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COVID-Associated Pulmonary Aspergillosis(CAPA): An Underrated COVID Superinfection

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Abstract

Severe acute respiratory syndrome coronavirus–2 (SARS-CoV-2) has spread fast over the world. Immune dysfunction linked with acute respiratory distress syndrome (ARDS) make patients more vulnerable to opportunistic infections. Direct damage to the airway epithelium has been seen, which gives an opportunity for Aspergillus species to infiltrate tissues. The hazards of bronchoalveolar lavage in COVID-19 patients and the poorer sensitivity of galactomannan tests makes the diagnosis challenging. Drug–drug interactions associated with broad-spectrum azoles, renal tropism, and damage induced by SARS-CoV-2, which may hamper the use of liposomal amphotericin B, as well as the formation of azole-resistance, all complicate COVID-associated pulmonary aspergillosis (CAPA) therapy. This clinical reality necessitates the development of novel antifungal medicines with more promising pharmacokinetic and pharmacodynamic profiles.

Keywords: Severe acute respiratory syndrome coronavirus–2, co-infection, prevalence, pulmonary aspergillosis, Aspergillus fumigates, COVID-associated pulmonary aspergillosis

INTRODUCTION

Fungi are increasingly acknowledged as major pathogens in critically ill patients. Candida species and Cryptococcus species are the yeasts most frequently isolated in clinical practice. Several reasons can be attributed to the increasing prevalence of invasive fungal infections, some of which include use of antineoplastic and immunosuppressive agents, broad-spectrum antibiotics, prosthetic devices and grafts, and more aggressive surgery.[1] Aspergillus species are the most commonly isolated invasive moulds and the infections caused by these species are responsible for affecting millions of lives since the inception of COVID-19. Only a few of the 200 or so species are pathogenic to man, primarily Aspergillus fumigatus, Aspergillus flavus and Aspergillus niger.

Invasive pulmonary aspergillosis (IPA) is a well-known complication in immunocompromised patients, and it is particularly common in recipients of haematopoietic stem cell or solid organ transplants.[2] This necessitates the importance of creating awareness regarding the COVID-associated pulmonary aspergillosis and timely detection as well as management of the condition.

METHODS

The PUBMED and GOOGLE SCHOLAR databases, as well as the bibliographies of retrieved publications, were searched, and publications examining post-COVID pulmonary aspergillosis were included in the review.

DISCUSSION

CAPA PREVALENCE

Patients that develop acute respiratory distress syndrome (ARDS) as a result of a viral infection are at risk of developing secondary complications. Despite the absence of an underlying immunocompromising condition, patients with ARDS caused by viral infection are at risk for secondary complications such as invasive aspergillosis.[3]

Secondary fungal infections were seen in 3 of 9 (33.3%) patients and 6 of 17 (35.3%) critically ill patients in studies from Wuhan, China.[4] In a case study from France, CAPA was suspected in 9 of 27 (33.3%) ICU patients with COVID-19, while in a study from Germany, CAPA was suspected in 5 of 19 (26.3%) ICU patients. In the French CAPA series, all-cause mortality was three out of nine (33.3%), but in the German series, it was four out of five (80%).[5,6] This high prevalence of secondary aspergillosis in COVID-19 patients is similar to the high rates of influenza-associated pulmonary aspergillosis (IAPA) that have been observed in ICUs in the Netherlands and Belgium (16% and 23%, respectively).[7]

Several Chinese researchers found that COVID-19 patients had elevated rates of Aspergillus infections. In one study from China's Jiangsu province, 60/257 COVID-19 patients (23.3 percent) had throat swabs that tested positive for Aspergillus species and were diagnosed with Aspergillus co-infections.[8] Influenza has been described as a risk factor for invasive pulmonary aspergillosis and has been linked to a high mortality rate.[9] In medical mycology, culture is still the gold standard diagnostic process, but it is insensitive and time-consuming. As a consequence, some of these recorded statistics are possibly an underestimation of the true burden of IPA in COVID-19 patients needing ICU entry, whilst others could be an overestimation due to possible misinterpretation of Aspergillus colonization in the upper respiratory tract.[10]

