REVIEW ARTICLE

A Possible Warning for COVID-19 Patients on Complications of Fungal Infection: A review

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ABSTRACT

New problems are emerging in the health sector as the global Coronavirus Disease 2019 (COVID-19) pandemic expands worldwide. The big global emergency is the need for effective testing tools, therapies, and vaccines for COVID-19. Although these targets are particularly important, the increasing risk of coinfections is a significant threat to health systems and patients' lives. Although statistical data are still not adequately released, coinfections in patients with COVID-19 developed secondary systemic mycosis. Any of these significant results will be discussed in this review with the main objective of warning the population of the high risk of concomitant systemic mycosis in individuals with COVID-19 induced weakness**.**

Keywords: Associated Pulmonary Aspergillosis, COVID-19, Invasive fungal infections, systemic mycosis.

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1 CORONAVIRUS (COVID-19):

1.1. Structure and Genome:

Coronaviruses are further categorized by their general in, alpha-, beta-, gamma-, and delta Coronaviruses, a class of viruses within the superfamily of nidoviruses. Among these, only mammals can be infected by alpha and beta species while infecting birds with the other two genera and may also infect mammals.[1,2] Two of these genera belong to human viral pathogens (hcovs). human coronavirus 229e (hcov229e) and human coronavirus nl63 (hcovnl63) and human coronavirus hku1, human coronavirus oc43, and human coronavirus nl63 (hcovnl63), human coronavirus middle east respiratory syndrome coronavirus (MERS-Cov), and human coronavirus sars-cov (severe acute respiratory syndrome coronavirus).[3] The covid-19 (coronavirus disease 2019) is now known as the severe acute respiratory syndrome Cov-2 (SARS-Cov-2).[4] genome sequencing and phylogenetic analysis have shown that the covid-19-causing coronavirus is a beta-coronavirus belonging to the same sars virus subtype but still occurring in the various group. The receptor-binding gene region appears to be completely similar to that of SARS-Cov, and it is thought that the same entry.[5] Structurally enveloped coronaviruses belong to the group of positive-strand RNA viruses that have the largest known RNA genomes.[6] Coronavirus structures are more spherical in shape, but their structure has the potential to change their morphology, being pleomorphic in response to environmental conditions. Usually, the capsular membrane representing the outer envelope has glycoprotein projection and covers the nucleus, consisting of a matrix protein containing RNA with a positive strand. the structure consists, as shown (Figure 1), of hemagglutinin esterase (he) (only present in certain beta-coronaviruses), spike (s), small membrane (e), membrane (m) and nucleocapsid (n).[7]

The glycoprotein-containing envelope is responsible for binding to the host cell, which has primary antigenic epitopes, specifically those recognized by neutralizing antibodies. In a spike shape, the spike S-protein is subjected to a structural rearrangement process so that it becomes easier to fuse the virus' outer membrane with the host-cell membrane. The latest SARS-CoV work has also shown that the ACE enzyme (angiotensin-converting enzyme) membrane exopeptidase acts as a COVID-19.[8] When the host cell enters, and there is a process of uncoating, the genome is transcribed and then translated. A characteristic replication function is that all mRNAs form a standard 3' end enclosed group; the

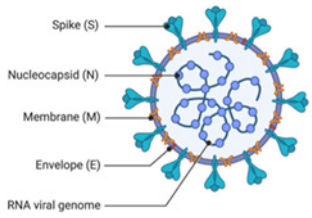

Figure 1: Coronavirus structures

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unique portions of the 5' end are translated. About 7 mRNAs are produced in total. The synthesis of another genome section for nucleoproteins can be represented by the shortest mRNA codes and the others. These proteins are accumulated in the cell membrane and genomic RNA is initiated by burgeoning from the inner cell membrane as a mature particle type.[9,10]

