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Clinical Characteristics of Patients with Probable Coronavirus Disease 2019-associated Pulmonary Aspergillosis at a Tertiary Care Hospital in the Republic of Korea: A Case Series

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Background: Coronavirus disease 2019 (COVID-19)-associated pulmonary aspergillosis (CAPA) is a life-threatening invasive fungal infection in critically ill patients with COVID-19. However, only a few studies have reported CAPA in the Republic of Korea.

Objective: To describe clinical characteristics of CAPA in patients at a tertiary care hospital in the Republic of Korea.

Methods: This retrospective, observational consecutive case series study was conducted by reviewing the electronic medical records of patients who developed CAPA at Seoul National University Hospital from January 1, 2020, to August 31, 2021. CAPA was defined by European Confederation of Medical Mycology/International Society for Human and Animal Mycology (ECMM/ISHAM) consensus criteria. Patient demographics, comorbidities, corticosteroid use, clinical presentation, treatment, and outcomes were investigated.

Results: Eleven patients were diagnosed with probable CAPA according to the ECMM/ISHAM criteria. One patient had classical host factor for invasive pulmonary aspergillosis before admission. All patients received corticosteroid therapy before CAPA diagnosis. The mean total corticosteroid administered before CAPA diagnosis was 220 mg of dexamethasone equivalent dose (range, 80~572 mg), and the mean duration of steroid therapy was 15 days (range, 4~34 days). The median time from intensive care unit admission to CAPA diagnosis was 12 days (range, 5~36 days). All individuals showed aggravation on chest X-rays. Ten patients were diagnosed with positive serum galactomannan (GM), and one was diagnosed with positive GM in a bronchoalveolar lavage specimen. Of the 11 patients, 8 received voriconazole-based antifungal therapy for a median of 30.5 days. Only two patients survived after antifungal treatment.

Conclusion: These cases illustrate CAPA complicated in critically ill COVID-19 patients. The challenges in diagnosis and poor outcomes of CAPA emphasize the clinical suspicion and needs for further investigation.

Key Words: Case series, COVID-19, Pulmonary aspergillosis, SARS-CoV-2

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INTRODUCTION

Coronavirus disease 2019 (COVID-19)-associated pulmonary aspergillosis (CAPA) is a life-threatening fungal infection that affects critically ill patients with COVID-19[1-3]. Invasive *Aspergillus* infection is an opportunistic infection that affects immunocompromised hosts[4,5]. Aspergillosis cases continue to increase with the growing number of the immunosuppressed population such as patients with hematologic malignancy and organ transplantation recipients[6]. Severe influenza and COVID-19, which deteriorates the mechanical and immunologic barrier functions of airways, are novel risk factors for invasive *Aspergillus* infection[5,7]. CAPA has become a cause of excess mortality in critically ill patients with COVID-19[8], following the announcement of the European Confederation of Medical Mycology/International Society for Human and Animal Mycology (ECMM/ISHAM) consensus criteria for CAPA diagnosis[1]. Previous multicenter prospective[9-11] and retrospective[10,12] cohort studies have suggested underlying pulmonary disease and treatment with high-dose corticosteroids as risk factors for CAPA development. Similar results were reproduced in two large, multicenter, retrospective cohort studies in Korea, which showed chronic pulmonary disease and treatment with high-dose steroids as risk factors for CAPA development[13,14]. However, CAPA diagnosis remained challenging because of its atypical presentation with manifestations ranging from fungal colonization to angioinvasive disease[7,15]. Patients diagnosed with CAPA are usually less immunosuppressed than with invasive pulmonary aspergillosis (IPA). It contributed to less prominent angioinvasion in patients with CAPA, which is associated with lower serum galactomannan detection prevalence[9], and infrequent typical imaging finding such as halo, reversed halo, and air-meniscus signs[16]. Additionally, distinguishing between clinical deterioration caused by COVID-19 progression and CAPA development is difficult[3,16]. Needs for CAPA diagnosis and treatment remained unmet as the COVID-19 pandemic continues. The present report describes 11 patients diagnosed with CAPA in a tertiary care hospital in the Republic of Korea and summarizes their clinical presentation, management, and outcomes.

