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PERSPECTIVES

Invasive Aspergillosis as an Under-recognized Superinfection in COVID-19

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Severe acute respiratory syndrome coronavirus–2 (SARS-CoV-2) has rapidly spread across the globe, accounting for >5 million cases to date of the disease designated as coronavirus disease 2019 (COVID-19). The spectrum of illness in COVID-19 ranges from asymptomatic or mild infection to critical illness with acute respiratory distress syndrome (ARDS) [1]. Up to 20% of persons with symptomatic COVID-19 may develop ARDS [2]. The mortality rate in this subgroup is high, and recovery may be fraught with complications including arrhythmia, cardiac injury, shock, coagulopathy, or superinfections [2–5].

Opportunistic infection following respiratory viral infection has been recognized since the 1918 influenza pandemic [6]. During the influenza A (H_1N_1) 2009 outbreak, cases of invasive pulmonary aspergillosis were quickly recognized in those with ARDS in the absence of classic risk factors for fungal disease [7, 8]. Subsequent studies have found high rates of invasive pulmonary aspergillosis complicating influenza (7.2%–28.1%) [9–12] in patients with respiratory failure, prompting clinical trials of preemptive antifungal therapy (clinicaltrials.gov NCT03378479).

Other respiratory viruses, including parainfluenza virus and respiratory syncytial virus, have similarly been found to predispose patients to invasive pulmonary aspergillosis [13]. The pathophysiologic mechanisms responsible for invasive pulmonary aspergillosis in this group have yet to be fully elucidated. Direct damage to the airway epithelium has been observed with influenza and parainfluenza viruses [13, 14], which may provide an opportunity for *Aspergillus* spp. to invade into tissues. Respiratory viruses also disrupt normal ciliary clearance [15], cause leukopenia and/or lymphopenia [16, 17], and result in transient defects in cellular-mediated immunity [18]. Immune dysregulation associated with ARDS may further predispose to opportunistic infections [19]. Interestingly, influenza has been found to be the most frequent preceding infection, and this is possibly secondary to the effects of neuraminidase inhibitors (oseltamivir) on reducing the immune response [20].

The pathophysiology of COVID-19 is not well understood, although putative factors predisposing to fungal diseases are commonly observed in symptomatic patients, including leukopenia (9%–25%) [21, 22], lymphopenia (35%–63%) [21, 22], and T-cell perturbations [23]. Furthermore, the utilization of glucocorticoids in 44.9% of patients with COVID-19-associated ARDS has been described [2], which may further predispose to opportunistic infections such as aspergillosis. Finally, severe COVID-19 is associated with host immune dysregulation, which appears to differ from that reported with SARS-CoV-1 (the coronavirus that is the etiologic agents of SARS) infection by impacting Th2 and Th1 responses [21, 24]. Severe COVID-19 is often characterized by respiratory distress developing 7–10 days after initial symptoms [2, 3]. Patients with severe COVID-19 have higher proinflammatory (eg, interleukin-2 [IL-2], soluble IL-2 receptor, IL-6, tumor necrosis factor–alpha [TNF-α]) and anti-inflammatory (eg, IL-10) cytokine levels, fewer CD_4 and CD_8 cells, and less IFN-γ expression by CD_4 cells than those with moderate disease [24]. It is plausible that this immune dysregulation and/or lung damage stemming from COVID-19 immunopathology facilitates *Aspergillus* superinfection in a way that is at least partially distinct from other respiratory viruses.

There are limited data on secondary infections complicating severe COVID-19. Studies of critically ill patients with

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COVID-19 at several centers have reported a high incidence of secondary infections in patients within the intensive care unit (5%–31%), although diagnostic criteria were not provided [4, 21, 22, 25]. Despite a lack of systematic screening for invasive aspergillosis, *Aspergillus flavus* or *A. fumigatus* was reported in 4% of patients with severe SARS-CoV-2 infection in Chinese hospitals [22, 26]. Another report from France similarly found *A. flavus* infection in patients with severe SARS-CoV-2 [27]. More recently, probable aspergillosis was diagnosed in 9/27 (33%) patients requiring mechanical ventilation using screening protocols aimed at early detection [28]. These studies have been limited by lack of tissue-proven diagnoses. It is notable that invasive pulmonary aspergillosis is often associated with tissue necrosis stemming from fungal angioinvasion and thrombosis, and COVID-19 is associated with a hypercoagulable state and microthrombi, although it seems unlikely that the 2 processes are related. Antiphospholipid antibodies have been proposed as a potential etiology for COVID-19-associated hypercoaguability [29], as has endothelial dysfunction observed with ARDS [30]. Limited autopsy data from patients who died with COVID-19 have not described invasive aspergillosis or reported hyphal angioinvasion; microbiologic cultures and fungal staining were not performed [31, 32].

