspergillosis in severe Covid-19 infections, those who were under intensive care management, and were put on corticosteroids for longer duration. There are tests to rapidly diagnose Aspergillosis unlike the case with mucor mycosis [3].

National scenario

Six Ophthalmologists in five cities of Mumbai, Bangalore, Hyderabad, Delhi, and Pune - reported 58 cases of the mucor mycosis infection between December 2020 and February 2021. They had contracted the fungal infection between 12 to 15 days after recovery from Covid-19. Indian Doctors opine that mucor mycosis, has an overall mortality rate of 50%. Irrational and long-term use of corticosteroids, for severe and critically ill Covid-19 patients, especially those having diabetes increases the risk of mortality. Though Steroids reduce pulmonary inflammation of Covid-19 patients and help to minimize the damage, but in the process the immune system goes into overdrive to fight off coronavirus. This process reduces immunity and push up blood sugar levels in both diabetics and non-diabetic Covid-19 patients levels up to 400mg/dl increasing the vulnerability for MM infection. If the blood sugar levels neither monitored nor controlled with appropriate diet, drugs etc, the fungus fulminates. This happens especially when the patient is discharged and asked to monitor post-covid events at home but fails to monitor Blood sugar and come back with the fungal infection.

Magnitude of the problem

India at present has over 12,000 black fungus cases approximately and the number increasing every day [7,8].

An expert task force working on Mucor mycosis reports that the states most affected by the black fungus are Gujarat (2859), Maharashtra (2770), AP (768), MP, (752), Telangana (744), UP, Rajasthan (492) Karnataka (481) lead the reported mucor mycosis

On Saturday 8th May 2021 morning, a Mumbai-based eye surgeon, was waiting to operate on a 25-year-old woman, a diabetic, who had recovered from a bout of Covid-19 three weeks ago. Inside the surgery, an ear, nose, and throat specialist had inserted a tube in her nose and was debriding tissues infected with mucor mycosis, a rare but dangerous fungal infection. After his colleague finished, an Ophthalmologist was to remove the patient's eye to save her life.

Figure b

infections [4-7].

Gujarat

The state has reported 2,859 cases of Mucor mycosis and accounts for one-fourth of the cases in the country. The state has reported 70 deaths so far. In Surat district, during the first fortnight of May21, 40 cases were reported and among them 8 people had lost at least one eye due to mucor mycosis after recovering from Covid-19. Eight out of 200 such patients treated so far in various parts of the state have died due to mucor mycosis as per Director Medical Education of the state [11]. At least eight people have lost their eyesight in Gujarat's Surat district due to mucor mycosis after recovering from Covid-19. In the last fortnight, Surat has reported at least 40 cases of mucor mycosis.

Recently Aspergillosis infection has stirred fear among recov-

S. No.	State/UT	Patients under Treatment on 25 th May 09:36 PM (As per Portal)	Draft Allocation 25 th may	Draft Allocation Rounded off
1	A&N Islands	0	0	0
2	Andhra Pradesh	768	1950	1930
3	Arunachal Pradesh	0	0	0
4	Assam	0	0	0
5	Bihar	215	546	550
6	Chandigarh	83	211	210
7	Chhattisgarh	103	262	260
8	D&D & D&N		0	0
9	Delhi	119	302	300
10	Goa	10	25	50
11	Gujarat	2859	7260	7210
12	Haryana	436	1107	1110
13	Himachal Pradesh	3	8	50
14	J&K(UT)	5	13	0
15	Jharkhand	29	74	70
16	Karnataka	481	1221	1220
17	Kerala	36	91	100
18	Ladakh (UT)	0	0	0
19	Lakshadweep	0	0	0
20	Madhya Pradesh	752	1910	1910
21	Maharashtra	2770	7034	6980
22	Manipur	0	0	0
23	Meghalaya	0	0	0

24	Mizoram	0	0	0
25	Nagaland	0	0	0
26	Odisha	15	38	50
27	Puduchery	2	5	50
28	Punjab	141	358	360
29	Rajasthan	492	1249	1250
30	Sikkim	0	0	0
31	Tamil Nadu	236	599	600
32	Telangana	744	1889	1890
33	Tripura	1	3	0
34	Uttar Pradesh	701	1780	1780
35	Uttarakhand	124	315	320
36	West Bengal		0	0
37	Central Institutions	592	1000	1000
	TOTAL	11717	29250	29250

Table 1: No of mucor mycosis cases and allocation of amphotericin B injection by states.

Source: <https://www.ndtv.com/india-news/coronavirus> 27 May2021.

ered COVID-19 patients in Gujarat as 8 cases of nasal aspergillosis have been reported from two of the government hospitals in Vadodara in the last fortnight of May 2021 [24].

Maharashtra

The state of Maharashtra on Thursday 27 May 2021 deposed in Bombay High Court that they have recorded 3,200 cases of mucor mycosis [7].