MATERIALS AND METHODS

This retrospective, observational consecutive, case series evaluated patients who developed CAPA at Seoul National University Hospital (SNUH), which is a large, tertiary care hospital in Seoul, Republic of Korea. Inclusion criteria were patients aged >18 years, had laboratory-confirmed COVID-19 and were admitted to the intensive care unit (ICU) at SNUH from January 1, 2020, to August 31, 2021. Patients positive on galactomannan (GM) assays and those with confirmed *Aspergillus* growth on fungus culture were included. Serum GM optical density index of >0.5 or bronchoalveolar lavage (BAL) GM optical density index of ≥1 were regarded as GM positive according to mycological evidence of CAPA in 2020 ECMM/ISHAM consensus criteria. The electronic medical records of patients with definite, probable, or possible CAPA were reviewed according to ECMM/ISHAM consensus criteria[1]. The demographic characteristics, underlying medical conditions, total prescribed corticosteroid dosage, and duration before CAPA diagnosis were recorded. Clinical data on patient presentation, management, and outcomes were summarized. This study was approved by the Institutional Review Board of SNUH (H-2108-172-1248). Details of the case series were reported according to PROCESS guidelines[17].

RESULTS

This stud included 11 patients, including 6 (54.5%) males and 5 (45.5%) females, with a median age of 72 years (range, 49~85 years) were diagnosed with probable CAPA according to ECMM/ISHAM consensus criteria[1]. Their underlying medical conditions are shown in Table 1. One patient (patient 2) had a hematologic malignancy, which is a classical host factor[4] for IPA, and she was the only patient who has the classical host factor before admission. This patient had undergone autologous hematopoietic stem cell transplantation for diffuse large B-cell lymphoma a month before the COVID-19 diagnosis. Three patients had a history of solid cancer, including two with active malignancy receiving chemotherapy. None had documented evidence of prolonged neutropenia. All patients had received corticosteroid therapy before the CAPA diagnosis. The mean total dose of corticosteroid therapy from admission to CAPA diagnosis was 220 mg of dexamethasone equivalent dose (range, 80~572 mg), and the mean duration of corticosteroid treatment was 15 days (range, 4~34 days). The mean daily dexamethasone dose before CAPA diagnosis was 14.6 mg (range, 9.2~16.8 mg). The median time from ICU admission to CAPA diagnosis was 12 days (range, 5~36 days). Initial mycological evidence in 10 patients consisted of serum GM positivity (mean optical density index: 1.59), whereas only one patient (patient 1) was diagnosed based on the presence of GM in BAL fluid. The BAL sample from patient 1 was obtained after the end of isolation because an in-house regulation limited the BAL sample analysis from isolated patients with active COVID-19

Table 1. Characteristics of patients with COVID-19-associated pulmonary aspergillosis