Taken together, these early findings suggest that invasive aspergillosis may be an important, yet under-recognized, complication of SARS-CoV-2 infection. The frequency of post-COVID-19 aspergillosis is likely to differ significantly between hospitals and geographic sites, as has been observed with postinfluenza aspergillosis [9]. The host factors discussed above have been found in multiple studies of different ethnicities, and they are likely to be relevant in all affected populations. Host genomic risk factors for aspergillosis identified in other cohorts may similarly play a role in susceptibility [33]. Environmental factors may also play a large role in increasing exposure beyond what would normally be encountered within hospitals and/or intensive care units. The rapid spread of COVID-19 to a nonimmune population has seen temporary facilities/hospitals rapidly assembled that do not adhere to the rigorous ventilation requirements that are present within permanent hospitals. These temporary sites are essential to increase health care capacity; however, dust and construction-related increases in ambient air spore counts will very likely increase patient colonization with *Aspergillus* and other fungal species predisposing to infection.

We are living in an unprecedented era of fungal infections, characterized by the emergence of previously unrecognized human pathogens and well-recognized pathogens causing new manifestations of disease. The spectrum of "at-risk" populations for invasive *Aspergillus* infections is expanding, with increased appreciation of diseases such as chronic pulmonary infection and postinfluenza aspergillosis. Fungal superinfections are difficult to distinguish from severe COVID-19 based on clinical or imaging findings, and a high index of suspicion is necessary to diagnose aspergillosis. If aspergillosis is a complication of COVID-19 in a significant minority of critically ill hospitalized patients, failure to recognize or diagnose the disease will likely lead to excess mortality. For this reason, it is imperative to establish the incidence, clinical characteristics, and outcomes of COVID-19-associated aspergillosis as quickly as possible.

The most immediate need in defining the incidence and clinical features of COVID-19-related aspergillosis is for detailed data from large cohorts of patients who presented in the first wave of cases globally; existing databases can be utilized for this purpose. As the pandemic is likely to continue for many months or years until a vaccine is available to establish herd immunity [34], a second priority will be to establish consortia to conduct systematic prospective studies of COVID-19-associated pulmonary aspergillosis (CAPA). Such studies can employ uniform diagnostic testing and criteria, including galactomannan, (1→3)-β-D-glucan assays, and other evolving diagnostics. Consortia can be built upon existing European and US networks studying influenza-associated aspergillosis. Large collaborative studies might also serve to link immune profiling data or whole-genome/exome sequencing data from COVID-19 patients with infections. A third priority is for autopsy studies of SARS-CoV-2-infected patients to perform microbiologic cultures and tissue staining for aspergillosis and other infections, particularly in the lungs. Finally, if the studies above verify that aspergillosis is a common COVID-19-related complication in certain patient subgroups, clinical trials of screening protocols using galactomannan and/or (1→3)-β-D-glucan and prophylactic, preemptive, or empiric antifungal therapy would be warranted.

In conclusion, we recommend consideration of aspergillosis as a cause of superinfection in COVID-19 patients with worsening clinical or radiographic findings. The diagnosis can be difficult to determine given the risks of bronchoalveolar lavage in COVID-19 patients and the lower sensitivity of galactomannan testing in the non-neutropenic population. Computed tomography (CT) of the lung may be similarly difficult to assess in patients with ARDS-associated COVID-19 [35], and CT pulmonary angiography has not been validated in this population [36]. Positive endotracheal cultures thus may be the major predictive laboratory finding and should be scrutinized in an attempt to delineate putative aspergillosis from *Aspergillus* colonization [37]. In those deemed to have active infection, antifungal therapy with voriconazole or isavuconazole should be initiated to optimize patient outcomes.

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