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Pulmonary aspergillosis: A COVID-19 associated deadly disease its epidemiology, immunology, diagnosis & treatment

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Abstract
The COVID-19 virus causes lung infections that lead to inflammation and a cytokine storm in the affected person, ultimately impairing their immune system. Tocilizumab and steroids, which are used in the treatment of COVID-19, further reduce an individual's immunity. A secondary or supra-added infection, which could be bacterial or fungal, results from the person's temporary immune compromised state. COVID-associated pulmonary aspergillosis is one such fungal illness. Patients with impaired immune systems, such as those admitted to intensive care units and on mechanical breathing, are more likely to contract this lethal fungus. This review article covers the PULMONARY ASPERGILLOSIS epidemiology, immunology, diagnosis and treatment.

Keywords: COVID-19, COVID associated pulmonary aspergillosis, epidemiology, immunology, diagnosis, treatment

Introduction
A fungal illness called aspergillosis can harm patients with compromised immune systems. The airborne fungus Aspergillus is spread by tiny respiratory droplets. The disease's primary organ that is impacted is the lung. At this time, invasive pulmonary aspergillosis (IPA) is found to be more likely in cases of severe viral lung infections. Acute respiratory distress syndrome (ARDS) due to viral pneumonitis is indicative of severe COVID-19 [1]. Treatment options for ARDS may include extracorporeal membrane oxygenation or mechanical ventilation. A variety of infections in humans, such as invasive pulmonary aspergillosis (IPA), chronic pulmonary aspergillosis (CPA), allergic broncho pulmonary aspergillosis (ABPA), chronic rhinosinusitis, fungal asthma, and Aspergillus bronchitis, are caused by the Aspergillus genera, most commonly *Aspergillus fumigatus*, which is always present in the environment. In December, 2019, COVID-19 come out from Wuhan, China, and has become pandemic [2]. There were many reports of COVID-19-associated pulmonary aspergillosis (CAPA), raising trouble about this superinfection as an extra contributing factor to mortality. European investigators have put forward case definitions for CAPA, which includes positive Galactomannan (GM) results in serum or broncho alveolar lavage samples, recovery of *Aspergillus* species in BAL culture, positive polymerase chain reaction for *Aspergillus* species in BAL or blood samples, or chest imaging consistent with a fungal infection. The causative agents of CAPA were *A. Fumigatus* (44%), *A. niger* (31%) and A. flavus (6%), as well as unidentified *Aspergillus* spp. (19%); two or more *Aspergillus* spp. were isolated in 12% of case [3]. Given the high mortality associated with CAPA, a concerted effort is needed to develop a diagnostic strategy that is both safe and sensitive. Furthermore, it may also need to take into account that the process of sample collection and environmental hygiene in various hospital settings may contribute to false diagnosis of aspergillosis [4]. The clinical relevance of Aspergillus positive cultures obtained on respiratory tract specimens is often difficult to distinguish actual infection from colonization as the more diagnostic procedures performed, the higher the chances of detecting Aspergillus microorganisms [5].

Pathophysiology

COVID-19 is a contagious virus that mostly affects the lungs. If a healthy person comes into close contact with an infected person, the sickness can spread through the infected person's aerosols. First off, COVID-19 vandalizes the lung's epithelium, which allows the fungus to take the lead and cause its effects. Second, the COVID-19 virus also impairs respiratory cilia function, which results in incorrect clearance and an immunological disorder. Thirdly, the COVID-19 also causes the T lymphocyte count to decrease. Since T cells are essential for an individual's immunity, a decrease in T cell count results in a serious immunological condition [6].

Epidemiology

Regarding CAPA, the captured incidence by L. Frederic has varied from 4% to 35% among ICU COVID-19 cases. In fact, some reports shows that the occurrence of IPA among severe COVID-19 is less than 5-10% which does not exceed its incidence among ICU patients with other respiratory infections [7]. To evaluate the predictive performance of different cases, compared cases of CAPA and cases of PIPA. In spite of the identification of IPA as a rare super infection due to influenza in immunosuppressive patients has been described since 1952, the 2009 influenza A H1N1pandemic put forward this association in attention. PIPA has been reported not only due to H1N1 infection, but also in all influenza types and subtypes including influenza B, commonly in patients requiring ICU admission and mechanical ventilation. Different clinical perspectives and definitions may account for the varied approximates [8]. The incidence may be diagnosed by different methods as the evaluation of serum galactomannan (GM; periodic screening vs. utilize an “adjunct” diagnostic tool) and the timing and the performance of bronchoscopy for detection of aspergillus infection [9]. Despite, the accurate pathogenesis of organizing pneumonia remains unknown, it is examined that it is a consequence of alveolar epithelial injury. This initial epithelial injury later result in leakage of plasma proteins, that give rise to cascade of host responses with hyper inflammation. Systematize diagnostic algorithms and definitions are defit clinicians are reserved to carry out aerosol-generating broncho alveolar lavages for galactomannan testing and microscopic and cultural examination, and questions nearby the diagnostic sensitivity of different serum biomarkers [10]. The frequency of CAPA ranged from 35% to 3.8% of all ICU patients with COVID-19. In comparison, the rate of influenza-associated (model post-viral) pulmonary aspergillosis (IAPA) is estimated between 16% and 23%. Some authors recommend empirical antibiotic prophylaxis, including antifungal drugs. Indeed, the difficulty and time involved in isolating Aspergillus from bronchoalveolar lavage fluid further support the adoption of an empirical antifungal approach to COVID-19 therapy in critically ill patient [11].

