



Black Fungus: A New Threat Under the Shadow of COVID-19

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Abstract

It was not long ago when the world started to see new hopes against the COVID-19 that a new threat emerged, yet once again echoing the deep scars that this new virus has left in the face of our civilization. Informally publicized as “Black Fungus”, mucormycosis is an opportunistic, iatrogenic fungal disease primarily infecting the paranasal sinuses. Harmless to healthy individuals, this fungal pathogen preys upon individuals with a disrupted immune system. Therefore, it is of no surprise that COVID-19 patients are easy victims of this disease. In this present article, we talked about the predominant culprits of mucormycosis, their mechanism of infection, and probable ways of preventing it.

Keywords: COVID-19; Black Fungus; Opportunistic; Iatrogenic; Paranasal Sinuses; Immune System; Mucormycosis

Introduction

The mucormycosis is an opportunistic, often iatrogenic, fungal infection that was publicized by the media as the infamous “Black Fungus” disease owing to the appearance of black coloured necrotic lesions in COVID-19 patients [1]. This painful illness, which often appears after a COVID-19 infection, can cause not only a recognizable “black” eschar in the nose cavity, but also nose obstruction and other problems like eye pain, oedema, crusting, ptosis, chemosis that could ultimately cause permanent disfiguration of facial features, blindness and nerve palsies [2]. The disease, collectively a fungal sinusitis, is caused by the order of Mucorales of which at least seven genera are the most active pathogenic agents of mucormycosis. *Rhizopus oryzae* is one of them, accounting for almost seventy percent of all cases [3].

One of the primary reasons for the occurrence of the infection is the unprecedented and unmanaged use of corticosteroids that lower the body’s innate immunity by suppressing the action of the phagocytic cells. Another important reason is the prior presence of underlying conditions like Diabetes Ketoacidosis (DKA) that lower the chemotactic factors exerting detrimental effects on the neutrophils [4]. The net effect of both the cases is an acute neutropenia that raises the susceptibility for this kind of opportunistic infections. In COVID-19, the patient suffers from deleterious alveolar damage and consequent respiratory distress syndrome. Such patients also have lowered CD4⁺ and CD8⁺ T-helper cells in their body [2]. It is due to this lowered cell mediated immunity that their susceptibility towards fungal infection increases. All these combined with the exposure of the patients to contaminated oxygen tubing and other items in ICU greatly increases the chance of the infection [4].

Order	Genera	Member Species
Mucorales	Rhizopus	1. <i>Rhizopus arrhizus</i> (formerly <i>Rhizopus oryzae</i>) 2. <i>Rhizopus microsporus</i> 3. <i>Rhizopus rhizopodiformis</i> 4. <i>Rhizopus homothallicus</i> 5. <i>Rhizopus azygosporus</i> 6. <i>Rhizopus stolonifer</i>
	Mucor	1. <i>Mucor irregularis</i> 2. <i>Mucor circinelloides</i> 3. <i>Mucor indicus</i> 4. <i>Mucor hiemalis</i> 5. <i>Mucor velutinosus</i>
	Lichtheimia	1. <i>Lichtheimia corymbifera</i> 2. <i>Lichtheimia ramosa</i>
	Cunninghamella	1. <i>Cunninghamella bertholletiae</i>
	Apophysomyces	1. <i>Apophysomyces elegans</i> 2. <i>Apophysomyces trapeziformis</i> 3. <i>Apophysomyces variabilis</i>
	Rhizomucor	1. <i>Rhizomucor pusillus</i> 2. <i>Rhizomucor variabilis</i>
	Saksenaea complex	1. <i>Saksenaea vasiformis</i> 2. <i>Saksenaea erythrospora</i>
	Others	1. <i>Syncephalastrum</i> 2. <i>Thamnostylum lucknowense</i> 3. <i>Cokeromyces spp.</i> 4. <i>Actinomucor elegans</i>

Table1: Potential species under the order Mucorales causing mucormycosis [3].

According to a study, the doctors predict that the hypoxic condition imposed due to the respiratory distress augment the tissue

damage and allow for better angioinvasion (a characteristic of mucormycosis) and consequent establishment of the fungal infection in the sinuses [1].

