COVID-19-Associated Candidiasis

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The recent global pandemic of COVID-19 has predisposed a relatively high number of patients to acute respiratory distress syndrome (ARDS), which carries a risk to develop secondary infections. Candida species are major constituents of the human mycobiome and the main cause of invasive fungal infections with a high mortality rate, and are also increasingly reported as complication of severe COVID-19. Despite the marked immune dysregulation in COVID-19, no prominent defects have been reported in immune cells that are critically required for immunity to Candida. This suggests that relevant clinical factors, including prolonged ICU stays, use of central venous catheters and often broad-spectrum antibiotics may dominate over immune-mediated mechanisms to drive susceptibility to candidemia in the setting of COVID-19. Although diagnostic performance evaluations are often lacking in COVID-19 patients, a combination of serological and molecular techniques may present promising diagnostic options for identification of COVID-19-associated candidiasis. Clinical awareness and screening of invasive candidiasis is needed, as those are difficult to diagnose, particular in the setting of severe COVID-19. Echinocandins and azoles are the primary antifungal used to treat invasive candidiasis, yet therapeutic failures exerted by prominent nosocomial pathogens such as C. auris and C. glabrata calls for the development of new antifungal drugs with novel mechanisms of action.

Keywords: Candidemia, Candidiasis, COVID-19

1. Introduction

Yeast species belonging to the *Candida* genus, including *Candida albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis,* and *Candida krusei,* are the most prevalent fungal species inhabiting various mucosal surfaces, such as the skin and the respiratory, digestive, and urinary tracts [1][2]. Although being commensal within the human host, *Candida* species are equipped with virulence attributes, enabling them to invade when opportunities arise and cause various infections in humans, especially when the immune system is impaired [2]. Superficial infections, such as skin disorders; mucosal infections, including oropharyngeal or vulvovaginitis candidiasis; and invasive candidiasis are established clinical entities of candidiasis [3][4][5][6][7][8]. *Candida* is among the most frequently recovered pathogen in the intensive care unit (ICU), affecting between 6% and 10% of patients, and some studies have noted an increasing trend for candidemia [9]. The estimated mortality attributed to invasive candidiasis is 19–40% [10]. This mortality is even higher among ICU patients, approaching 70% [11]. Apart from being associated with excess economic costs and approximately 1.5 million annual deaths [8], the new landscape of candidemia reveals an increasing incidence of non-*albicans Candida* (NAC) species, with intrinsic resistance to antifungals and/or with a propensity to rapidly acquire antifungal resistance [12]. More troubling is the recent emergence of multidrug-resistant (MDR) *Candida* species, including *C. glabrata* and *C. auris* [13][14][15][16], the increasing trend of fluconazole-resistant *C. parapsilosis* and *C. tropicalis* [13][17], and inherently resistant *C. krusei*, which notoriously affect the efficacy of antifungal treatment.

The recent global pandemic of COVID-19 has resulted in an unprecedented 890,000 deaths worldwide [18]. A notable proportion of COVID-19 critically ill patients develop acute respiratory distress syndrome (ARDS), requiring intensive care unit (ICU) admission and mechanical ventilation, which in turn predisposes them to nosocomial infections due to bacterial and fungal infections [19][20]. Understanding the burden of COVID-19 patients with secondary infections and their etiologic agents is paramount for the optimal management of COVID-19 patients. This knowledge will help to refine empiric antimicrobial management for patients with COVID-19 with the hope to improve patient outcomes.

Despite the recognition that airborne *Aspergillus fumigatus* is increasingly recognized as an important cause of fungal super-infections among critically ill COVID-19 patients [19], the incidence of candidiasis has not been evaluated in this context. Indeed, the wide use of antibiotics, corticosteroids, and central venous catheters, along with the damage exerted by SARS CoV-2 among patients with ARDS [19], may allow commensal *Candida* to cells to invade internal organs [20][21][22][23][24][25][26][27].

2. General Pathophysiology of SARS COV-2

Similar to other SARS coronaviruses, the pathophysiology of SARS-CoV-2 involves targeting and invading epithelial cells and type II pneumocytes through the binding of the SARS spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor [28]. During the course of the host–virus interaction, the type 2 transmembrane protease TMPRSS2 cleaves the S1/S2 domain of the viral spike protein [29] and promotes viral entry into the target cells. ACE2 is required for protection from severe acute lung injury in ARDS [30], and the viral-mediated manipulation of this receptor is considered one major mechanism contributing to severe lung injury in selected COVID-19 patients. The degree of variability in the severity of disease is also supported, at least in part, by the existence of genetic variants that affect the ACE2 activity and underlie an increased susceptibility to ARDS and worse prognosis [31]. Besides the implications of ACE2 in the pathogenesis of COVID-19, recent studies have also suggested that the disruption of the renin-angiotensin system and/or the kallikrein-kinin system could contribute to the detrimental inflammatory phenotype observed in patients with severe COVID-19 [32] [33].

3. Does Immunity Renders Susceptibility to Invasive Yeast Infections?

Infection with SARS-CoV2 elicits an immune response that triggers an inflammatory cascade as the result of the activity of innate immune cells. However, the dynamics of how the immune system senses and responds to SARS-CoV-2 is just unfolding, which limits our understanding of possible immune-mediated pathways contributing to the pathogenesis COVID-19-associated candidiasis (CAC). Cell types important for host defense against *Candida*, such as neutrophils and monocytes/macrophages, are not affected by SARS-CoV-2, suggesting that they are not responsible for CAC. Indeed, single-cell analyses of bronchoalveolar lavages from critically ill patients with COVID-19 showed an abundance of monocyte-derived macrophages [34]. Similarly, an increased peripheral neutrophil-to-lymphocyte ratio was also observed in severe cases of COVID-19, and was likely associated with unfavorable prognosis [35]. While the increasing numbers (and activation profiles) of these cells may contribute to tissue damage and the severity of disease, they are an unlikely risk factor for invasive candidiasis. One exception is the decreased expression of human leukocyte antigen DR on the membrane of circulating monocytes [36], which is considered a marker of immune paralysis; however, its relevance in susceptibility to candidemia is unclear. The clear immune defect in patients with COVID-19 is, on the other hand, lymphopenia; however, an isolated decrease in lymphocyte numbers, as also experienced by HIV patients, is not associated with an increase in susceptibility to systemic *Candida* infections. Taken together, these findings support the concept that classical risk factors for invasive candidiasis, rather than an overt immune dysfunction, are the major drivers of susceptibility to CAC.

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