Review

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The increase in *Aspergillus* infections during and after the COVID-19 pandemic

Zeynel Öztürk[1], Nuray Bayar Muluk[2], Oğuzhan Oğuz[3], Mustafa Yazır[4], İmran Özdemir[5], Cemal Cingi[6]

[1]*Department of Otolaryngology, Baypark Hospital, İstanbul, Turkiye*
[2]*Department of Otorhinolaryngology, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkiye*
[3]*Department of Otolaryngology, Dr. Oğuzhan Oğuz Wellnose Clinic, İstanbul, Turkiye*
[4]*Department of Otolaryngology, Yazır Private Otorhinolaryngology Clinic, İzmir, Turkiye*
[5]*Department of Pulmonology, Türkiye Private Hospital, İstanbul, Turkiye*
[6]*Department of Otorhinolaryngology, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkiye*

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ABSTRACT

This paper aims to identify the correlation between *Aspergillus* infections and the COVID-19 pandemic. The literature review used PubMed, EBSCO, Proquest Central at Kırıkkale University, Google, and Google Scholar. Between 2024 and 1980, the keywords "*Aspergillus*," "aspergillosis," "invasive pulmonary aspergillosis," "IPA," "COVID-19-associated pulmonary aspergillosis," "CAPA," and "COVID-19" were searched. An association between COVID-19 pneumonia and invasive pulmonary aspergillosis (IPA), a complication seen in patients with severe respiratory syndromes, has been recently demonstrated, and the clinical features of COVID-19-associated pulmonary aspergillosis (CAPA) have been detailed. Due to diagnostic delays and the quick deterioration of respiratory diseases, infections caused by the *Aspergillus* genus are frequently recognized after the fact, which is a sad reality. From direct angioinvasion to hypersensitivity reactions, *Aspergillus* may inflict various human diseases. Invasive *Aspergillus* infections are sporadic in immunocompetent people and nearly always affect those immunosuppressed due to lung illness, immunosuppressive medication, or immunodeficiency. *Aspergillus fumigatus (A. fumigatus)* was found in most COVID-19 patients, and CAPA was also detected in several of these individuals. Also, patients with severe respiratory illnesses, like influenza and MERS-CoV, have been found to have multiple instances of IPA as super-infections. The function of antifungal prophylaxis in CAPA is unknown even though *A. fumigatus* was detected before the start of CAPA. On the other hand, voriconazole medication may be effective if begun right after.

Keywords: Aspergillus, invasive pulmonary aspergillosis, COVID-19 associated pulmonary aspergillosis, COVID-19, *Aspergillus fumigatus*

INTRODUCTION

Recently, there was an association between COVID-19 pneumonia and invasive pulmonary aspergillosis (IPA), a complication seen in patients with severe respiratory syndromes. The clinical features of COVID-19-associated pulmonary aspergillosis (CAPA) have been detailed. Diagnostic delays and the quick deterioration of respiratory problems typically result in the late diagnosis of *Aspergillus* genus infections.[1]

Due to the immune-compromising properties of SARS-CoV-2 and medications such as tocilizumab and dexamethasone, some researchers were concerned that COVID-19 patients could have a fungal superinfection.[2-6] The reported cumulative rates of CAPA range from 0.7 to 7.7 percent in COVID-19 patients[7,8], 2.5 to 39.1 percent in COVID-19 intensive care unit patients[9,10], and 3.2 to 29.6 percent in COVID-19 patients requiring mechanical ventilation.[7,11]

Aspergillus infections and the COVID-19 pandemic are the foci of this research.

METHODS

The literature review utilized Google, Google Scholar, PubMed, EBSCO, and Proquest Central at Kırıkkale University. From 2024 to 1980, we searched for "*Aspergillus*," "aspergillosis," "IPA," "COVID-19-associated pulmonary aspergillosis," "CAPA," and "COVID-19."

ASPERGILLOSIS

The fungus *Aspergillus* is present in all organic materials. There are more than a hundred species of *Aspergillus*, but only

Corresponding Author: Oğuzhan Oğuz , oguzhanoguz2023@outlook.com

two—*Fumigatus fumigatus* and *Aspergillus niger (A. niger)*—cause severe sickness in humans. *Aspergillus flavus (A. flavus)* and *Aspergillus clavatus* are less common. Fungal spores can infect humans through the air we breathe.[12]

From direct angioinvasion to hypersensitivity reactions, *Aspergillus* may inflict various human diseases. The following four primary syndromes[12] are caused by *Aspergillus*, which primarily affects the lungs:

