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Review Article

Mucormycosis and COVID-19: A Review of the Black Fungus and Opportunistic Fungal Infections

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Abstract

The novel coronavirus disease (2019) (COVID-19) arose from Wuhan, China in late 2019. It has posed a threat to global healthcare systems across developed and developing countries. The symptoms of the fungal disease may manifest similarly to those with COVID-19, including shortness of breath, cough, and fever. Recently, reports also describe the incidence of COVID-19-associated pulmonary aspergillosis, in addition to bloodstream infections including candidemia, histoplasmosis, blastomycosis, and Valley fever. Of imminent concern is mucormycosis which affects the brain, lungs, sinuses, and is life-threatening for severely immunocompromised patients such as patients with HIV/AIDS or cancer, and diabetics. In the following review, we intend to propose the correlation of mucormycosis and COVID-19 and support the associations to opportunistic fungal infections. We suggest that a multidisciplinary approach is required to ensure the reversal of any underlying or associated conditions to mucormycosis and other fungal infections.

Keywords: COVID-19; Fungal Infection; Mucormycosis: WHO; SARS-CoV-2; Black Fungus

1. Introduction

The enveloped novel coronavirus, a single-stranded RNA betacoronavirus of the coronaviridae family arose from Wuhan, China in late 2019 [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) posed a global threat to healthcare systems in developed and developing countries, upon the World Health Organization (WHO) declaring it a public health emergency [2]. While many preventative measures such as vaccination, hygiene, standard operating protocols, and boosting wellness in nutritional intake have been promising, no antiviral drugs can currently prevent coronavirus disease (2019) COVID-19 incidence [3]. Clinical signs of the disease include cough, coryza, dry cough, myalgia, sore throat, shortness of breath, body aches, loss of sense of smell or taste, nausea, or vomiting [4-6]. In the case of critical COVID-19 disease, respiratory failure leading to acute respiratory distress syndrome and multiorgan failure may occur, eventually leading to death of the patient [3]. Until May 27, 2021, there have been 169 million cases reported worldwide, with 3.5 million deaths reported [7]. The highest number of cases have been reported in the USA with 33.2 million cases, and 0.592 million deaths, whereas India has reported 27.4 million cases, with 0.315 million deaths, until May 27, 2021 [7]. Mucormycosis has double compounded the threat of the COVID-19 pandemic in India and other South-East Asian countries [3]. In the following review, we intend to propose the correlation of mucormycosis and COVID-19 and support the associations to opportunistic fungal infections.

2. The Correlation of COVID-19 to Fungal Infections

The symptoms of the fungal disease may manifest similarly to those with COVID-19, including shortness of breath, cough, and fever [8]. A study finds that SARS-CoV-2-associated pulmonary aspergillosis (CAPA) is one of the many predominant fungal diseases that adds more insult to injury in COVID-19 patients with ARDS [9]. While the pathogenesis is unclear, various immunological mechanisms contribute to the development of CAPA amid a myriad of other fungal diseases [9]. Laboratory testing is essential to determine the nature of the fungal infection and to corroborate COVID-19 present. Patients may present with a fungal infection and COVID-19 at the same time. Moreover, patients in the intensive care unit are especially vulnerable to fungal and bacterial infections. The most common fungal infections that have been documented by the Centers for Disease and Control (CDC) include invasive candidiasis or aspergillosis [10, 11]. The fungal

co-infections are of imminent concern due to the growing associations to increased mortality and severity of SARS-CoV-2 disease [12, 13]. The awareness of possible fungal superinfections is pivotal in reducing diagnostic delays and preventing adverse outcomes from infection.

2.1 COVID-19-associated pulmonary aspergillosis (CAPA)

Current literature is still expanding on the relationship of COVID-19-associated pulmonary aspergillosis (CAPA), an infection caused by the fungus Aspergillus, in people with severe COVID-19 disease. Published literature corroborates the notion that aspergillosis occurs specifically in patients with compromised immune system. However, an increased number of cases have been reported in patients who do not have weakened immune systems, but who have severe respiratory viral infections, particularly COVID-19 and influenza. Recently, reports describe COVID-19-associated pulmonary aspergillosis (CAPA) [10, 12, 14-17]. One study in the Jiangsu province reported that 23.3% patients with COVID-19 had positive throat swab tests for Aspergillus spp [18]. Several case series and studies from Europe, including Belgium, France, Germany, and the Netherlands have also reported high rates of CAPA among COVID-19 patients with ARDS ranging from 20-35% [9]. The common findings suggest that CAPA has more affliction to severe COVID-19 infections such as patients admitted to the ICU and that it rapidly developed among the COVID-19 patients with a median of six days post ICU admission [6, 9, 11, 14]. It may be difficult to diagnose the fungal disease as patients may present with atypical symptoms and confirmatory testing essentially requires deep specimen from the lungs [16]. Therefore, healthcare workers ought to consider the presence of aspergillosis in patients who present with severe COVID-19 disease, and face worsening respiratory functions or sepsis as the disease progresses, even if there are no seemingly high-risk factors pointing to aspergillosis. The diagnostic modality for CAPA includes obtaining a specimen from the lower respiratory tract of the patient, which is then tested for Aspergillus galactomannan antigen and fungal culture.