Patient no.	Age/ Sex	Comorbidities	Total steroid dose* from admission to CAPA, mg	Duration of steroids from admission to CAPA diagnosis, days	Time from ICU admission to CAPA diagnosis, days	ECMM/ ISHAM criteria	Radiologic features	Bronchoscopic features	Mycologic evidence (OD index)	Fungus culture
1	72/M	Asthma, COPD, DM, osteoporosis	572	34	36	Probable	Increased consolidation, bilateral pleural effusion on X-ray	Whitish thick secretion	BAL GM (2.14)	*Aspergillus* sp. on BAL
2	66/F	DLBCL, post-HSCT	64	6	8	Probable	Increased consolidation on X-ray	Whitish secretion, hyperemic mucosa†	Serum GM (1.26)	No growth
3	67/F	Pancreatic cancer on CTx, HTN, DM	141	10	11	Probable	Increased consolidation or nodules on X-ray	Whitish patches with ulcerative lesions	Serum GM (2.71)	*Aspergillus fumigatus* on BW
4	76/M	DM	334	21	21	Probable	Increased patchy opacities on X-ray	Whitish patches, grey secretion	Serum GM (5)	*Aspergillus fumigatus* on BAL
5	49/M	Rectal cancer on CTx, HTN	184	20	20	Probable	Increased consolidation on X-ray	Hyperemic mucosa†	Serum GM (1.03)	No growth
6	83/F	DM, HTN, DL, AF	120	8	8	Probable	Increased consolidation on X-ray	Bloody secretion†	Serum GM (1.54)	No growth
7	85/M	CAD, HTN, BPH	90	5	5	Probable	Cavitary change on X-ray	Minimal amount of secretion†	Serum GM (1.29)	No growth
8	79/F	–	154	12	12	Probable	Multiple pulmonary nodular opacities on X-ray	Hyperemic mucosa†	Serum GM (0.55)	No growth
9	58/M	–	80	4	6	Probable	Increased consolidation on X-ray	Scanty mucous secretion†	Serum GM (0.61)	No growth
10	64/F	HTN, DM	229	16	17	Probable	Increased consolidation on X-ray	Small to moderate amount of secretion†	Serum GM (1.26)	No growth
11	72/M	Lung cancer, DL	454	32	33	Probable	Increased consolidation on X-ray	Small amount of mucoid secretion	Serum GM (0.63)	No growth

Abbreviations: AF, atrial fibrillation; BAL, bronchoalveolar lavage; BPH, benign prostatic hyperplasia; BW, bronchial wash; CAD, coronary artery disease; CAPA, COVID-19-associated pulmonary aspergillosis; COPD, chronic obstructive pulmonary disease; CTx, chemotherapy; DL, dyslipidemia; DLBCL, diffuse large B-cell lymphoma; DM, diabetes mellitus; GM, galactomannan; HSCT, hematopoietic stem cell transplantation; HTN, hypertension; ICU, intensive care unit; OD, optical density

*Dexamethasone equivalent dose

†Bronchoscopy performed after initial clinical diagnosis of CAPA

Table 2. Treatment and outcomes of patients with COVID-19-associated pulmonary aspergillosis

Patient no.	Antifungal treatment	Time from diagnosis to treatment, days	Duration of antifungal treatment, days	Reason for termination of antifungal treatment	Outcome
1	None	–	–	–	Death
2	Voriconazole	2	41	Treatment completion	Death
3	Voriconazole	6	189	Treatment completion	Alive
4	Voriconazole	-3*	58	Treatment completion	Alive
5	Voriconazole	6	36	Futility of treatment	Death
6	Voriconazole	13	2	Deceased patient	Death
7	Voriconazole	2	8	Futility of treatment	Death
8	(Fluconazole)†	–	–	–	Death
9	None	–	–	–	Death
10	Voriconazole	0	25	Futility of treatment	Death
11	Voriconazole	1	2	Uncertain diagnosis	Death

*Patient 4 started empirical voriconazole treatment prior to confirmation of mycological evidence presented in ECMM/ISHAM consensus criteria
†Patient 8 started fluconazole 10-days after the diagnosis of CAPA due to azole-sensitive *Candida albicans* from one pair of blood culture from a central catheter. The clinician discontinued fluconazole after the 7-day course of treatment because the *C. albicans* was regarded as contaminated organism rather than true pathogen

due to concerns about transmission. The respiratory specimens of two other patients with probable CAPA were culture positive for *Aspergillus*, although all microbial identification results were obtained after the clinical CAPA diagnosis.

Upon CAPA diagnosis, all 11 patients showed aggravation on chest X-ray images. One patient (patient 7) showed a cavitary change and two patients (patients 3 and 8) had pulmonary nodules, which is a pulmonary aspergillosis indicator[1,4]. The other patients showed increased pulmonary consolidation or patchy opacities and findings that are nonspecific and indistinguishable from signs of aggravated COVID-19 pneumonia. Computed tomography (CT) was not considered upon diagnosis because of the risk of transmission and clinical instability although some patients were evaluated by CT. All patients underwent bronchoscopy during their hospital stay, but only four were evaluated before their clinical CAPA diagnosis. Two patients (patients 3 and 4) showed patchy lesions and one (patient 3) had ulcerative lesions on the airways, which are signs considered suspicious of *Aspergillus* tracheobronchitis[1]. Nonspecific bronchoscopic findings, such as hyperemic mucosa and secretions, were observed in nine patients.

