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Mini Review

A Brief Note on Mucormycosis: The So-Called Black Fungus Causing Co-Infection with the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Afia Ibnat Ava[1], Abrar Hamim Fayz[1], Shahreen Sultana[1], Priangka Bhattacharya Pingki[2] and Rashed Noor[1]*

[1]Department of Life Sciences (DLS), School of Environment and Life Sciences (SELS), Independent University, Bangladesh (IUB), Bangladesh

[2]Department of Life and Medical Sciences, Water and Environmental Management, University of Hertfordshire, College Lane, Hatfield, Hertfordshire, United Kingdom

***Corresponding author:** Dr. Rashed Noor, Associate Professor, Department of Life Sciences (DLS), School of Environment and Life Sciences (SELS), Independent University, Bangladesh (IUB), Plot 16, Block B, Bashundhara, Dhaka-1229, Bangladesh

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Abstract

In association to the ongoing COVID-19 pandemic caused by the Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2), the recent onset of fungal co-infection (Mucormycosis), generally known as black fungus, have made the COVID-19 situation clinically more complicated with increased mortality. Such fungal co-infection has been noticed in the severe COVID-19 patients especially who had the history of diabetes; and used steroid drugs. The fungal infection causes serious damage to the COVID-19 patients; and in many instances surgery of the affected region becomes mandatory in addition the prescribed but limited anti-fungal drug. Present review briefly discussed the clinical consequences of the black fungus co-infection in the COVID-19 patients based on the recently published literatures.

Keywords: COVID-19 pandemic; Severe acute respiratory coronavirus 2; Mucormycosis; Black fungus; Co-infection

Background

Mucormycosis, usually caused by Mucor, Rhizopus oryzae (responsible for ~70% of all cases of Mucormycosis), and also by Absidia and Cunninghamella, which is also known as Zygomycosis or Phycomycosis, or sometimes called as "black fungus", is a very rare and lethal angio-Invasive Fungal Disease (IFD) causing the dysbiosis in the immune system; and is characterized by the presence of hyphal invasion of sinus tissue with the onset of nasal blockade, crusting, proptosis, facial pain and oedema, headache, fever, visual loss, lethargy, and various neurological signs in the affected individual [1-3]. A number of people with cancer or with an immunocompromised state around the world get affected with such IFD instigated by Candida albicans, Aspergillus fumigatus, Cryptococcus neoformans, Pneumocystis jirovecii, endemic dimorphic fungi and Mucoromycetes (belonging to the order Mucorales and the class Zygomycetes) [3]. Although the disease is very unusual; recently, the prevalence of such infection has been noticed with the patients admitted into the Intensive Care Unit (ICU) suffering from Acute Respiratory Syndrome Distress (ARDS) due to the onset of severe COVID-19, the ongoing pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [4]. Such a fungal co-infection may be a result of (1) the overexpression of inflammatory cytokines, (2) the impaired cell-mediated immune responses including decreased CD^{4+} T and CD^{8+} T cells during the SARS-CoV-2 pathogenesis; (3) the underlying factors like immunocompromised state, uncontrolled diabetes mellitus, prolonged neutropenia, Hematopoietic Stem Cell Transplantation (HSCT), Hematological Malignancies (HM), iron overload, use of glucocorticoid (GC) and broad spectrum antibiotics, solid organ transplant (SOT), inherited or acquired immunodeficiencies, underlying tumors, etc., and (4) the severe COVID-19 patients requiring the ventilator or supplemental oxygen [1-5].