Several studies and case-series from Europe (France, Germany, Belgium, and the Netherlands) have recently recorded high rates of CAPA among COVID-19 cases with ARDS, ranging from 20% to 35%. CAPA emerged quickly, with a median of 6 days and a period of 3–28 days after ICU entry.[11,12] The total mortality rate was 63% (22/35), with 4 females (4/8; 50%) and 14 males (18/27; 67%) among those who died. In case series from France, Germany, Belgium, and the Netherlands, mortality ranged from 44.5 to 66.7%. The Netherlands posted a 100% fatality rate for people with underlying illnesses, while the two patients without underlying disorders both survived.[11,12,13]

RISK FACTORS IN THE DEVELOPMENT OF CAPA

CAPA appears to develop quickly a few days after ICU admission, similar to the findings observed for IAPA. Because significant death rates have been documented, early diagnosis and immediate treatment for CAPA in ICU patients is necessary.[11]

COVID-19 risk factors for secondary pulmonary aspergillosis are comparable to those seen in influenza-IPA superinfections.[9] Severe lung injury during COVID-19, the use of corticosteroids in people with ARDS, the extensive use of broad-spectrum antibiotics in critical care units, and the existence of comorbidities such as structural lung anomalies are the most relevant risk factors.[11,12] While interstitial lung fibrosis does not lead to the development of IPA, a small percentage of COVID-19 survivors may require long-term corticosteroid therapy, which might predispose them to CAPA, years after the acute phase of the virus. Overall, systemic corticosteroids were used in 29% of the CAPA cases described to date. Systemic corticosteroids are used to reduce immune responses and avoid cytokine storms in people with ARDS, but they can also make people more vulnerable to secondary infections.[9,14] Although no specific case studies on antibiotic use among patients have been published, it is estimated that 75% of COVID-19 patients admitted to the ICU were given broad-spectrum antibiotics.[12] Because the human gut microbiome is a complex network of bacteria and fungus, antibiotics disrupt the microbiome's steady-state composition, allowing fungi to thrive and predispose the host to invasive fungal infections once the immune system is compromised.[15]

COVID-19 individuals may potentially be predisposed to CAPA due to medical issues like

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hypertension (17/35; 49%), diabetes (9/35; 26%), obesity (8/35; 23%), COPD (5/35; 14%), heart diseases (5/35; 14%), hypercholesterinaemia (4/35; 11%), and asthma (3/35; 9 %) which were among the most common comorbidities found in the 35 CAPA cases published to date. While hypertension, coronary heart disease, and diabetes all increase infection risk, structural lung damage associated by Chronic obstructive pulmonary disease(COPD) or asthma may predispose individuals to IPA.[16,17,18] Acute invasive pulmonary aspergillosis affects mostly immunocompromised individuals, with an increasing number of instances of invasive aspergillosis being documented among patients with COPD. Patients with significant pulmonary infiltrates who are taking steroid therapy for COPD should be suspected of invasive aspergillosis.[19]