Immunology

Recent pandemic COVID-19 is linked with unbalanced immune that may response not only impact the clinical decline or worsening of patients, but also tamper the sensitivity to secondary infections, for example by impairing host antifungal defences and accelrate the risk of Aspergillus infection. The complex pathophysiology beyond the elaboration of CAPA is not completely recognized but there are many hypotheses have been put forward [12]. *Aspergillus* spp. is abundant in the environment in the form of airborne conidia that can easily reach the alveoli. Alveolar macrophage-driven neutrophil recruitment and transient flux of the cytokine and TNF-α thar are key factors in eliminating these conidia from the airways. Structural damage to the lungs by SARS-CoV-2 infection and an impaired immune system may provide optimum conditions for the conidia to develop and invade tissue and vessels. *Aspergillus* spp. can cause co-infections in patients with COVID-19, especially in severe/critical illness [13]. Two possible mechanisms can be accepted to explain the evolution of CAPA. The first implies the release of danger-associated molecular patterns (DAMPs), signal molecules delivered by dying or damaged cells that act as endogenous danger signals to assist and aggravate the immune system and inflammatory response governs to lungs injury [14]. It is significant that DAMPs have also been manifested to control inflammation in fungal diseases The DAMP/receptor for advanced glycation end-products axis was found to combine with Toll-like receptors (TLRs) to cause and magnify the inflammatory reaction in experimental aspergillosis. Beside recipients of allogeneic stem-cell transplantation harboring genetic variants underlying a hyper activation of danger signaling regarding infection show an increased risk of developing IPA. This appearing idea could help to explain fungal pathogenesis in conditions of ebullient inflammation like as that observed in COVID-19 patients and highlights DAMP earmark as potential immune modulatory strategy in CAPA [15]. A second possibility involves the pledge effects of recognition pathways required for the triggering of antiviral immunity that may contradictory, contribute to an inflammatory response that esteem secondary infections. ACE2 is not fully expressed on immune cells and SARS-CoV are acknowledge by TLR4 and TLR3, start the activation of MyD88- or TRIF-mediated signaling, respectively Set down, this may be enhance in the presence of *Aspergillus* spp. which activate TLR4/MyD88/TRIF through the breakdown of fibrinogen [16].

Discussion of some case report

It has been reported that 19%e 33% of COVID-19 patients with severe disease develop CAPA. We review some known case of CAPA here in table 1.

Table 1: Case Report [17, 18]

	Age	Sex	Spieces	Diagnosis	Treatment	outcome
Zhang SX *et al.*	70	Female	*Aspergillus fumigatus*	Serum BDG152 CHEST CT	Voriconazole Micafungin	Decreased
Alanio *et al.*	79	Male	*A. Fumigatus*	BAL 100	Voriconazole Caspofungin	decrease
Van Arkel *et al.*	83	Male	A. spp	Serum GM 0.4	NA	Died
Van Biesen *et al.*	76	Female	A. spp	BAL3.33 CT	NA	
Chauvet *et al.*	54	Male	*A. Fumigatus*	BAL50	Lip.AMB	Alive
Helleberg. *et al.*	63	F	*A. Fumigatus*	BAL 50 ETA 100	Voriconazole	Death
W.imoto *et al.*	72	M	*A. Fumigatus*	CT	NA	Death
D.armstrong *et al.*	62	F	*A. Fumigatus*	BAL/PCR	NA	Death
Paramythiotou *et al.* 2021	82	F	*A. Fumigatus*	BAL CT	Isavuconazole	Death
Johnson *et al.*	79	M	Asp. spp	CT BAL	Amphotericin B	Decreased
Meijer *et al.*	65	M	*A. Fumigatus*	CT Chest finding	Voriconazole AMB	Death

Diagnosis

In published cases in review articles from Pakistan by Nosheen *et al.* 2020 CAPA was diagnosed based on clinical parameters, radiological findings and mycological data. In iran by Nasri *et al.* 2020 testing for the presence of Aspergillus in lower respiratory secretions and galactomannan in consecutive serum samples of COVID-19 patients Chest-computed tomography (CT) and the positive serum GM results, a diagnosis of probable invasive pulmonary aspergillosis with COVID-19. In France by Alanio *et al* France in MV patients in the ICU by routine screening for aspergillosis. European investigators have proposed probable CAPA definitions that substantially reflect clinical practices that include aggressive bronchoscopy, use of PCR-based assays, and application of antigen (Platelia galactomannan) assay cut-offs at higher index levels (positive BAL GM index ≥1.0) to define positivity compared to what is currently recommended by the FDA [19, 20]. Perhaps a more pragmatic approach to the diagnosis of CAPA would be, in the setting of a patient with severe COVID-19 pneumonia in critical care, to combine ≥2 mycological criteria to include the following:

