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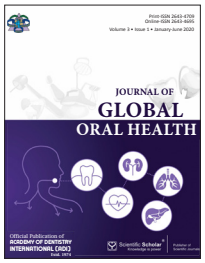

Review Article

COVID-19-associated fungal spectrum: The intraoral purview

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ABSTRACT

COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 has created havoc all around the world. The COVID-19 virus is reportedly responsible for causing severe immunodeficiency states in patients. This has led to a rise in opportunistic infections, majorly being fungal in form. This increase in fungal infections may also be linked to other factors such as immunosuppressive drugs or antiviral drugs which have been discussed on this platform. Fungal infections most commonly associated with COVID-19 virus are those which majorly affect upper respiratory tract and/or lungs, that is, *Mucor*, *Aspergillus*, and *Candida*. Fungal infections can cause great discomfort to the patient and, hence, need to be diagnosed at the earliest followed by subsequent therapeutic management or else can prove to be fatal. Conclusively, this review suggests that clinicians need to be vigilant about the possible opportunistic infections, and thus, COVID-19 management should be done judiciously.

Keywords: Mycoses, COVID-19, *Mucor*, *Aspergillus*, *Candida*

INTRODUCTION

Since 2019, the world has been battling a devastating pandemic in the form of COVID-19 infection, which has afflicted more than 170 million people and has led to 3.6 million deaths worldwide.[1] Dealing with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was dwelling into an unexplored universe with limited knowledge about disease presentation, the possibility of rapid and frequent viral mutations, an individual's immune response, as well as in the context of the resources available in the prevailing health-care system. With this finite understanding, India entered the catastrophic second wave that witnessed numerous COVID-19 patients being managed with diverse treatment protocols which included multivitamins, antiparasitics, systemic corticosteroids, and injectable antivirals (Remdesivir). Several cases of severe COVID-19 required administration of oxygen, hospitalization, prolonged stay in ICU, and mechanical ventilator support.

The immune dysregulation triggered by SARS-CoV-2 along with the already prevalent immunosuppressive states such as diabetes mellitus, hematological malignancies, lung diseases, and the concurrent administration of immunosuppressive corticosteroid therapy served as a causal pathway for the initiation and progression of other opportunistic infections dominated by ones of fungal origin.[2] The exact etiology of COVID-19-associated fungal spectrum (CAFS) is yet to be realized. However, with various fungal infections being declared as an epidemic in

India, the critical reality demands urgency for special focus on different aspects of CAFS.

AN INSIGHT INTO CAFS

CAFS encompasses *Aspergillus*, *Candida*, *Mucor*, *Coccidioides*, *Cryptococcus*, *Pneumocystis,* and *Saccharomyces*. The fungal coinfections linked with COVID-19 remain to be largely missed or misdiagnosed. Interestingly, the fungi that commonly colonize the respiratory tract and oropharyngeal mucous membrane have been most regularly associated with COVID-19 infection, namely, *Mucor*, *Aspergillus,* and *Candida*.[3] Moreover, the treatment of these possibly fatal infections has become an additional burden to the already stressed health-care system. The mycological conditions have varied intraoral presentation ranging from superficial to deep fungal infections of the oral tissues. Hence, a dental professional can play a key role in the early diagnosis and prompt management of fungal infections, thereby, reducing the mortality rate significantly. The present perspective is to summarize the fungal infections reported in COVID-19 patients.

COVID-19 AND *MUCOR*

Mucormycosis is the fungal infection caused by fungi of *Mucorales* order; genus *Mucor*, *Rhizopus*, *Rhizomucor,* and *Absidia* in *Zygomycetes* class. Immunosuppression caused due to COVID-19 infection leads to a reduction in the number of circulating CD4 T and CD8 T cells and an overwhelming inflammatory response that renders the body weak and susceptible to infections. This is aggravated by the immune suppressing effects of underlying conditions especially diabetes and use of steroids. Other factors such as humid climate and high temperature also provide a conducive environment for the growth of these fungi, leading to an increased risk of these infections.[4]

During the second wave of COVID-19, India has seen an increase in the incidence of rhino-orbitocerebral mucormycosis in patients suffering from COVID-19 or recovering from the infection.[5,6] Recently, in May 2021, the Health Ministry of India urged the state governments to declare the mucormycosis infection also known as black fungus, as a notifiable disease. Following this advisory, many Indian states and union territories have declared mucormycosis as an epidemic among which Rajasthan was the first state to declare mucormycosis epidemic on May 19, 2021.[7]

Clinical signs and symptoms

Mucormycosis can show a varied clinical presentation based on anatomical involvement that includes gastrointestinal, rhinocerebral, pulmonary, cutaneous, and disseminated form of mucormycosis.[8] General presentation may be of fever, headache or facial pain. Nasal stuffiness or purulent discharge, unpleasant smell, epistaxis, ulcerations, or inflammation in the nasal mucosa with ischemia or eschar may be seen. Ophthalmic involvement includes periocular edema or discoloration; facial pain and swelling; periorbital pain, tenderness, or pain in sinus region or toothache. Severe mucormycosis may present with proptosis or ptosis, loss of vision, diplopia, facial palsy, paralysis, or even seizure attacks.[9]

