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Mucormycosis in COVID-19 pandemic: Risk factors and linkages

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ABSTRACT

Mucormycosis is a serious and potentially fatal fungal infection caused by a type of rare but opportunistic fungal pathogen called mucormycetes. Recently, mucormycosis, also known as black fungus, made severe chaos in India during the second wave (between April and June 2021) of the tragical COVID-19 epidemic by its sudden and devastating surge with up to 50% mortality rate. While the exact cause of its sharp rise suddenly and specifically during the second wave still remains debatable, it has been noted that the people who are diabetic and have recovered from COVID-19 infection are more predisposed to mucormycosis. Nevertheless, the precise reason and mechanism(s) underlying the surge of this deadly infection needs to be investigated to comprehend its pathogenesis and pathological elements and discover rationale preventative/ therapeutic solutions. It is speculated that the indiscriminate use of steroids, antibiotics and zinc as a self-medication practice that increased during the COVID-19 epidemic may have promoted the dysbiosis of gut microbiota thereby inducing immune-suppression and making the risk group highly susceptible to this mycotic disease. In these contexts, this timely article attempts to contemplate and discuss some of the possible factors and potential mechanisms that can help to understand and explain the conundrum of sudden, steep and deadly upsurge of mucormycosis infections during the second wave of COVID-19 epidemic.

Introduction

Since its inception in late 2019s, COVID-19 has devastated the human health worldwide while also heavily impacting the global economy. SARS-CoV-2 has affected over 220 countries and territories, with approximately 4176,185 deaths so far across the globe (worldometers 2021). While the 'second wave' of SARS-CoV-2 and its variants-mediated COVID-19 continue to affect the global population (Kirby, 2021), the deadly rise of myriads of manifestations and complications and, specifically, the rise of fatal fungal infection, the mucormycosis, has put the lives of COVID-19 patients further at high risk (Revannavar et al., 2021; Werthman-Ehrenreich, 2021). COVID-19 and mucormycosis (also known as black fungus) are causing comorbid conditions to worsen the extent of infection and mortality rates. Aggressive mucormycosis may infect nose, eyes and sometimes the brain. In severe cases, eyes have to be removed to save the life of patients.

Notably, the developing countries such as India, the second most COVID-19-affected country in the world, have seen a sudden surge of mucormycosis incidences with variable degree of severity and pathologies. In India, more than 45,432 cases and 4252 deaths due to mucormycosis have been reported as on 15th July 2021, either among COVID-19 infected patients or in patients who had recovered from COVID-19 with Rhinocerebral mucormycosis (77.6%) being the most common type of presentation (Hindustantimes 2021).

Etiologically, mucormycosis is a serious fungal infection caused by a family of mold called mucormycetes. These fungi are widely distributed in the environment, with particularly higher prevalence in moist soils, decaying plants and foods, bird and animal feces, water and air around construction sites (Sugar, 1995; Meyers and Gurtman, 1998). Mucoymycocetes are rare but opportunistic pathogens and primarily affect immunocompromised people. Their invasion in blood vessels and vasculotropism leads to tissue infarction (Meyers and Gurtman, 1998; Eucker et al., 2000). It has been noted that people with co-morbidities

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such as diabetes, neutropenia, iron overload, deferoxamine therapy, renal failure, protein-calorie malnutrition, cancer and other diseases, all of which affect or are linked with immune system, are particularly highly susceptible (Bhattacharyya et al., 1992; Radner et al., 1995; Brown et al., 1998).

An epidemiological survey conducted about two decades ago suggested that mucormycosis, if left untreated, could be fatal, with mortality rate rising as high as up to 54% (Roden et al., 2005). Previously, the anticipated load of mucormycosis in India was about 14 cases per 100,000 populations, which is one of the highest at the global level. Whereas, recently, an alarming increase in the number of COVID-19-associated mucormycosis has been observed in India (A Patel et al., 2021) (Table 1). In view of this, the Government of India has declared mucormycosis as an epidemic in many states and territories. Since there was almost no instance of COVID-19-associated mucormycosis throughout the first wave of SARS-CoV-2, questions arise about the factors and elements that may have instigated or caused this sudden surge of mucormycosis, particularly during the second wave (Box-1).