1. GM detection from serum/BALF/ETA
2. Isolation of *Aspergillus* sp. from BALF/ETA/sputa
3. Serum BDG detection
4. Detection of *Aspergillus* DNA by real time PCR in blood or respiratory sample

Test that are commonly performed are chest radiography [21]. Alternatively, and according to the modified Asp ICU algorithm and ECMM/ISHAM CAPA criteria, no such specific host factors are obligatory, and radiological findings, although still preferably reported by CT scan, can also be documented by chest X-ray. The diagnosis and distinction between putative and probable forms of CAPA results from the combination of radiologic abnormalities pulmonary infiltrate or cavitating infiltrate not attributed to another cause and mycological criteria positive BAL culture, direct microscopic evidence of *Aspergillus* species in BAL or positive serum or BAL markers [22]. The following are also considered as mycological criteria in the ECMM/ISHAM CAPA criteria: two or more positive Aspergillus PCR tests in plasma, serum or whole blood; a single positive Aspergillus PCR in BAL or a single positive Aspergillus PCR in plasma, serum or whole blood; and a single positive in BAL To perform invasive diagnostic procedures such as BAL over-reliance on sputum and ETA specimens is not unexpected [23]. Elevated serum levels of procalcitonin and higher neutrophill to low lymphocyte ratio from dys regulated immune response has been suggested to predict secondary bacterial infection in critically ill COVID-19 patients [24]. The sensitivity for detection of resistance in primary cultures with the VIPcheck plate depends on the number of *A. Fumigatus* colonies that are tested, as clinical cultures may contain both mixed azole-susceptible and azole-resistant isolates during an infection. Molecular detection could have given a suggestion to the presence of a mixed culture but PCR could not be performed. Susceptibility testing is of huge importance to detect azole-resistance early in the course of disease to enable effective treatment [25, 26].

Treatment

Triazoles are preferred agents for treatment and prevention of IA in most patients (Strong recommendation; high-quality evidence. Patients should also be monitored for the development of resistance by *Aspergillus* spp. to azoles [27-30]. Triazole-resistant *A. Fumigatus* was isolated in a patient who was possibly exposed to organic matter. Monitoring of exposure to ensure adequate exposure by means of therapeutic drug monitoring (TDM) and is an important component in triazole treatment of patients with CAPA. Critical illness with (multi) organ failure predisposes patients to a high degree of variability in drug exposure. This is further complicated by factors such as drug-drug interactions, alterations in protein binding, use of vasopressor agents impacting organ perfusion and the frequent use of renal replacement techniques as well as extracorporeal membrane oxygenation (ECMO) [31, 32]. Inhaled liposomal amphotericin-B in view of its successful and safe use in hematological disease and in solid organ transplant patients. It was choosed over prophylactic triazoles to minimize the risk of azole resistance. Specifcally, 12.5 mg Ambisome, dissolved in 3 mL of sterile water with the addition of 5 drops of salbutamol, was nebulized. Voriconazole (VRC) or isavuconazole (ISV) have been used as the first-line treatment options for possible, probable, and proven CAPA; liposomal amphotericin B (L-AMB) has also been administered as an alternative agent [33, 34]. It was reported a non-statistically significant lower mortality rate among patients with putative aspergillosis who were treated with VRC vs. those not treated. Voriconazole or isavuconazole are the first-line antifungals recommended by the ECMM/ ISHAM for CAPA Voriconazole and isavuconazole have mainly been evaluated in immunocompromised patients [35-40]. Voriconazole is metabolized by cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4, resulting in multiple drug-drug interactions [41, 42]. Even though>90% of CAPA patients received antifungal treatment, there was also one CAPA case not receiving antifungal therapy among the survivors, indicating that not all patients who are diagnosed

with CAPA based on consensus definitions may in fact have invasive fungal disease [43, 44]. Nephrotoxicity is the main consideration when liposomal amphotericin B is used as an alternative treatment, especially in COVID-19-related acute kidney injury [45, 46].

Conclusion

Aspergillosis linked with COVID-19 is a superadded infection that is primarily observed in individuals with impaired immune systems who are admitted to an intensive care unit and are on mechanical ventilation. The diagnosis of this fatal supra added infection on the basis of clinical symptoms and signs is extremely challenging because the symptoms and indicators of this infection are nearly identical to those of COVID-19 infection. If this fatal fungus is identified early on, the patient may be able to survive and receive the appropriate therapy; if the diagnosis is made later, the patient will undoubtedly die. In order to diagnose this infection, diagnostic techniques such as culture and histopathology findings from biopsy or sterile site sample might be used.

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Conflicts of interest

The authors have no conflicts of interest.

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