Oral manifestations appear usually in the form of ulcer, necrosis, crusting, or black eschar of the palate. It may also present as aphthous and tongue lesions or even loosening of teeth. The infection may progress to palatal perforation if it spreads to nasal cavity or involves the paranasal sinuses through the palatal vessels.[10]

Diagnosis

It can be detected using fluorescent stains in direct microscopy which shows *Mucorales* hyphae. Routine culture can also be done at 30–37° temperature and it shows cotton white or grayish-black fungal colonies. Advanced diagnostic tests as molecular level include polymerase chain reaction and rDNA analysis.[2,11]

Management

Effective management involves antifungal therapy with amphotericin B (AMB) which is considered as the first-line treatment of mucormycosis along with surgical debridement of necrotic lesions besides comprehensive control and management of associated underlying systemic illness.[12] The Indian Council of Medical Research guidelines advise strict monitoring of diabetic patients, judicious use of steroids, and antimicrobials for the prevention of this disease. Use of sterile water in humidifiers for oxygen therapy is also advised for hospitalized patients requiring oxygen support. A strict clinical and radiographic monitoring of patients is advised to assess treatment response and progression of infection.[13]

COVID-19 AND *ASPERGILLUS*

Spores of *Aspergillus* are typically present everywhere around us, hence, can be inhaled easily and subsequently enter the human lung tissues and/or paranasal sinuses causing local to disseminated aspergillosis. They are known to cause life-threatening invasive aspergillosis in immunocompromised individuals with bone marrow transplantations or hematological malignancies. The species causing invasive aspergillosis (*Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus*) have 30–95% mortality rate even if diagnosed early and despite appropriate antifungal treatment.[14]

As reported by Lei *et al*. in China, patients with severe COVID-19 had high rates of positive galactomannan, thereby increasing the probability of concomitant fungal infection.[15] Furthermore, patients with COVID-19 have presented with high serum levels of pro-inflammatory cytokines such as interleukin (IL)-6 and IL-10. Following an increase in IL-10 levels, greater Th2 response and Th1 immune depression are seen which increase host susceptibility to lethal *Aspergillus* infection. IL-6 plays an important role in protective immunity against *Aspergillus*. Immunomodulatory treatment with tocilizumab which has been approved in patients with severe COVID-19 as an anti-IL-6 agent can, nevertheless, potentially cause *Aspergillus* infection by reducing IL-6 immune response.[16] In the study by Bartoletti *et al*., most patients received anti-IL-6 treatment with tocilizumab as well as corticosteroids.[17]

Clinical signs and symptoms

Aspergillus spores once inhaled, can affect both upper and/or lower respiratory tract and clinical manifestations are seen in paranasal sinuses, larynx, eyes, ears, or oral cavity. Refractory fever for more than 3 days, worsening respiratory status (e.g. tachypnea or increasing oxygen requirements), chest pain, cough, hemoptysis, or pleural friction rub can suggest diagnostic investigations for invasive pulmonary aspergillosis. Invasion of the orbit and adjacent craniofacial areas may occur in cases of chronic and/or aggressive invasive sinonasal aspergillosis.[18]

Oral aspergillosis manifests as black or yellow necrotic tissue on an ulcer base over the palate or in the posterior tongue. *Aspergillus* invades soft-tissue lining of maxillary sinus, from where it progresses down to the bone and causes palatal infarction and manifests in the oral mucosal tissues or disseminates into systemic organs. Aspergillosis organisms eventually develop into ball-shaped masses due to their centrifugal linear growth.[19]

Diagnosis

Fungus culture, PCR, galactomannan tests, and b-D-glucan test are used to detect the presence of *Aspergillus* species. Detection of galactomannan in bronchoalveolar lavage fluid is highly suggestive of aspergillosis. Histopathological examination reveals invasive growth of septate fungi that branch at 45° angle along with conidiospores and fruiting bodies. In addition, radiographic picture of patients with COVID-19-associated pulmonary aspergillosis shows peripheral nodule, air crescent, reverse halo sign, nodular consolidation, ground-glass opacities, crazy paving pattern, pleural effusion, and pulmonary cysts.[16]

Management

Cases of aspergillosis have shown favorable responses with AMB, voriconazole, isavuconazole, and caspofungin. Surgical management has a significant role in treating invasive aspergillosis of sinus. Few reports have suggested local debridement with AMB as an adjunct treatment modality following surgical treatment.[18]