In fact, the DKA in more than one way supports the growth of the pathogenic fungi. Due to the acidosis, there is an increased concentration of hydronium ions in the body which displaces the Fe³⁺ (ferric ions) from the transferrin. Once the ions are stripped off from the transferrin (TF) those are transported to the interior of the cell via a fungal oxidase-reductase system. Not only that, the DKA induced (along with increased iron concentration) condition upregulates the expression of an Hsp70 chaperone protein known as the glucose regulated protein or GRP78 that act as a receptor and allows the receptor mediated entry of the fungus. Iron is an essential component for mucormycosis and could act as a limiting condition. The fungi contain the copper oxidase-iron permease (FTR1) membrane bound complex that helps in transporting the iron inside the cell. Apart from the DKA induced condition it could also obtain the mineral from heme [5].

Once surplus iron is available, fungal spores penetrate the epithelial cells via the interaction between the spore coat protein (CoH) and the GRP78 on the nasal epithelium [6]. Additionally, the platelet-derived growth factor receptor B (PDGFRB) signals damage the epithelium and provides the necessary factors for proper proliferation of the fungal hyphae. Under neutropenic condition, the hyphae flourish and stimulate the production of the Mucorales specific T-cells that release the interleukin-4, 10, 17 and interferon-γ (all of which damage the host cells). Also, there is the reduction in the release of RANTES, an immunomodulatory molecule. In COVID-19 patients, the application of heavy doses of steroids takes a huge toll in their body. Apart from the inflammation of immune system (causing cytokine storm and organ damage) it also causes excessive sugar release in the body providing for more fuel for hyphal growth and paving the way for more extensive angioinvasion [4]. The most commonly affected portions are the ethmoid and the maxillary sinuses [2].

An early detection and treatment combining anti-fungal drugs like Amphotericin-B deoxycholate (with liposomal preps) and aggressive surgical procedures are the ways to escape the malady [2]. Furthermore, it is wise to use the prophylactic formulations of Isavuconazole (ISA) and the less effective posaconazole (POS) as they could be very helpful [7]. Apart from these, trainings should be

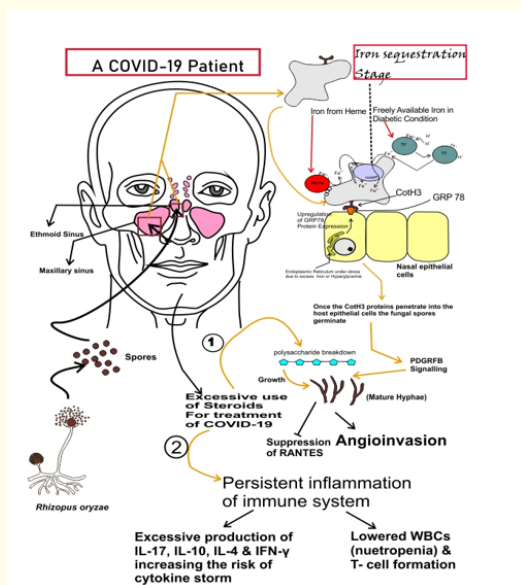


Figure 1: Mechanism of black fungus infection in the ethmoid and maxillary sinus.

Legends: TF: Transferrin; GRP 78: Glucose Regulated Protein 78; PDGFRB: Platelet-Derived Growth Factor Receptor B.

given to ICU personnel for maintaining the necessary hygiene and sanitation of health devices, not only that, over the counter sales of antibiotics should be banned as the unregulated use of these drugs on the advice of a non-medical professional can lead to the wiping out of the 'good' native bacteria from the body and thereby preparing the essential playground for the development of 'bad' secondary infections. Strict legislation must be imposed to ban unscientific and morally misleading practices like that of the 'cow dung therapy' of India that imposes baseless claims to cure COVID-19 infection. While we still don't have any data that testifies the truth of the treatment, what we already know is that by-products like cow dung are a potential substrate for organisms like that of Mucorales [8]. Until all these regulations are not strictly followed opportunistic infections such as that of mucormycosis would continue maiming the lives of its victims.

Conclusion

One of the major challenges in the treatment of mucormycosis is the early detection of the disease. Fatalities mostly result if there is a delay in the diagnosis of the pathological condition. For this,

better assays to detect the condition must be searched and found out. Also, better therapeutics and treatment strategies are the need of the hour. Strict government legislation must be imposed to curb the use of unscientific treatment methods. Extravagant use of steroids must be avoided. Until all these regulations are not strictly followed opportunistic infections such as that of mucormycosis would continue maiming the lives of its victims.

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