- Aspergillosis of the airways and lungs (ABPA)
- *Aspergillus* chronic pneumonia with necrotizing microorganisms (CNPA)
- Aspergilloma
- Aspergillosis with metastasis

Endophthalmitis, endocarditis, and abscesses in the myocardium, kidneys, liver, spleen, soft tissue, central nervous system (CNS), and bone can result from *Aspergillus* hematogenously disseminating beyond the lung in patients with severely impaired immune systems. Regarding fungal endocarditis, Candida species is the most common culprit, followed closely by *Aspergillus*. In cardiac surgery, wound infections and endocarditis caused by *Aspergillus* can arise.[12]

ABPA, a hypersensitivity reaction to A fumigatus colonization of the tracheobronchial tree, co-occurs with asthma and cystic fibrosis (CF). Both ABPA and allergic fungal sinusitis are possible. Two uncommon hypersensitivity lung illnesses induced by *Aspergillus* species are broncho-centric granulomatosis and malt worker's lung.[12]

A mycetoma, or fungus ball, occurs in the lung parenchyma when an aspergilloma grows in an existing hollow. Cavitary disease can have several underlying causes, such as CF, sarcoidosis, emphysematous bullae, treated tuberculosis, or another necrotizing infection. Although the fungus ball can move inside the cavity, it will not penetrate the cavity wall. The risk of hemoptysis, however, is twelve.

Patients with immunosuppression, whether from drinking, long-term corticosteroid treatment, underlying lung disease, or any other cause, are more likely to experience CNPA, a subacute process. The gradual cavitary pulmonary infiltration that CNPA causes is sometimes not noticed for weeks or months due to how rare it is.[12]

Rapidly progressing and frequently deadly invasive aspergillosis affects immunocompromised individuals, such as those who are profoundly neutropenic, have undergone bone marrow or solid organ transplants, have advanced AIDS[13] or chronic granulomatous disease, and so on. In this infectious process, blood vessel invasion causes multifocal infiltrates, which can be cavitary, wedge-shaped, and based on the pleura. The CNS is a potential target for dissemination.[12]

Pathophysiology

Aspergillus causes colonization, hypersensitivity reactions, persistent necrotizing infections, and potentially fatal, quickly progressing angioinvasion. Invasive *Aspergillus* infections are sporadic in immunocompetent people and nearly always occur in immunosuppressed patients due to underlying pulmonary illness, immunosuppressive medication therapy, or immunodeficiency.[12]

Aspergillus hyphae stand out histologically compared to other fungi due to the many septae that branch at 45° angles. Tissue stained with silver allows one to see the hyphae more clearly. Even though other *Aspergillus* species have been found in nature, the one most commonly infecting humans is *Aspergillus fumigatus (A. fumigatus)*. The occurrence of *A. flavus* and *A. niger* is reduced. This disparity in frequency is likely associated with the fact that *A. fumigatus* can thrive at average human body temperature, in contrast to the majority of *Aspergillus* species.[12]

The respiratory system's mucous membrane and ciliary activity are the first lines of protection against inhaled spores in humans. The fungus is engulfed and destroyed by macrophages and neutrophils. However, poisonous compounds produced by numerous *Aspergillus* species prevent macrophage and neutrophil phagocytosis. Additionally, corticosteroids hinder the activity of neutrophils and macrophages.[12]

Neutrophil malfunction or reduced numbers can be caused by underlying immunosuppression, such as HIV illness, chronic granulomatous disease, or pharmaceutical immunosuppression. Vascular invasion is more common in immunocompromised people and can cause lung infarction, bleeding, and necrosis. In people with CNPA, granulomas form, and alveoli consolidate. Hyphae can be seen inside the granulomata.[12]

Risk Factors

Several factors can increase the likelihood of invasive aspergillosis following a bone marrow transplant. These include central venous catheters, prolonged neutropenia, graft-versus-host disease, high-dose corticosteroid therapy, disruption of standard mucosal barriers, and transplants from unrelated or unmatched donors.[12,13]

People on long-term corticosteroid treatment for severe sickness or chronic obstructive pulmonary disease (COPD) are at increased risk of developing an invasive *Aspergillus* infection, even if they do not have a history of cancer or chemotherapy and are likely not immunocompetent.[14]

About a quarter of intubated patients with severe coronavirus disease 2019 (COVID-19) had pulmonary aspergillosis, which is associated with a higher risk of death within 30 days.[15-19] The incidence of CAPA among intensive care unit patients was reported to be between 4% and 35% in a report from April 2021.[20] The question of whether CAPA is a separate entity is still up for debate, according to a March 2021 comparative investigation. However, the high mortality rate (60-70%) among the presumed ICU cases provides support for this theory.[21]