Epidemiology of mucoromycetes

In 2003 SARS-CoV epidemic, the incidence of fungal infection was estimated as 14.8-27 %, and surprisingly this co-infection accounted for the main reason of death for the SARS-CoV affected patients [1]. It is to be noted that among the alpha (α), beta (β), gamma (γ), and delta (δ), the β-coronaviruses, SARS-CoV-2, SARS-CoV has been found with 79% sequence homology together with a highly conserved genomic organization [6,7]. SARS-CoV-2, being under the same species as well as resulting in ARDS in the affected individuals, may also instigate such sort of fungal infection [1]. Different studies showed the fungal co-infection within the COVID-19 infected patients; for example, in one study 26.7% invasive fungal infections were found among 135 severe COVID-19 patients, and in another study the co-infection rate was 8%, thereby revealing that a huge number of patients affected by or recovered from Covid-19 are may be at high risk of developing the invasive fungal infections [1,3,8,9]. In China, one case study noticed 5 incidences of the fungal co-infections (*A. flavus* in one case, one case of Candida glabrata and C. albicans in three cases) out of 99 COVID-19 patients; in Germany, five patients out of 19 severe COVID-19 patients were found to develop the IFD; in Netherlands, six ICU patients among 31 were diagnosed with *A. flavus*, thereby revealing the global epidemiology of Mucormycosis [4]. COVID-19 Associated Mucormycosis (CAM) and the COVID-19 Associated Pulmonary Aspergillosis (CAPA) have also been evident in Brazil, Italy, and the United Kingdom with the patients having high blood sugar and the last stage kidney disease as well as with the history of steroid usage [10]. In December, 2020 India reported 12 cases of CAM caused by Aspergillus and Candida species; and afterwards many COVID-19 recovered patients were found to be infected with this infection who were then brought back

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into ICUs [11].

Clinical features of Mucormycosis in COVID-19 patients

As stated earlier, patients undergoing such fungal infection usually have symptoms of one-sided facial swelling, stifling and bleeding nose (black patches of skin around the nose), dark lesions on the nasal bridge or upper interior of the mouth, pain in the eye with its swelling with the wilting of eyelids, compression of the optic nerve (if the infection emerges behind the retina), blurred and even the complete loss of vision, chest pressure, and shortness of breath resulting in 54% all-cause mortality rate [11]. The extensive angioinvasion results in vessel thrombosis ensuing tissue necrosis [12]. The disease is not contagious; however, the fungal spores in their atmosphere may invade the lungs or sinuses followed by spread to eye, brain, heart, and spleen *via* the bloodstream [11,12]. Even though most cases are intermittent, mucormycosis outbreaks have occurred in the past. Prolong staying in hospital (by the severe COVID-19 patients) may induce this disease as the non-sterile health care equipment, hospital linens, adhesive bandages, wooden tongue depressors, and insufficient air filtration may trigger the dispersal of mucoromycetes [11]. Routine clinical diagnosis includes histopathology; i.e., the demonstration of fungal hyphae in biopsies or Bronchoalveolar Lavage (BAL) using Grocott Methenamine-Silver (GMS)-and periodic acid-Schiff PAS stains; direct microscopy (for a rapid presumptive diagnosis of mucormycosis); positive cultures from a sterile site (which confirms the diagnosis); molecular methods like the nested Polymerase Chain Reaction (PCR), real-time PCR (qPCR), nested PCR combined with the Restriction Fragment Length Polymorphism (RFLP) to detect the Internal Transcribed Spacer (ITS) region (the most widely sequenced DNA region for the detection of fungi), 18S ribosomal RNA genes, 28S rDNA, the mitochondrial gene rnl, the cytochrome b gene, and the Mucorales-specific CotH gene using the gene specific primer sets; serological tests like sandwich ELISA and lateral flow immunoassay (LFIA); and metabolomics-breath test (volatile metabolite profiles) using thermal desorption Gas Chromatography/Tandem Mass Spectrometry (GC-MS) [13,14]. The treatment of mucormycosis is quite difficult; and so far, only Amphotericin B (LAmB) and its lipid formulations have been studied as first-line therapy for mucormycosis [11,15]. Also, implementation of surgery to remove the affected organ/region is another strategy [11].

Conclusion

In fine, according to the above discussion as well as to the recently published literatures, it is clearly evident that there is an immunopathological interaction between the Mucoromycetes and the SARS-CoV-2. Till date the virus caused 3,480,480 deaths out of 167,423,479 confirmed cases [16]. In addition, such co-infection with fungi may transform the current fatal situation to worse in terms of morbidity and mortality, possible ineffectiveness of the vaccines that are currently in use commercially to mitigate COVID-19. However, the cases mucromycosis should be taken into consideration by the relevant health professionals right now since they are appearing either as a co-infecting state or as the post COVID-19 situation. Besides, restrictions in glucocorticoids usage and monitoring the pre-disposing factors especially diabetes should be brought up as a preventive measure against the disease.

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