2.2 Increased spread of candida auris during COVID-19 pandemic

Candida Auris is an emerging fungus having the potential to cause outbreaks of severe nature in healthcare centers across the world. The spread has been documented in long-term care patients having severe co-morbidities. However, since the dawn of the COVID-19 pandemic, C. Auris has been reported in the acute care setting which is a point of contention. An outbreak of C. Auris was documented among 12 patients with COVID-19 in ICU at a Mexican hospital [19]. In the report, the 12 patients had a prolonged lag between the first COVID-19 infected patient at the hospital and the current patients; three months post the first outbreak of the infection. Hence, it was theorized that the transmission of C. Auris by healthcare workers might be unlikely due to the adequate use of personal protective equipment [19]. The classic risk factors of C. Auris infections include the use of multiple antibiotics, diabetes mellitus, central venous catheters use, renal failure and other COVID-19 associated factors like the use of excessive corticosteroids possibly leading to immunosuppressive effects on macrophages and neutrophils [19]. A critical component of C. Auris containment is screening for the fungal disease, which has been limited due to the limitations of resources across health departments and facilities that have more so focused on responding to COVID-19. Nevertheless, it is essential to elucidate the relationship of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), predispositions to candida infections, and immune responses [19].

2.3 Invasive candidiasis in patients with COVID-19

Hospitalized COVID-19 patients are at an increased risk for healthcare-associated infections such as bloodstream infections or candidemia caused by Candida [20, 21]. However, once these are identified, the treatment plan is complex as the infections are resistant to available anti-fungal infections. Despite the progress of hospital care and public health, fungal infections continue to develop in hospitalized patients with COVID-19; those admitted to the ICU are at higher risks of acquiring nosocomial infections [22]. While invasive candidiasis is a rare association, it has been documented in critically ill patients. A study finds that the main risks for acquiring invasive candidemia include 1) central venous catheter use, 2) prolonged hospital stays, 3) surgical procedures, and 4) the use of broad-spectrum antibiotics [22]. The double compounded risk of Candida and COVID-19 leads to resistance and higher adverse events. Regular monitoring for Candida infections, particularly those that are resistant to available therapies such as azole-resistant Aspergillus and C. Auris may reduce fungus-associated deaths in patients with COVID-19 [23].

2.4 Fungal pneumonia and proximity to COVID-19 pneumonia

Fungal diseases such as histoplasmosis, blastomycosis, Valley fever (coccidioidomycosis) may cause similar symptoms to those observed in COVID-19 and bacterial pneumonia [24]. These fungi originate in the soil, and the risk of transmission may peak in unhygienic housing conditions as individuals breathe the air with fungi present. A 145-patient study across five ICUs in France aimed to assess the occurrence of fungal respiratory superinfections with severe COVID-19, using respiratory and serum sampling to screen for fungal complications [25]. Invasive fungal infections were diagnosed in 7 of 145 patients, amounting to a 4.8% incidence [25]. The French study concluded that patients with no severe SARS-CoV-2 related pneumonia and/or underlying severe immunosuppression were at low risk of invasive secondary fungal infections [25]. As the outbreak continues, it is pertinent for healthcare workers to consider the possibility of fungal pneumonia as a causative factor for respiratory illness, particularly among those who have an un-confirmed COVID-19 test result. Moreover, fungal diseases may occur at the same time as COVID-19 [26, 27].

3. Mucormycosis and Incidence in COVID-19 Patients

Treatment modalities used to treat serious COVID-19 disease primarily consist of corticosteroids, which reduce the immune-mediated damage from SARS-CoV-2 infection to the body. However, corticosteroids are immunosuppressive and increase blood sugar levels in both, the diabetic and non-diabetic patient groups [28]. These two effects have now been documented to contribute to mucormycosis. In addition, mucormycosis also affects the brain, lungs, sinuses, and is life-threatening for severely immunocompromised patients such as patients with HIV/AIDS or cancer, and diabetics. The Indian Council of Medical Research (ICMR) recommends that healthcare workers must pay heed to the signs of mucormycosis including unilateral nasal obstruction/headache, sinus pain, numbness or swelling, loosening of teeth, and toothache [29]. Mucormycosis also leads to reddening or discoloration of the nose, chest pain, double or blurred vision, difficulty breathing, and coughing up blood, which double compounds the already heavy burden of COVID-19 in low and middle-income countries like India [29]. It is pivotal to note that India has so far reported a high number of mucormycosis cases, named as the black fungus in the region [29]. The International Diabetes Federation states that India also presents with a high incidence of type 2 diabetes, with around 9% of the entire adult population (77 million patients) present in the large country [29]. Because diabetes and the use of

corticosteroids for severe COVID-19 infection are closely related to mucormycosis, susceptible individuals in countries with high diabetes and COVID-19 burden may face a higher incidence of mucormycosis [29].

4. Conclusion

Fungal infections, particularly CAPA and more recently, mucormycosis increase the severity of disease among COVID-19 patients and are associated with high mortality rates. These must be encountered by initiating appropriate antifungal therapy and early diagnosis. Another public health emergency is the severity of mucormycosis infection and the rapid progression of the disease. Healthcare workers must act promptly particularly in those patients who are on poorly controlled anti-diabetic medications and are suspected to have mucormycosis. Moving forward, a multidisciplinary approach is required to ensure the reversal of any underlying or associated conditions.

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