COVID-19 AND *CANDIDA*

Candida albicans is a common resident of the oral mucosa, however, its growth is suppressed by other organism in the oral microbiome, thus, remaining non-virulent. Species such as *Candida tropicalis*, *Candida glabrata*, *Candida krusei,* and *Candida parapsilosis* are found at various mucosal surfaces, such as the skin and the pulmonary, gastrointestinal, and urinary tracts.[20,21] A literature of 11 cases by Moser *et al*. reported upregulated monocyte CD80 and negate release of IL-6 and IL-1α, thus increasing the susceptibility for candidemia in critically ill COVID-19 patients.[22] India reports the rate of superficial and invasive candidiasis to be 2.5% in the first wave.[23] Researchers support the concept of classical risk factors such as prolonged ICU hospitalization, central venous catheters, and broad-spectrum antibiotic use[24] for invasive candidiasis despite the marked immune cell dysregulation seen in COVID-19 patient.[25]

Clinical signs and symptoms

Infections on skin and mucosa including vulvovaginal or oropharyngeal regions are the most prevalent clinical entities of superficial candidiasis.[26] Invasive candidiasis is a serious infection that can affect the blood (candidemia), heart, brain, eyes, bones, and also other parts of the body and can project symptoms accordingly. The most common symptoms are fever and chills that do not improve after antibiotic treatment for suspected bacterial infections.

The recent case reports of patient infected with SARS-CoV-associated oropharyngeal candidiasis present an array of symptoms ranging from white membranous non-scrapable patches on the mucosa, tongue, and palate to throbbing pain in the oropharyngeal region. Loss of taste, severe burning sensation, and erythematous patches of candidiasis have also been observed. Majority of cases had oral pseudomembranous candidiasis described as white plaque extending over tongue dorsum and oral mucosa responding well to topical antifungal agents.[27]

Diagnosis

The clinical presentation with its classical features, exfoliative cytology, potassium peroxide staining, oral swab specimen for culture analysis, and oral mucosal biopsy of candidiasis is used for diagnosis of candidiasis. Definitive diagnosis is obtaining with the help of special staining procedure such as periodic acid-Schiff.[19,25]

Management

The empirical approach for candidiasis treatment is with nystatin oral suspension which is discontinued after 48 h of disappearance of perioral symptoms. At times, endocrine-associated candidiasis may not responds to nystatin treatment for which alternative antifungal regime should be suggested. Oropharyngeal candidiasis is approached with clotrimazole tablets or fluconazole. Systemic candidiasis respond well with flucytosine and flucytosine oral rinse is recommended for the oral lesions of systemic candidiasis.[28]

OTHER FUNGAL INFECTIONS ASSOCIATED WITH COVID-19

Although not diagnosed in India yet, there are other fungal organisms reportedly associated with COVID-19. Coccidioidomycosis and COVID-19 coinfection have been reported in Southwest United States, both diseases having common symptoms that include fever, dry cough, dyspnea, myalgia, and headache. Infection with COVID-19 might reactivate Coccidioides fungus which remains in the lung in a latent state. This has been seen in certain conditions such as pregnancy or immunocompromised states.[29]

Histoplasmosis and *Cryptococcus* are seen as opportunistic fungal coinfections in COVID-19 patients with AIDS and immunosuppression. *Histoplasmosis capsulatum* causes *Histoplasmosis* infection which is a deep fungal infection affecting pulmonary tissue or mucocutaneous areas. Mucocutaneous form may produce solitary, painful or painless, ulcerative, erosive lesions on the tongue, palate, and/or buccal mucosa. Oral ulcerations are typically characterized by firm rolled borders that mimic a malignant neoplasm.[30]

Cryptococcemia caused by *Cryptococcus neoformans*, a known cause of meningoencephalitis in immunocompromised patients, has been reported in COVID-19 patients with a history of receiving tocilizumab and corticosteroids.[31]

Cases of *Saccharomyces cerevisiae* have been reported in a few COVID-19 patients hospitalized in ICU, who have taken probiotics containing *Saccharomyces*. These infections are often misdiagnosed as *Candida* infections.[32]

Pneumocystis pneumonia, mostly seen as an opportunistic fungal infection in AIDS patients, was reported as a coinfection in a patient with COVID-19 but with no known immunodeficiency or risk factors for the development of *Pneumocystis jirovecii* infection.[33]

CONCLUSION

There is enough evidence to suggest that COVID-19 infection causes immunosuppression, hence, increasing the susceptibility of developing opportunistic fungal infections. India has reported multiple cases of such fungal infections as post-COVID complications, often nicknamed as white fungus (*Candida*), black fungus (mucormycosis), and yellow fungus (aspergillosis). The development of these diseases may be attributed to the use of glucocorticoids, and hence, judicious use of these drugs has been suggested. Further, in the absence of a clear benefit, drugs targeting immune pathways such as tocilizumab should be discouraged.

The stewardship in managing COVID-19 patients needs to focus on expanding knowledge about the risk factors associated with the development of opportunistic fungal infections. Early diagnosis and timely management of these infections can improve patient outcomes significantly. These infections have proven to be fatal, and thus, it is important to be vigilant about opportunistic fungal pathogens and robust surveillance of high-risk hosts is required to reduce the number of these infections.

Declaration of patient consent

Patient consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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