There are multiple views regarding the current mucormycosis outbreak in India. As per the WHO statistics, India has a total of 15.3% of the global diabetic population (Roglic, 2016; Zhou et al., 2016). It has been noted that the people who are diabetic and have recovered from Covid-19 infection are more predisposed to mucormycosis (Garg et al., 2021). On the other side, it has also been observed that about 85% of mucormycosis patients have diabetes or uncontrolled diabetes (To, 2021).

The fungal disease has been found to be more prevalent in co-morbid or sometimes in non-diabetic Covid-19 patients, particularly those who were given high doses of steroids for a long time or were on oxygen/ventilator support. In addition, poor clinical hygiene and/or inappropriately managed diabetes provides opportunistic environment for fungal infection. Earlier studies implicated poorly controlled type-2 diabetes as one of the main risk factors for mucormycosis, although type-1 diabetes (10–15%) and secondary diabetes have also been reported in few cases (Chakrabarti et al., 2006). Type-2 diabetes has been implicated as the main cause of up to 44–88% cases and nearly half of the cases were diagnosed with ketoacidosis (Chakrabarti et al., 2006; Nithyanandam et al., 2003; Chakrabarti et al., 2009). It was recorded that of all the cases of COVID-19 associated mucormycosis, about 80.4–96.7% of the patients had diabetes mellitus (mean HbA1c ~ 10) and 87.8% patients were on corticosteroid treatment (AK Singh et al., 2021; John et al., 2021; Ravani et al., 2021). Apart from systemic use of corticosteroid and diabetes, several other factors including the immune-suppressive therapy (for example, the use of tocilizumab), immunodeficiency, organ transplant, and iron overload may also predispose for mucormycosis. In addition, post-pulmonary tuberculosis and chronic kidney disease are also speculated to be the emerging risk factors for increased incidences of mucormycosis (Sen et al., 2021; AK Singh et al., 2021).

Other reasons could be the excess of uncontrolled conventional precautions. One such example is repeated steaming, which may distress the nasal tract's beneficial microbiome and virome. Nasal microbial imbalance (dysbiosis) may suppress local immunity and thus may provide opportunity for fungal infection. During Covid-19, in an attempt to prevent/ameliorate viral infection, an increasing number of people have been taking Zn disproportionately through vitamins and other dietary supplements. It is evident that the Zn deprivation inhibits fungal growth in the body (Staats et al., 2013). Therefore, Zn-depletion-based approach could be used for mucormycosis therapy (Leonardelli et al., 2019). In addition, many patients that were receiving medical treatment and were not on oxygen therapy were infected and diagnosed with mucormycosis. Therefore, there seems no definite link between oxygen therapy and the susceptibility to infection. In addition, mucormycosis depends on climatic factors such as seasonal variation, humidity, and ambient temperature (Al-Ajam et al., 2006); therefore, such and other reasons thereof must be investigated to figure out potential conclusion and rationale solutions.

Self-medication, drugs overuse, and microbial dysbiosis: effects on immune system

During COVID-19, many countries have reported remarkably high incidences of self-medication and home remedies among infected as well as uninfected people (Fig 1a), which may have had high probabilities of incorrect dosages. Extensive use of steroids during COVID-19 lockdown period has been observed in India, which seems to be the highest ever at the global level (Chaudhry et al., 2021). There has been a trend towards increased use of different antibiotics, steroids, vitamins, and Zn, etc. that may cause dysbiosis of gut and nasal microbiomes (He et al., 2019; Kishimoto et al., 2020). Steroids function mainly through interaction with glucocorticoid receptors, or by causing defects in the function of macrophages and neutrophils (Barshes et al., 2004), which down-regulates the expression of proinflammatory cytokines such as tumor necrosis factor (TNF)-α, IL-1β, IL-6, IL-8, and IL-12 secreted by macrophages thereby leading to immunosupression.

Gut-associated lymphoid tissue (GALT), the well-developed and largest lymphoid immune organ in the human body, protects the host against various pathogens and infectious agents, besides also playing an important role in postnatal immunity (D'Inca et al., 2010). The gut bacteria, particularly the well-studied commensal genus Bacteroides

Table 1
Number of mucormycosis cases reported in India before and during COVID-19.(* Consist of 187 cases of CAM, # ROCM cases only in COVID-19 patients).