COMPLICATIONS OF COVID-19

Some of the many complications that can arise from contracting COVID-19 include pneumonia, acute respiratory distress syndrome, heart damage, arrhythmia, septic shock, dysfunction of the liver and kidneys, and failure of multiple organs.[22]

Severe symptoms requiring intensive care are experienced by around 5% of COVID-19 patients and 20% of those hospitalized. Acute liver injury (19%), pneumonia (75%), acute respiratory distress syndrome (15%), acute kidney injury (9%), and AKI (9%). More and more cases of cardiac damage, such as myocarditis, dysrhythmias, abrupt heart failure, and troponin increase, have been documented. Thrombotic coagulopathy, which can lead to venous and arterial thromboembolic events, affects 10% to 25% of COVID-19 hospitalized patients. Impaired consciousness and stroke are examples of neurologic symptoms.[22] Up to 40% of patients in the intensive care unit die.[23]

Long COVID

More and more patients have suffered long-term, post-infection consequences as the COVID-19 epidemic has progressed. Although the majority of patients make a full recovery, a small percentage may experience side effects such as exhaustion, shortness of breath, coughing, anxiety, depression, trouble concentrating (often known as "brain fog"), issues with the digestive system, disturbed sleep, pain in the joints, and chest discomfort that worsens weeks or months after the initial sickness has passed. Researchers are conducting long-term investigations to learn more about these problems.[24]

The medical word for what is usually referred to as long COVID or "long haulers" is post-acute sequelae of SARS-CoV-2 infection (PASC). In their recommendations on the clinical spectrum of COVID-19, the National Institutes of Health address issues such as long-lasting symptoms or organ failure following acute infection.[25]

Future Public Health Implications

According to Datta et al.[26], who evaluated the topic, the public health consequences of extended COVID need to be investigated. Late inflammatory and virologic consequences may manifest, similar to other illnesses such as Lyme disease, syphilis, and Ebola. To know what this disease is all about, we need to look at evidence beyond acute infection and post-acute hyperinflammatory sickness.[26]

The capacity of SARS-CoV-2 to infiltrate endothelial cells through the surface-expressed angiotensin-converting enzyme-2 (ACE-2) causes thrombotic symptoms in severe COVID-19. Microthrombotic consequences, such as deep vein thrombosis (DVT), peripheral edema (PE), and stroke, might result from immunothrombosis, which is itself caused by endothelial inflammation, complement activation, thrombin production, platelet, and leukocyte recruitment, and the start of innate and adaptive immunological responses.[27]

Immunosuppressive treatments may cause an increase in *Aspergillus* infections. It should be kept in mind and if necessary, *Aspergillus* treatments should be given to the patients.[28]

INVASIVE PULMONARY ASPERGILLOSIS (IPA) AND COVID-19-ASSOCIATED PULMONARY ASPERGILLOSIS (CAPA)

Patients with severe respiratory syndromes often experience interstitial pneumonia (IPA), which is caused by the *Aspergillus* species and is associated with significant fatality rates.[18,29] Several risk factors can lead to IPA, the most common of which is lung epithelial injury and long-term corticosteroid treatment.[26] Multiple reports have reported IPA as super-infections in patients with severe respiratory illnesses, such as influenza and MERS-CoV.[18,30]

In reality, postmortem diagnosis is often made in patients with COVID-related pulmonary aspergillosis. Unfortunately, due to their essential concerns, we could not routinely obtain samples from the patient's lower respiratory tract. The likelihood of defining an *Aspergillus* fungal colonization and the promptness of an accurate diagnosis of pulmonary aspergillosis were both negatively affected by this discomfort. The patient's respiratory condition quickly deteriorated due to these delays and other risk factors, such as significant lung injury and protracted therapy with corticosteroids.[30] The patient has a history of diabetes, which increases the risk of fungal angioinvasion due to changes in blood artery structure. Agar gel immunodiffusion was used to identify Aspergillus-specific antibodies in serum to clarify the eventuality of a prior chronic *Aspergillus* infection. Based on the negative result, it is highly probable that the patient contracted an illness while intubating in a healthcare facility. Most recent findings indicate that *Aspergillus* spp. in immunocompetent hosts is acknowledged as a possible source of VAP.[31,32]

