REVIEW ARTICLE
J Mycol Infect 2021; 26(2): 23-27
pISSN:1226-4709, eISSN:2465-8278
https://dx.doi.org/10.17966/JMI.2021.26.2.23

JMI

COVID-19-associated Pulmonary Aspergillosis: A New Entity

Hyun-Min Seo, Ji Hun Park, Se Uk Oh, Se Kwang Park and Joung Soo Kim†

Department of Dermatology, Hanyang University Guri Hospital, College of Medicine, Hanyang University, Gyeonggi-do, Korea

In March 2020, the World Health Organization declared the COVID-19 outbreak a pandemic. This resulted in the discovery of a new clinical *Aspergillus* disease phenotype, COVID-19-associated pulmonary aspergillosis. This review aimed to collect and share clinical experiences from this new disease.

Key Words: Aspergillosis, COVID-19, Deep fungal infection, Fungus, SARS-CoV-2

INTRODUCTION

Since the first case of severe acute respiratory syndrome 2 (SARS-CoV-2) was identified in Wuhan, China in December 2019, the outbreak of SARS-CoV-2 has spread to many other countries[1]. In January 2020, the World Health Organization (WHO) Emergency Committee declared this a global health emergency, and in March 2020, the WHO declared the COVID-19 outbreak a pandemic[2].

Early studies reported a high mortality rate due to secondary infections among patients admitted to the intensive care unit (ICU) for COVID-19[3]. Invasive pulmonary aspergillosis (IPA) is an important cause of morbidity and mortality in immunocompromised patients, including the solid organ or hematopoietic stem cell transplant (HSCT) recipients[4,5]. An early diagnosis of IPA has become a major focus in improving the management and outcomes of this life-threatening disease. The COVID-19 pandemic has resulted in the discovery of a new clinical *Aspergillus* disease phenotype, COVID-19-associated pulmonary aspergillosis (CAPA). This review aimed to collect and share clinical experiences from this new disease in critically ill patients with COVID-19.

IPA

In 1953, Rankin et al. first described a fatal case of IPA in a patient with chloramphenicol-related agranulocytosis[6]. IPA is a severe pulmonary disease that occurs primarily in severely immunocompromised patients. The significance of this infection has increased as the number of immunocompromised patients associated with the management of malignancy, organ transplantation, autoimmune conditions, and human immunodeficiency virus infection has increased[7]. The most important risk factor for IPA is neutropenia, and the others include HSCT, solid organ transplantation, neutrophil dysfunction (primarily in chronic granulomatous disease), prolonged and high-dose corticosteroids therapy, hematological malignancy, chemotherapy, and advanced acquired immune deficiency syndrome[8,9]. The mortality rate of IPA is

Received: April 7, 2021 Revised: May 27, 2021 Accepted: May 31, 2021
†Corresponding: Joung Soo Kim, Department of Dermatology, Hanyang University Guri Hospital, 153, Gyeongchun-ro, Guri-si, Gyeonggi-do, 11923, Korea.
Phone: +82-31-560-2285, Fax: +82-31-560-2282, e-mail: tuentuen@hanyang.ac.kr

>50% in patients with neutropenia, and it reaches 90% in HSCT patients[10,11]. Similar to bronchopneumonia, its symptoms include cough, sputum, dyspnea, and fever unresponsive to antibiotics. Patients also can present with hemoptysis, which is usually mild[12]. Recent studies reported that a severe influenza infection is a potential risk factor for developing IPA in non-neutropenic patients, a syndrome termed influenza-associated pulmonary aspergillosis (IAPA)[13]. Unlike patients with traditional IPA, a significant proportion of patients with IAPA, including previously healthy individuals, was considered to be at low risk for IPA. In addition, the clinical presentation of patients with IAPA was often atypical, and its radiological features were not suggestive of IPA.