PATHOPHYSIOLOGY

The knowledge of the physiological pathways through which infection with SARS-CoV-2(Severe acute respiratory syndrome coronavirus–2) enhances fungal development is required to unravel the complicated aetiology of CAPA. SARS-CoV-2, like other SARS coronaviruses, targets and infects epithelial cells and type II pneumocytes by attaching to the carboxypeptidase angiotensin-converting enzyme 2 (ACE2) receptors via the SARS spike protein. SARS-CoV-2 directly damages the airway epithelium, allowing Aspergillus to infiltrate.[20] The SARS S protein is 1,255 amino acids long and contains 23 N-linked consensus sequences for N-linked glycosylation.[21] The type II transmembrane serine protease (TMPRSS2) proteolytically processes SARS S. Depending on the presence of TMPRSS2 on SARS S-expressing cells or adjacent susceptible cells, cleavage resulted in shedding of SARS S fragments and interference with antibody-mediated neutralisation or inactivation of SARS S for cell-cell and virus-cell fusion.[22] The angiotensin-converting enzyme (ACE) and angiotensin-converting enzyme 2(ACE2) are homologues with distinct roles in the renin–angiotensin system. ACE cleaves angiotensin I to produce angiotensin II, whereas ACE2 inactivates angiotensin II and acts as a system negative regulator. ACE2 is expressed in lungs and recently, ACE2 has been identified as a potential SARS virus receptor.[20,23] Proinflammatory cytokines and chemokines such as tumour necrosis factor (TNF), interleukin 1 (IL-1), IL-6, granulocyte-colony stimulating factor, interferon gamma-induced protein-10, monocyte chemoattractant protein-1, and macrophage inflammatory proteins 1 were found to be significantly elevated in COVID-19 patients. The cytokine storm, like in a severe influenza infection, may play an important role in the immunopathology of COVID-19.[24]

The IFN response is a critical first line of defence against viruses. IFN types I and III appear to play a role in limiting infection for many respiratory viruses, including SARS-CoV-1, by establishing a cellular state of viral resistance and activating adaptive immune responses.[25] Type I IFNs are the first line of defence in the innate immune response to viral infection, inducing viral resistance in both infected cells (autocrine effect) and neighbouring cells (paracrine effect). Infection with SARS-CoV-1 and MERS-CoV, which cause acute respiratory disease, is characterised by a dysregulated inflammatory response in which delayed production of type I IFN favours the accumulation of inflammatory monocyte-macrophages.[26] Blanco-Melo et al. discovered that SARS-CoV-2 infections cause very low IFN I and IFN III expression, as well as a limited response from IFN-stimulated genes, while inducing normal expression of chemokines and proinflammatory cytokine genes.[27] Type III IFNs play a more specialised role in the mucosal immune response and adaptive response regulation. Type III IFNs play a unique role in pulmonary immune responses because they are induced earlier and by a lower viral load (when compared to type I), and they also limit the virus's initial spread.[28] IL-6 may play an important role in initiating a preliminary response to virus infection by supporting neutrophil-mediated viral clearance, as one study found that IL-6 or IL-6R deficiency led to the persistence of influenza infection and eventually death in mice.[29] COVID-19 disease severity appears to be modulated not only by viral infection but also by abnormal immune and inflammatory responses in the host.[24]

The complement system is essential in host defence against infections because it efficiently recruits phagocytes and engulfs pathogens and cellular debris via (C3b- or C5-mediated) opsonisation.[30] Gao et al discovered a common mechanism linking the viral N proteins to binding and potentiation of Mannan-

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binding lectin (MBL)-dependent auto activation of MBL-associated serine proteases-2(MASP-2), resulting in uncontrolled activation of the complement cascade. Prolonged complement activation results in uncontrollable inflammation and lung disease.[31] The IL-1/IL-6 pathway is thought to be central to the severe complications of COVID-19.[32] Blanco-Melo et al. reported findings suggesting a dysregulated host response in their recent study of transcriptional responses to SARS-CoV-2 compared to other respiratory viruses (influenza A and SARS-CoV-1) because SARS-CoV-2 did not trigger a robust IFN I/III response (at least at lower viral loads) but did induce robust production of chemokines capable of recruiting inflammatory cells.[27] Recent evidence suggests that this immune dysregulation may be involved in an immunosuppression phase.[24] In turn, Silvin et al. discovered that severe COVID-19 was specifically associated with a burst of circulating calprotectin, which follows the cytokine release syndrome; low levels of non-classical monocytes in peripheral blood; and emergency myelopoiesis, which stimulates the release of immature and dysplastic myeloid cells with an immunosuppressive phenotype.[33] SARS-CoV-2 infection can harm lymphocytes, particularly B cells, T cells, and NK cells, impairing the immune system during the disease. The decrease in lymphocytes, specifically CD4T and CD8T cells, as well as host immune function, may be the primary cause of the coinfection.[34,35] Patients with severe COVID-19 infections are much more likely to develop subsequent bacterial or fungal infections.[36] People with severe SARS-CoV-2 infection are more likely to develop CAPA, according to a growing body of evidence. In this regard, patients who needed urgent care had higher levels of circulating proinflammatory cytokines like TNF than those who had less severe infections.[24]