	Study Period	Study duration	Place of study	Total cases	References
Pre-COVID-19 period	1990–2004; 2006–2007	15 years 6 months	Chandigarh (North India)	382	(Chakrabarti et al., 2001; Chakrabarti et al., 2006; Chakrabarti et al., 2009)
	2005–2015	10 years	Tamilnadu (South India)	184	(Manesh et al., 2019)
	2010–2014	5 years	Chandigarh (North India)	82	(Chander et al., 2018)
	January 2013– May 2015	2 years 5 months	Gujarat (West of India)	27	(Patel et al., 2017)
	2013–2015	3 years	North and South India	388	(Prakash et al., 2019)
	January 2016–September 2017	1 year and 9 months	Across India	465	(Patel et al., 2020)
	2015–2019	4 years	Tamilnadu (South India)	38	(Priya et al., 2020)
	September 1–December 31, 2019	4 months	Across India	112	(A Patel et al., 2021)
COVID-19 period	September 1–December 31, 2020	4 months	Across India	295*	(A Patel et al., 2021)
	January 1, 2020 - May 26, 2021	17 months	Across India	2826#	(Sen et al., 2021)

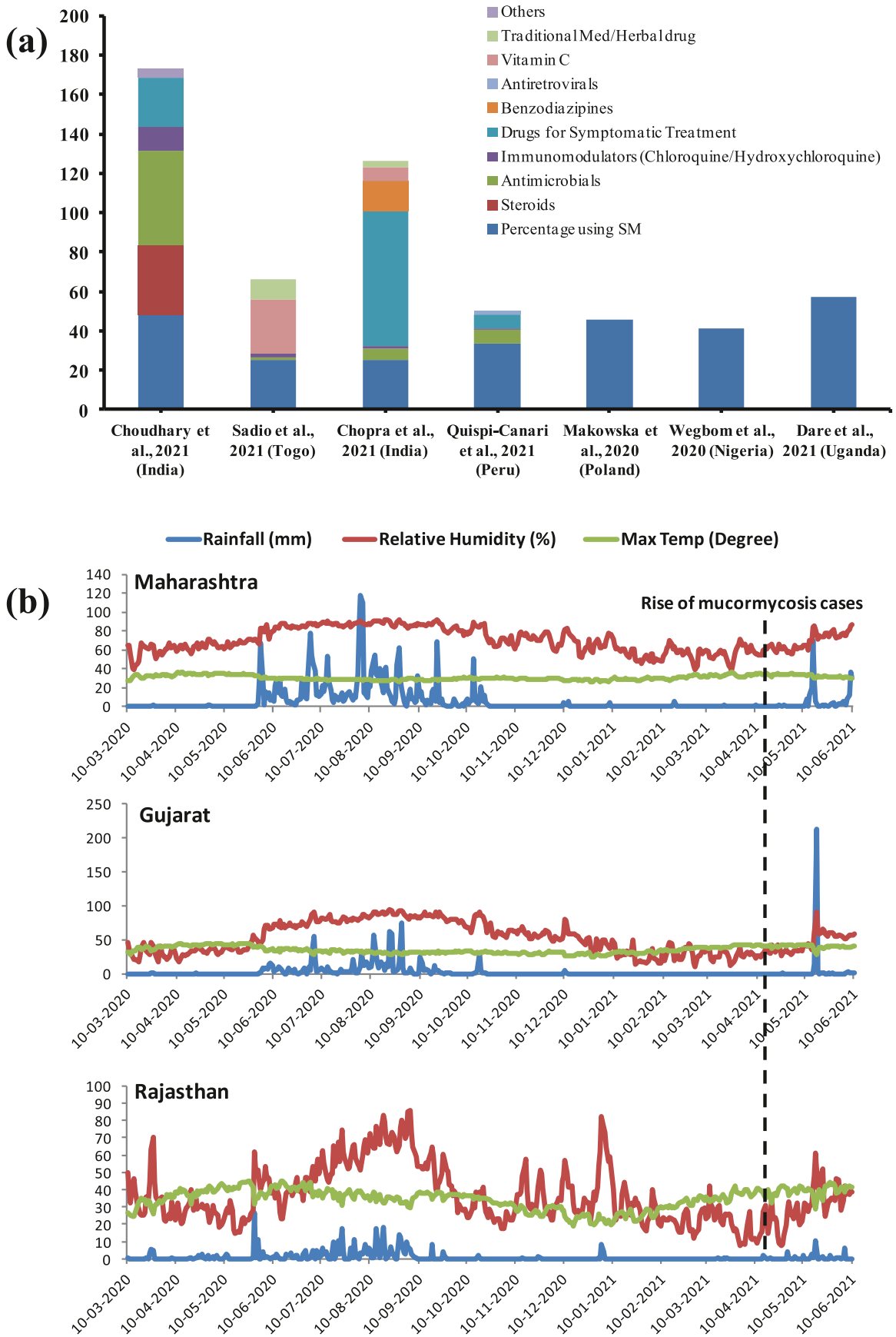

Fig. 1. (a) Trend of self-medication and usage of different types of drugs during the COVID-19 epidemic55–61. (b). Climatic conditions of the three Indian states most heavily affected by mucormycosis. (Ramakrishna et al., 2019; Choudhary et al., 2021; Sadio et al., 2021; Chopra et al., 2021; Quispe-Cañari et al., 2021; Makowska et al., 2020; Wegbon et al., 2021; Dare et al., 2021)

fragilis, promote symbiosis and host immune system education by producing Polysaccharide A (Ramakrishna et al., 2019), thus playing a vital role in the progression and maturation of intestinal mucosal immunity (Chung et al., 2012) and contributing to host's health by colonizing the mucosal entry sites of pathogens. Excessive use of systemic glucocorticoids impairs the gut epithelial barrier and causes gut dysbiosis thereby allowing toxins and bacteria leak into the bloodstream (leaky gut). This in turn affects immune response while providing favorable conditions for fungal growth and nourishment, which may in turn damage the gut lining (Paray et al., 2020). The excess of vitamin A is known to attenuate humoral immunity (by impairing the antibody response against Newcastle disease virus) (Yuan et al., 2014) and hamper vitamin D absorption (Maurya and Aggarwal, 2017). Excessive usage of typical vitamins is likely to cause toxicity and adversely affect the immune system and the utilization of other vitamins.