COVID-19 ASSOCIATED PULMONARY ASPERGILLOSIS

Coronaviruses are enveloped, positive, single-stranded, large RNA viruses that infect humans and various animals. Coronaviruses were first described in 1966 by Tyrell and Bynoe, who cultivated the viruses from patients with common colds[14]. Before SARS-CoV-2 was identified, six coronavirus species were known to cause human diseases, including SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), which are zoonotic in origin and have been associated with fatal diseases. The recently identified SARS-CoV-2 is the seventh member of the coronavirus family that infects humans[15]. *Aspergillus* spp. are abundant in the environment in the form of airborne conidia that can easily reach the alveoli. An impaired immune system and structural damage to the lungs by SARS-CoV-2 infection provide the conditions suitable for conidia to germinate, produce hyphae, and invade tissues and blood vessels[16]. Since IPA co-infection in critically ill patients with influenza has been recently identified, multiple studies have reported *Aspergillus* infections among critically ill patients with COVID-19[17-31]. In a study from Germany, CAPA was found in 5/19 (26.3%) critically ill COVID-19 patients with acute respiratory distress syndrome[32]. In a French, multicentric, retrospective, cohort study, a probable CAPA was diagnosed in 21 out of 366 COVID-19 patients (5.7%) admitted to the ICU and in 108 patients (19.4%) who received respiratory sampling. Patients with CAPA had significantly increased mortality (15/21 versus 32/87). Interestingly, studies suggested that azithromycin can contribute to an increased susceptibility of COVID-19 patients to CAPA[17]. In another study from New York City, most CAPA patients received a much higher dose of systemic glucocorticoids than the dose with a proven mortality benefit[19]. In another retrospective cohort study on 396 mechanically ventilated COVID-19 patients, those with CAPA were more likely to have an underlying pulmonary vascular disease, liver disease, coagulopathy, solid tumor, multiple myeloma, or corticosteroid exposure, and they had a lower body weight index[26]. Spontaneous intrapulmonary bleeding and hemoptysis are the common complications of IPA. Ground-glass opacities characterize COVID-19 and IPA, and a comprehensive microbiological evaluation is important to prevent the misdiagnosis of CAPA[32].

DIAGNOSIS OF IPA

An early detection of IPA is difficult. Histopathological examination with lung biopsy plays an important role in the diagnosis of IPA. Gomori's methenamine silver stain and periodic acid-Schiff stain or fluorescence application are essential methods to identify fungal organisms[33]. *Aspergillus* typically shows septate hyphae with dichotomous acute angle branching. A fungal culture from a clinical sample is the gold standard in diagnosing IPA, and it allows antifungal susceptibility testing. However, fungal cultures are limited by the amount of time required to achieve a positive result. Moreover, the cultures of respiratory tract secretions have low sensitivity, as *Aspergillus* is grown from sputum in only 35% and from bronchoalveolar lavage (BAL) in 63% of patients with active infection[34]. Indirect tests, such as galactomannan, (13)-β-D-glucan assays, or polymerase chain reaction (PCR), are helpful in diagnosing IPA. Galactomannan is a cell wall polysaccharide of *Aspergillus* that proliferates during invasive infections; the testing of BAL is a good tool to diagnose invasive aspergillosis[35]. However, the galactomannan sensitivity was only 25% in IPA patients who did not have neutropenia[36]. In addition, the polysaccharide (13)-β-D-glucan is a fungal cell wall component that is not specific for *Aspergillus*; it is also found in *Acremonium*, *Candida*, *Fusarium*, *Saccharomyces*, *Trichosporon*, and *Pneumocystis jirovecI*[35]. Collectively, a mycologic study of BAL, histopathologic examination with lung biopsy, and serum galactomannan test or (13)-β-D-glucan assays in critically ill COVID-19 patients should be considered early if CAPA is suspected.

TREATMENT OF CAPA

The most commonly used antifungal agent for IPA is voriconazole, followed by caspofungin, isavuconazole, and liposomal amphotericin B[37]. In a previous trial, voriconazole

had a higher efficacy than amphotericin B deoxycholate in mycologically documented invasive aspergillosis[38]. On the other hand, a surveillance study in the Netherlands reported the triazole resistance in 101 out of 784 (12.9%) patients with a positive *Aspergillus fumigatus* culture. The authors suggested that a liposomal amphotericin B treatment is recommended when azole resistance is confirmed or when susceptibility testing is not possible, and the local azole resistance rate is >10%[39].

CONCLUSIONS

In conclusion, SARS-CoV-2 infection is a risk factor for IPA. Because of its potential detrimental consequences, an early diagnosis and prompt treatment of CAPA are paramount. The respiratory specimens for mycologic studies, including fungal culture, histopathologic examination, galactomannan test, (13)-β-D-glucan assays, or PCR, can help reach an early diagnosis. A systemic antifungal therapy should be initiated in patients with suspected CAPA while waiting for the results of mycologic studies.

CONFLICT OF INTEREST

In relation to this article, we declare that there is no conflict of interest.

ORCID

Hyun-Min Seo: 0000-0002-6897-494X
Ji Hun Park: 0000-0002-4481-7333
Se Uk Oh: 0000-0001-7770-5488
Se Kwang Park: 0000-0002-2342-9577
Joung Soo Kim: 0000-0002-3014-9645

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