Head of Ophthalmology at Fortis Hospital in Mulund, Mumbai, had treated at least 10 MM patients in the past two weeks, which is roughly twice the number they had seen in the entire year before the pandemic. All cases were among COVID-19 cured patients and most of them were diabetic or had received corticosteroids. A consultant ophthalmologist at Hinduja hospital in Mumbai, apparently sees a case every week now as compared one case per year before this pandemic and doubted the infection from the contamination of oxygen pipes and humidifiers in hospital. A private Ophthalmologist from Nagpur, treating cases of mucor reported that he had to take tough decision to remove the patient's one or sometime both eyes. Though exact number of patients of losing at least one eye is not known ballpark figures indicate that 75 people have lost either

one or in some cases both eyes [13].

Brihanmumbai Municipal Corporation (BMC) confirmed that 111 COVID-19 survivors are undergoing treatment for mucor mycosis in various Mumbai hospitals and one 44-year-old man lost his eyesight due to the fungal infection [14]. Similarly, Sion Hospital reported 24 cases in the past two months, as compared to 6 in a typical year. An eye surgeon in Mumbai, told the BBC that he had seen 10 cases over the previous two years, and in April 2021, alone he saw 40 MM cases and had to remove an eye of 11 (20 - 25%) of them to save the life [15].

According to Director of Medical Education, Maharashtra, out of 200 mucor mycosis patients treated in the state so far 8 persons have died. They survived Covid-19 infection, but the fungal infection attacked their weak immune system which proved fatal.

Karnataka

Health Minister of Karnataka reported on 30 May 2021 that 1250 cases and 35 deaths of black fungus since Covid-19 outbreak from various government and private centres. These institutions include Mysuru Medical College, Shivamogga Institute of Medical College, Gulbarga Institute of Medical Sciences in Kalaburgi, Kar-

nataka Institute of Medical Sciences at Hubballi, Kasturba Medical College and Wenlock District Hospital in Mangalore [15]. From the private sector an ENT specialist of the Trust Well Hospital, gave a media statement that he had seen over 65 cases in the last two weeks and fifteen of them had to undergo surgeries too. Bagalkot district authorities confirmed having seen three black fungus cases in patients recovering from COVID-19 [17]. Another private eye surgeon in Bengaluru had seen 19 cases in the past fortnight, among relatively young patients, and apparently some were so sick

cases SMS Hospital Jaipur has seen most cases 200 cases, Jodhpur-150, Kota-70 and Udaipur, Ajmer and other districts have also reported a few [18].

Haryana

While 50 cases of black fungus have been reported in Gurugram alone so far and about 50 more are suspected to be suffering from this disease [9].

Telangana

Around 50 MM cases from Apollo Hospitals, Jubilee Hills, in May 2021, five cases each from Continental Hospital and Aster Prime Hospitals in Hyderabad city were reported. Whereas Sixteen of the 50 cases at Apollo Hospitals, had shown good progress, 6 patients have succumbed to the disease and the remaining are fighting with mucor in ICUs and wards [19]. Sarojini Devi Eye Hospital officials had reported 11 patients are under treatment with Liposomal Amphotericin B IV injections. Three of them lost vision permanently [20].

Andhra Pradesh

The state Chief Minister was briefed on 29 May 2021 that there was a total of 808 cases reported across the State, and Amphotericin B vials to treat the fungal infection were not enough [21] while Visakhapatnam district reported 35 cases on 27 and 28th May 21, taking the district contribution to 90 and that of the four north

RARE CASE OF MUCOR MYCOSIS IN THALLAMUS

A 48-year-old woman from Gauribidanur, who recovered from Covid, began showing stroke-like symptoms not long after discharge and was brought to a Bengaluru hospital where doctors found mucor mycosis had directly affected her brain. Most importantly no trace of the fungus was found in her eyes, nose, or Sino-orbital nerve through which the fungus usually enters the body. It was present only in her brain and confirmed through a biopsy and tissue culture studies. This is a rare case. The woman has undergone a procedure to remove fungal debris from her brain at Bhagawan Mahaveer Jain Hospital, Vasanth Nagar, and is now recovering.

The woman had tested positive on May 4 and was admitted to a Covid Care Centre in her town. She was discharged on May 11. During Covid treatment, the woman was on mild oxygen support, but developed trouble in speaking a day prior to her discharge from the CCC. After reaching home, she developed weakness in the right side of the body. But she soon showed signs of having suffered a stroke and was taken to a government hospital in Chikkaballapura. From there, she was shifted to Jain hospital's non-Covid ICU on May 15 as she tested negative for the SARS-CoV2 virus. Curiously, the woman did not present any factors associated with mucor mycosis. She is not a diabetic, was not on steroids or any immunosuppressant drugs and was never treated in ICU or put on a ventilator.

At Jain hospital, she underwent a CT scan, suggestive of stroke, but her condition did not improve with medication. She had no fever nor face swelling. Though stroke is seen post-Covid, her case did not fit the pattern. Two days later a magnetic resonance imaging (MRI) scan showed there were white and black patches in the thalamus region, indicative of a tumour-like mass, a pattern of involvement was very unusual. "The surgeons thought it could be brain TB or toxoplasmosis, the central nervous system infection seen among HIV patients, and conducted a HIV test, but that too was negative. TB was ruled out after a biopsy, finally in the tissue culture study, the fungal presence was clearly seen, confirming that it was a case of mucor mycosis.