1.2. Pathogenicity

Coronaviruses are extremely accurate and develop in most airway epithelial cells, as demonstrated in both in vivo and in vitro tests. Due to the damage to the host cell, enhanced nasal secretion is observed along with local edema, which further promotes the synthesis of inflammatory mediators. in addition, by inducing airway inhibition, these reactions can cause sneezing, trouble breathing, and elevated mucosal temperature. When these viruses are released, they mostly impact the lower respiratory tract, causing clinical signs and symptoms. The virus frequently affects intestine lymphocytes, kidney cells, liver cells, and t-lymphocytes. Furthermore, the virus causes t-cell apoptosis, resulting in a disorderly t-cell response and the immune system's collapse.[11,12]

2. INVASIVE FUNGAL INFECTIONS (IFI) DURING COVID-19

The risk of developing invasive fungal infections (IFI) is high in severe COVID-19 cases with hemato-lymphohistiocytosis syndrome, not only because of the patient's clinical condition and the need for invasive care also because of the immune changes caused by SARS-CoV-2 and the treatment used.[13] A controversial point was the treatment of corticosteroids in patients with COVID-19. Dexamethasone, widely used to treat inflammatory and autoimmune illnesses, is a well-known drug. Recent studies support reducing the duration of invasive mechanical ventilation and hospital mortality in extreme COVID19 through dexamethasone.[14] Clinical trials, performed in the United Kingdom with dexamethasone, have identified dexamethasone as the first steroid to prevent deaths from serious COVID-19 events, but no influence was seen in patients who did not receive respiratory support.[15] Infection with SARS-CoV-2 is characterized by increased pro-inflammatory cytokines and decreased anti-inflammatory cytokines, resulting in cytokine storm syndrome status. The control of this inflammatory state can be decreased by dexamethasone. For other causes, this effect was already observed in ARDS.[16] Corticosteroid use is an intensively investigated risk factor in seriously ill patients for the progression of invasive aspergillosis[17] in a report conducted. It indicates that, relative to other patients who did not undergo steroid medication, patients receiving corticosteroids had a 3.33-fold increased chance of developing IFIs. Cyclosporine medication, particularly in post-transplant patients, has also been associated with IFI.[18] On the other hand, interferons have different effects on the innate and adaptive immune cells that activate other mediators during fungal infections. However uncertain, interferons can interfere with the immune response to infections with Candida albicans, Histoplasma capsulatum, and Cryptococcus neoformans.[19]

Since the end of the 20th century, fungal infections that cause systemic mycosis have become a significant threat, particularly affecting individuals with some immunological deficiency, a clinical and pharmaceutical challenge. Despite the fact that these fungal agents infect billions of people globally, killing more than 1.5 million every year, the effect of mycosis has been underestimated.[20] In patients with coronavirus infection, Aspergillus coinfection was under-diagnosed and under-reported, most likely due to lack of clinical consciousness and diagnostic screening. To date, 38 Aspergillus sp. cases COVID-19-related (CAPA) was released.[21,22]

Considering the radiological patterns of COVID-19 and the difficulty of isolating Aspergillus sp., we need to define the criteria for the diagnosis of Aspergillus-COVID-19. In samples of respiration. The fact that extreme COVID-19 constitutes a high-risk population must also be recognized, not only because of the immunosuppression triggered by the viral infection itself but also by the use of some drugs. Also, the prevalence of mycotic infections in patients with serious COVID-19 is possibly much higher than recorded in the scientific literature, given the complexity of diagnosis and the lack of specific tests.

2.1. Associated Pulmonary Aspergillosis COVID-19 Prevalence

Among COVID-19 patients, several studies from China reported high rates of Aspergillus infections. 60/257 COVID-19 (23.3 %) patients had samples of the throat swab which tested positive for Aspergillus spp. They were reported as coinfections of Aspergillus.[23] Another Chinese research from Zhejiang Province recorded that 8 out of 104 patients with COVID-19 (7.7%) had Invasive Pulmonary Aspergillosis.[24] Another study found that 27% of COVID-19 patients (13/48) had fungal infections but no additional details.[25] Lower rates of fungal infections ranging between 3.2–5 percent were reported in other studies from China.[26,27] In fact, pulmonary aspergillosis diagnosis is difficult for cultures with limited sensitivity. Therefore, none of those studies used specific definitions and standardized diagnostic methods.[28,29] Consequently, some of these recorded rates are likely to underestimate the actual burden of Invasive Pulmonary Aspergillosis in patients requiring ICU admission with COVID-19, While other rates may be overestimated because Aspergillus colonization in the upper respiratory tract is potentially mischaracterized as Aspergillus infection. More recently, many European studies (Germany, France, the Netherlands, and Belgium) have recorded high Associated Pulmonary Aspergillosis COVID-19 rates among COVID-19 cases, ranging 20 to 35%[30,31] (Table 1).