Aspergillus and Candida are the most common fungi that cause fungal co-infections in severe COVID-19 patients. Other less common opportunistic pathogenic fungi that cause lung infections, such as Mucor and Cryptococcus, must also be evaluated. In COVID-19 patients, Aspergillus species could be a major source of life-threatening infection, particularly in those with high risk factors.[37] Although other species, such as Aspergillus flavus, Aspergillus niger, Aspergillus terreus, Aspergillus clavatus, and Aspergillus nidulans, can also cause invasive aspergillosis and allergic illness, A. fumigatus is the most prevalent Aspergillus species that causes these disorders. Immunodeficiency is the most common cause that leads to invasive aspergillosis. In comparison to other Aspergillus species, asexual A. fumigatus conidia disperse quickly in the environment.[38] Humans inhale 100–1,000 conidia per day, with some of these reaching the alveoli in the lungs due to their small size of 2–3m10.[39]

Conidia remain in the lungs and can germinate to cause invasive disease in people who are unable to clear the inhaled conidia. Aspergillus fumigatus is recognised innately by a variety of pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), C-type lectin receptors (CLRs), NOD-like receptors (NLRs), and soluble PRRs. These receptors are capable of recognising pathogen-associated molecular patterns (PAMPs) found in the fungal cell wall that are foreign to the host. When PAMPs are recognised, PRRs activate a signalling network that includes both pro-inflammatory and anti-inflammatory cytokines.[38] Protective immunity against Aspergillus is a complicated process that requires both innate and adaptive immune systems. The airway epithelial cells and alveolar macrophages, which recognise and phagocytize the conidia as well as express various types of chemokines, cytokines, and proteins involved in innate immunity, are most likely the first line of defence. Polymorphonuclear neutrophils that have been recruited play an important role in host defence as well. Dendritic cells could migrate into draining lymph nodes and activate T helper (Th) cells in the presence of continuous Aspergillus exposure.[40] Coinfection can also disrupt intestinal homeostasis, triggering infection and causing immune cells to produce more severe inflammation.[34]

DIAGNOSIS

Fungal diseases, particularly CAPA, are difficult to diagnose and are likely underdiagnosed, especially in the setting of COVID-19 associated ARDS, where the clinical image and radiological findings of CAPA are similar to those of serious COVID-19 associated ARDS. Fungi are considered to be neglected

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pathogens, hence diagnosis necessitates specialized knowledge and awareness.[41]

For fungal diagnosis, respiratory samples are the preferable specimens.[42] Serum galactomannan(GM) testing (GM index > 0.5), sputum fungal cultures, tracheal aspirate (TA), chest computed tomography (CT) scan, and GM testing in respiratory samples (GM index 1.0) are used to diagnose CAPA.[43]

The most sensitive diagnostic test for aspergillosis detection is bronchoscopy since it allows the blind suctioning of tracheal fluids and more over it allows the direct visualization of trachea and bronchi by which patients with aspergillus tracheobronchitis can be identified.[42,44] However, owing to the nature of aerosol formation and the significant risk of viral transmission, bronchoscopy is generally contraindicated in patients with suspected and confirmed COVID-19 infection.[45,46] Bronchoscopy is usually recommended for individuals who have a suspicion of secondary infection, especially if they have already tested negative for SARS-CoV-2.[42] Bronchoalveolar lavage was rarely used in the COVID-19 patients. Because this invasive technique is categorised as an aerosol generating technique, it is contraindicated in COVID-19 patients to limit the risk of transmission.[47]