The barrier function of the nasal mucosa along with the regulation of local and distal immune responses are modulated by the colonizing microbial symbionts and are directly in contact with external ambiance (Man et al., 2017; Liu et al., 2020) . The microbiota modulate host physiological and pathological processes through multiple mechanisms (Atarashi et al., 2013; Atarashi et al., 2011; Faith et al., 2014). The GI microbiota cross-talk with the pulmonary microorganisms via the so-called 'gut-lung axis' and impact the immune system, thereby regulating and influencing the host's vulnerability to respiratory infections (Hua et al., 2018). Moreover, mucorales-specific T-cells producing $CD4^{+}$ and $CD8^{+}$are known to play a role in both resolution and worsening of invasive fungal infections by interacting with the gut microbiota, which influences the functionality of immune cell populations crucial for controlling the microbial infections (Speakman et al., 2020).

Like other mucosal surfaces, the nasal tract is also colonized by commensal microorganisms that are important for mucosal homeostasis and protection against infections (Dimitri-Pinheiro et al., 2020). Staphylococcus epidermidis, which increases during the process of human nasal microbiome maturation, stimulates the synthesis of antimicrobial peptides in nasal epithelium (Liu et al., 2020). Nasal- or nasopharynx-associated lymphoid tissue (NALT), which represents the immune component of mammalian mucosa-associated lymphoid tissue (MALT), provides additional support to the nasal barrier. NALT is widely diffused in children's nose, but may also be present in nasal posterior airways space in adults (Debertin et al., 2003).

Nasal microbiota is important for nasal immune responses against viral, bacterial and fungal infections (Salzano et al., 2018). Nasal microbiota acts in concert with different nasal immune responses found in persons with nasal inflammation (Salzano et al., 2018). Of note, the nasal microbiome is essential for the development and maturation of MALT as well as the modulation of IgA- and T cells-mediated adaptive immune responses.

We hypothesize that excessive water steaming and the uncontrolled use of drugs might have led to the dysbiosis of nasal and gut microbiomes and the suppression of immune system, which altogether may have promoted fungal infection. However, it is important to generate scientific/clinical evidence to unravel the relationship of the use of specific drugs or home remedies with the dysbiosis of gut and nasal microbiome.

Environmental factors and mucormycosis

Although mucormycosis is present in the environment throughout the year, a strong seasonal infection pattern is observed (Al-Ajam et al., 2006; Talmi et al., 2002; Shpitzer et al., 2005). Most infections are prevalent during the initial phases of hot and dry summer season, with peaks reaching at around the end of the season. During this period, the temperature goes high while both relative humidity and precipitation are minimal (Al-Ajam et al., 2006). Same has been observed with the mucormycosis prevalence in India, particularly during the current or second wave of Covid-19 epidemic.