3. FINDINGS THROUGH RADIOGRAPHIC

Several studies[30,32,33] have reported radiographic findings of pulmonary aspergillosis associated with COVID-19. Wang et al., 2020, showed that there could be a typical IPA presentation at the early stage, including cavity, nodules, and dendritic signs (Figure 2). In addition, several findings, such as air crescent, peripheral nodule, nodular consolidation, reverse halo sign, crazy paving pattern, ground-glass opacity, pulmonary cysts,

Table 1: A review of previously identified cases of pulmonary aspergillosis associated with COVID-19

Study	*Country*	*CAPA**	*Aspergillus species*
Alanio, 2020	France	9/27	*A. fumigatus* (7/9)
Rutsaert, 2020	The Netherlands	7/34	*A. fumigatus* (5/7)
Koehler, 2020	Germany	5/19	*A. fumigatus* (5/5)
Nasir, 2020	Pakistan	5/23	*A. flavus* (3/5), *A. niger* (1/5) *A. fumigatus* and *A. flavus* (1/5)
Antinori, 2020	Italy	1/1	*A. fumigatus*
Prattes, 2020	Austria	1/1	*A. fumigatus*
Wang, 2020	China	8/104	*A. fumigatus*

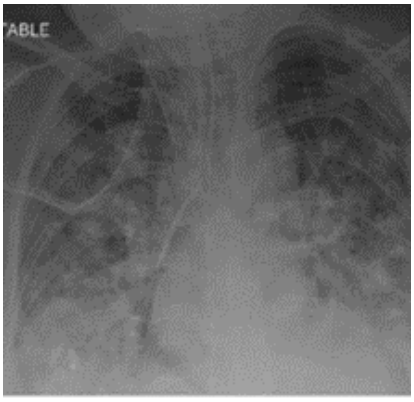

Figure 2: Chest radiograph showing marked progress in bilateral consolidation opacities. Aspergillus complex isolated from respiratory tract samples was obtained by non-bronchoscopic endotracheal

and pleural effusion, were reported in other reports among Covid-19 Associated Pulmonary Aspergillosis patients

4. THE CHALLENGES

The Challenges of CAPA can be Summarized:

Diagnosis of Patients: It is controversial to diagnose patients with CAPA. Recent cases show that known invasive pulmonary aspergillosis (IPA) agents are usually absent from the intensive care unit in COVID-19 patients, and radiological diagnosis is rarely unique to invasive fungal disease. The diagnosis of CAPA is usually based on the identification of Aspergillus in upper respiratory tract specimens such as sputum or tracheal spray because of the limited use of bronchoscopy, which may indicate colonization of the airway rather than IPA.[31,35] Treatment: For IPA, voriconazole remains the recommended first-line treatment. However, drug-drug interactions may particularly limit the use of voriconazole in the ICU setting, in addition, interactions with experimental COVID-19 treatments, including hydroxychloroquine, atazanavir, lopinavir/ritonavir. Therefore, Further research should also evaluate the effectiveness of using voriconazole in patients with COVID-19 who have received anti-SARSCoV-2 agents.[36]

CONCLUSION

The incidence of fungal infections has dramatically increased due to opportunistic pathogens. Our findings indicate that COVID-19 patients have an elevated risk of developing coinfections with fungi, such as aspergillosis. Given the radiological patterns of COVID-19 and the difficulty of isolating Aspergillus sp, the criteria for the diagnosis of Aspergillus-COVID-19 in respiratory samples need to be established. And with the problem, The occurrence of fungal infections is probably much higher in patients with severe COVID-19 than reported in the scientific literature. Also, the antifungal agent voriconazole should be used with care if a complex drug-drug interaction occurs.

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