Invasive aspergillosis and an increased fungal burden are indicated by elevated serum galactomannan levels. Galactomannan is a key polysaccharide found in the cell wall of Aspergillus and its serum levels are linked to angioinvasion and invasive fungal growth. In vitro, a link between fungal invasion of the endothelial cell layer and a rise in galactomannan levels has been discovered.[44] In neutropenic patients with pathology-proven invasive aspergillosis, serum galactomannan testing has been demonstrated to be a fairly sensitive diagnostic technique (70 % sensitivity). However, serum galactomannan sensitivity of roughly 25% has been reported in non-neutropenic patients.[48]

Chest CT is the imaging modality of choice in the case of microbiological confirmation of Aspergillus infection.[44] Radiographic reports typically described a mix of virus-related findings (ground glass opacities and crazy-paving), findings consistent with airway inflammation and mucous plugging (bronchiectasis, airway wall thickening and irregularity, bronchiectasis), and radiographic findings consistent with airway (consolidations, tree-in-bud nodules). Ground glass opacities characterize both COVID-19 and invasive pulmonary aspergillosis, thus in COVID-19 patients, mycological laboratory testing for Aspergillus special in lower respiratory secretions as well as galactomannan in serum samples are mandatory. As a result, a thorough microbiological evaluation can prevent the chance of missing IPA.[5,49]

TREATMENT

The treatment of CAPA is complicated and a real challenge. Patients having Aspergillus in their serum or bronchoalveolar lavage should be treated with antifungals, according to a recent expert panel's recommendation.[50] White et al reported that high mortality rate was found in patients who didn't receive antifungal therapy and mortality reduced significantly in those who received antifungal therapy.[51]

Voriconazole (loading dose 6 mg/kg twice a day for two doses, followed by 4 mg/kg twice a day) is recommended as the standard first-line treatment for CAPA.[52,53] But there are certain limitations on using triazoles in COVID 19 patients since they tend to interact with multiple drugs.[54] Voriconazole has narrow therapeutic window and since it is metabolized by CYP2C19, CYP2C9 and CYP3A4, it is one among the drugs that is frequently associated with major drug-drug interactions in the ICU.[55,56] It shows interaction with some COVID-19 therapy including hydroxychloroquine, atazanavir, lopinavir/ritonavir and remdesvir.[57] It also shows increased risk for QTc prolongation.[58] Comparing to Voriconazole, Isavuconazole(loading dose 200 mg three times a day for six doses, followed by 200 mg once a day, 12–24 h after the last loading dose) shows favourable pharmacokinetic profile, toxicities and less drug-drug interactions.[59] An effective alternative option is Liposomal amphotericin B(3 mg/kg per day) and also if azole resistance occurs, it is the treatment of choice.[52] However, since the drug is nephrotoxic, it may cause additional decrease in renal function. COVID patient, who has shown renal tropism and has been recognised as a common

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cause of kidney impairment, should be especially concerned.[60,61]

Posaconazole or echinocandins are the second line treatment of choice. Echinocandins are not indicated for use as monotherapy in primary invasive aspergillosis, but they may provide some therapeutic benefit in critically ill patients when combined with an azole.[62] It has limited antifungal activity against Aspergillus species but its synergistic interactions with some other antifungals, make it a good choice for combination antifungal therapy.[63] Posaconazole has strong in-vitro aspergillus activity and has been used successfully as a salvage treatment in COVID-19 negative patients.[64] New antifungal classes currently under development, such as fosmanogepix, ibrexafungerp, olorofim, and rezafungin could be a preferred choices in the near future.[65]

CONCLUSION

In conclusion, the prevalence of fungal co-infections and superinfections in COVID-19 infected hospitalised patients is rare; nevertheless, when they do occur, they can cause severe illnesses with poor outcomes. Our recommendations are intended to make clinical trials and clinical care easier while also increasing awareness of CAPA.

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