Dr Srinivasan conducted a procedure called MRI-guided stereotactic neurosurgery, a technique that locates targets of surgical interest within the brain, and the infectious matter in the thalamus was extracted. It would have been tough to reach out to the infected area, if not for this technique as they

Figure c

that they could not even operate on them [3].

Rajasthan

Rajasthan's tally of Mucor mycosis cases has increased to 1,300 as 500 cases were added between 25-29th May 2021. Of these

Following a couple turning Covid 19 positive 15 days ago and managed in home isolation, their infant developed fever 10 days ago. She was treated by a local pediatrician and then brought to the Outpatient Department of Kakinada GGH with periorbital swelling, was confirmed to be a case of Mucor mycosis a first Infant to affect in Andhra Pradesh.

Figure d

Andhra districts tally to 140.

Uttar Pradesh

The largest state in India UP has reported nearly 400 cases by now. Out of them leading contribution to this number is Meerut district, with a total of 147 cases of which 88 were still active. Luc-

know's KGMU has treated 96 patients of which 8 have died at the [23]. Three cases of Black Fungus have been recently reported from Prayagraj, 4 cases from Noida and Gorakhpur also continue to see a spike in the cases [22].

Uttarakhand

AIIMS, Rishikesh, has been treating 15 MM cases and reported one death on 17/05/21 among Covid 19 recovered patients of Uttarakhand [24].

Madhya Pradesh

A total of 1224 case are reported in the state of which five districts of Indore-506, Barwani-23, Khargone-25, Dhar 20 and Bhuranpur -03 contribute 48% [25].

Fulminating Fungal story in India will not be complete without referring to the damages of White and Yellow and Aspergillus fungi.

White fungus

Head of the ENT department of Netaji Subhash Chandra Bose Medical College hospital in Jabalpur, MP, usually reports five cases of Aspergillus Flavus (white fungus) cases every month. This is common in this part of rural MP, carried by dust, hay, or other such particles. It is not a new disease, nor is it as fatal as mucor mycosis. White fungus infection causing such damage has not been seen earlier. It mainly affects lungs and other parts like nails, skin, stomach, kidney, brain, genitals, and mouth. It can be detected only with a high-resolution CT scan on the infected part of the body. The pregnant women are at a higher risk of white fungus infection due to insanitary conditions. b) In the third week of May 2021 Four cases of white fungal infection have been reported from Patna in Bihar, including a famous doctor from Patna. c) Delhi's Ganga Ram Hospital reported a case of multiple perforations throughout the intestine due to white fungus on 27th May 21.

Yellow fungus

An ENT (Ear-Nose-Throat) specialist of Ghaziabad, was approached by a 59-year-old lawyer with COVID-19 and pain in abdomen. An endoscopy on May 24 revealed black, white, and yellow fungus infection. Another man is currently undergoing treatment at the same hospital for yellow fungus, detected near the brain of patient and half of his jaw had to be removed [26]. High humidity or the presence of old, tainted food helps propagation of yellow

fungus infections. Poor hygiene and unsanitary environments, however, continue to be the leading causes of the infection. Yellow fungus infection is regarded as more dangerous because, unlike the black fungus, which begins with a prominent facial disfiguration, the yellow fungus begins to cause symptoms by attacking the body's interior organs and disrupting vital bodily functions. Some case studies in India, indicate that a yellow fungus infection starts internally, causing delayed healing of wounds and prolonged recovery time, leading to oozing of pus from the wounds, organ failure, and in severe cases, acute necrosis. In some cases, the yellow fungus may affect the eyes, causing scrawny and sunken eyes due to malnutrition and organ failure [19].

Managerial challenges

- Looking at the daily increase in number of cases the prediction of international health experts, that around 2000 cases of mucor mycosis daily in India is a major challenge
- An unusual shortage of antifungal Amphotericin B injections due to sudden rise in demand, though Government of India is importing, may have to boost the domestic production
- Irrational use of Corticosteroids in the management of severe Covid 19 case need to be controlled
- Poor monitoring and control of blood sugar levels in post-Covid 19 care, especially after going home calls for follow up by the health system.

Conclusion

- Given the hygienic situation in most out hospitals, indiscreet use of corticosteroids to prevent complications of covid 19, post covid care services become important, and the governments have already moved in that direction.
- All discharged Covid 19 patients must be advised to report to a hospital as soon as they notice any of the symptoms-stuffy nose with bloody, blackish, or brown discharge from the nose, blackish discolouration of the skin, swelling or numbness around the cheek, one-sided facial pain, toothache, or jaw pain, drooping of the eyelids or eyelid swelling, double vision, red eye and decrease in vision.
- In view of the forbidding costs the national and state governments must continue to provide free treatment
- Health insurance companies may have to consider this com-

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