Although *Aspergillus niger* can cause severe lung disease, it is more commonly mentioned as the source of otomycosis and cutaneous infections rather than invasive aspergillosis.[33] Research into agricultural regions of southern Italy for the existence of triazole-resistant *Aspergillus* isolates also found other species of the fungus. Even though these species aren't as dangerous as *A. fumigatus*, which can cause invasive illness in susceptible people, they are often found isolated in Sicily.[34] The patient's respiratory status was so bad that he died even though the fungal etiology was determined, and voriconazole was given quickly. Therefore, including immunocompetent hosts, instances with severe respiratory syndromes should be evaluated for IPA as a potential consequence.[35,36]

According to Salmanton-García et al.[2], patients were expected to face the possibility of fungal superinfection due to the significant immunomodulation and lymphocyte depletion brought about by COVID-19 and the following use of medications targeting the immune system. From March 2020 to August 2020, 186 individuals worldwide with coronavirus disease-associated pulmonary aspergillosis (CAPA) were surveyed. A total of 182 patients were admitted to the ICU; among them, 175 required mechanical ventilation, and 180 had acute respiratory distress syndrome. On average, CAPA was detected ten days after the diagnosis of coronavirus illness.

Of the patient cultures tested, 80.3% included *A. fumigatus*, with four strains exhibiting resistance to azoles. A majority of patients (52.7%) were given voriconazole. Overall, 52.2% of patients passed away, with 33.0% of those fatalities being linked to CAPA. According to our findings, the cumulative incidence of CAPA in the intensive care unit ranged from 1.0% to 39.1%.

According to the study by Salmanton-García et al.[2], 26.9% of COVID-19 patients had positive results for *Aspergillus* in their BAL cultures, while 33.9% had positive results for galactomannan. In 35.4% of IAPA[36] and 35.4% of CAPA, cultures were taken from non-bronchial aspirates (such as sputum, bronchial aspirate, non-bronchial lymph node, or tracheal aspirate).

A patient diagnosed with CAPA and prescribed voriconazole was reported by Kitayama et al.[37] in their study. Radiological results and BDG levels both improved after treatment. Specifically, tocilizumab was likely pivotal in bringing about the illness in this instance. Despite the lack of solid evidence supporting antifungal prophylaxis medication for CAPA, this case demonstrates that the presence of *Aspergillus* in airway specimens before the start of the disease may indicate a high risk of developing CAPA. It should be taken into consideration when planning antifungal prophylaxis.

December 2020 saw the publication of consensus criteria for the identification of CAPA by the ECMM and the International society for human and animal mycology. These criteria classified patients as having probable, proved, or potential CAPA.[38] In 77.6% (149/192) of CAPA patients, the diagnosis was made by lower respiratory tract culture, with bronchoalveolar lavage fluid (BALF) being the primary source, according to a systematic study of CAPA.[39] Two fungal biomarkers documented in CAPA diagnosis are galactomannan antigen (GM) and BDG. Using a threshold value of 0.5 for serum and 1.0 for BALF, about 18.2% (35/192) of CAPA patients tested positive for GM in blood, and 45.3% (87/192) tested positive in BALF. Only 10.4% (20/192) of CAPA patients were positive for other BDG blood indicators. Overall, 48.4% (93/192) of patients diagnosed with CAPA died, with mortality rates varying among hospitals, according to the same analysis. Since there is a lack of reliable diagnostic tests, individuals thought to have IPA should begin antifungal therapy without delay to manage the disease better.[40]

The first defense against CAPA is voriconazole or isavuconazole.[38] Although the ideal number of weeks of antifungal treatment for CAPA is unclear, a group of experts has recommended 6-12 weeks.[38] From an infection control standpoint, BALF could not be explored; nevertheless, GM in serum was opposing, BDG was positive, CT revealed a new consolidation with a cavity, and *Aspergillus* was discovered in sputum culture. As a result, Kitayama et al.[37] promptly began treating patients with voriconazole after making a potential CAPA diagnosis using the ECMM criteria; this led to a positive outcome.

Furthermore, even though A. It still needs to be made clear what function antifungal prophylaxis plays in CAPA since fumigatus was discovered before the start of the disease. Antifungal prophylaxis decreases the likelihood of developing CAPA. Still, it does not enhance the outcome, according to Hatzl et al.[41] Since the article by Kitayama et al.[37] notes that COVID-19 patients with CAPA had bad outcomes, we cannot conclude that antifungal prophylaxis is effective in preventing CAPA. A multicenter randomized trial is necessary to establish the importance of antifungal prophylaxis in severe COVID-19 since their data is a single-center, non-randomized observational analysis.

Limitation of this review, the is a narrative review, it is not systematic review.

CONCLUSION

Although *A. fumigatus* was discovered before the pandemic, the function of antifungal prophylaxis in CAPA must be clarified. On the other hand, voriconazole medication may be effective if begun right after diagnosis.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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