The rise in mucormycosis infections has been observed mainly during May, the month of dry summer. Most of the highly affected Indian states such as Maharashtra, Gujarat and Rajasthan face a hot and dry summer during this month (Fig 1b). Therefore, the observed seasonality of mucormycosis can be correlated to the dominant weather conditions. And if seasonality prevails in India, it can be expected that during the upcoming monsoon season (mid June to September), the mucormycosis infection will decrease, albeit the persistence of hospital-acquired infections in immune-compromised individuals may not be ruled out. However, the availability of scientific data on the seasonality of mucormycosis in context to India is scanty.

Conclusion and perspectives

It is important to maintain and restore the natural gut and nasal microflora with dietary/lifestyle modification, prebiotics, probiotics, and digestive enzymes. Research is required to determine the associations of current treatment regime, the potential co-morbidities, and the environmental factors with mucormycosis infection. However, there is more than adequate evidence to justify the implementation of policies and interventions that might reduce mucormycosis in recovered COVID-19 patients.

Excessive use of antibiotics (such as azithromycin) and antifungal drugs (such as amphotericin B) during Covid-19 epidemic may lead to the development of resistance to these antibiotics and drugs in future (Sulis et al., 2021; Pelfrene et al., 2021). Therefore, the mucormycosis treatment should be screened continuously for the development of such resistance. Although there is a paucity of data on antimicrobial drug resistance during COVID-19 period, some recent studies have highlighted the prevalence of antibiotic resistance in bacteria causing secondary infections, mostly of nosocomial origin (Vijay et al., 2021), and antifungal resistance in Candida spp. in India (Vijay et al., 2021; Chowdhary et al., 2020). Further research must assess the antibiotic usage and stewardship in hospitals and to find out the correlation of drugs being used in Covid-19 with the gut microbiome dysbiosis, in particular context to immune suppression. Prescription-based policies must be strictly followed, and self-medication should be closely monitored and prohibited.

Though prime concern of healthcare authorities is to promote laws and guidelines in favor of prescribed drugs usage, the challenges accompanied with self-medication practices among general population cannot be ignored. Thus, improved public awareness and education about safe and rational use of drugs and ethnic herbal remedies are imperative and indispensable to overcome the challenge of self-medication. This information will help to develop and execute efficient health information system and protocols with public interventions to curb black fungus infections in recovered Covid-19 patients as well as to control its dissemination to healthy persons.

In conclusion, this communication contemplates and puts forward specific hypotheses related to the increased prevalence of and human susceptibility to mucormycosis during the Covid-19 epidemic in countries like India. We have retrospected, surveyed and extrapolated basic and causative elements of mucormycosis based on the current understanding and have put forward possible future directions. Understanding these mechanisms will pave the way to control mucormycosis epidemic through sustainable therapeutic strategies.

Authors' contribution

MK: conceptualization, writing original draft, and review and editing; DKS: data collection, presentation, manuscript review and editing; SS: manuscript editing; MK: visualization and manuscript editing; VV: conceptualization, and review and editing; BS: manuscript draft, and review and editing; RN: review and editing; RRT: supervision, manuscript review and editing; MK, DKS, SS, MK, VV, BS, RN, RRT: checked

Box 1. Outstanding Questions:

Though co-morbidities with diabetes seems a major risk factor for mucormycosis, to what extent does diabetes render the patient vulnerable to mucormycosis?

Why was mucormycosis low during the first wave of Covid-19 epidemic? Did the load of black fungus in environment vary during both waves?

How does the gut microbiota respond to COVID-19 treatment regimens such as steroids, antibiotics, zinc and multivitamins? What is the long-term downstream impact of these remedies on microbiome and immune health during and after recovery from COVID-19?

What are the microbial and host molecular interactions through which recovered COVID-19 patients become vulnerable to mucromycosis? Is it due to dysbiosis of gut and pulmonary microbiota and subsequently affected host immune system?

How do home-based treatments such as excess use of hot water or steaming and the ethnic or homemade decoction (kahda) interrupt normal resident gut and nasal bacterial, fungal and viral microbiomes?

and approved final version of the manuscript.

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Declaration of Competing Interest

The authors declare no conflicts of interest

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