Voriconazole-based antifungal treatment was administered in eight patients, whereas specific treatment targeting *Aspergillus* species was not administered in the other three patients (Table 2). One patient (patient 8) started fluconazole 10 days after the CAPA diagnosis because of azole-sensitive *Candida albicans* from one pair of blood cultures from a central catheter, but it was irrelevant to CAPA. The fluconazole was discontinued after the 7-day treatment course because *C. albicans* was regarded as a contaminated organism rather than a true pathogen. Other fungal pathogens and any other antifungal regimens for therapy among 11 patients were not reported. The median time from CAPA diagnosis to treatment initiation was 2 days (3 days before diagnosis to 13 days after diagnosis). One patient (patient 4) was started on voriconazole before meeting the ECMM/ISHAM diagnostic criteria. This patient was suspected of having CAPA based on ongoing respiratory distress accompanied by radiologic deterioration with two consecutive elevated serum 1,3-β-D-glucan levels and unspecified mold growth in respiratory samples despite the lack of definitive mycological evidence. This patient was later found to be serum positive for GM, and a culture of a BAL specimen showed growth of *Aspergillus fumigatus*.

The median duration of antifungal drug administration was 30.5 days (range, 2~189 days) in patients who received

antifungal treatment. The median antifungal treatment durations of survived and deceased patients were 123.5 days and 16.5 days, respectively. Among eight patients who received voriconazole, three completed antifungal therapy (Table 2). Two of them (patients 3 and 4) survived and were transferred to the general ward, and subsequently to a nursing hospital. The other three patients (patients 5, 7, and 10) discontinued the antifungal medication due to the grave clinical course and medical futility. They died within 10 days of treatment discontinuation. One patient (patient 6) died 2 days after the antifungal treatment initiation. Another patient discontinued voriconazole because of an uncertain CAPA diagnosis although the patient met the ECMM/ISHAM criteria. Overall, all patients who did not receive antifungal treatment died, as did 6 (75%) of the 8 patients treated with voriconazole treatment.

DISCUSSION

This study describes 11 patients who presented with probable CAPA from January 1, 2020, to August 31, 2021, at SNUH, which is a tertiary care hospital in the Republic of Korea. All patients received high-dose corticosteroid therapy before CAPA diagnosis, but most did not have classical host factors for IPA before admission. Classical host factors for IPA include prolonged neutropenia, hematologic malignancy, receipt of an allogeneic stem cell transplant or solid organ transplant, prolonged use of corticosteroids (≥0.3 mg/kg of corticosteroids for ≥3 weeks in the past 60 days), treatment with immunosuppressants, inherited severe immunodeficiency, and grade III-IV acute graft-versus-host disease[4]. This study revealed that only one patient had underlying hematologic malignancy as a classical host factor before admission. However, three patients received more than a three-week course of corticosteroids after admission which also met the classical risk factor for IPA. The international guideline on COVID-19 treatment recommended that hospitalized, critically ill patients with COVID-19 should be treated with 6 mg/day of dexamethasone for up to 10 days[18,19]. Additionally, a multicenter, randomized controlled trial published before the COVID-19 pandemic revealed the survival benefit of early administration of high-dose dexamethasone (20 mg/day for 5 days, followed by 10 mg/day for the next 5 days) on patients with moderate-to-severe acute respiratory distress syndrome (ARDS)[20]. All patients in this study who required mechanical ventilation had been already receiving 6 mg of dexamethasone when they were admitted to the ICU. We escalated the dose and duration of dexamethasone because they progressed to moderate-to-severe ARDS despite the usual dexamethasone dose. The mean daily dose of dexamethasone before CAPA diagnosis in the present study (14.6 mg/day of dexamethasone equivalent) was higher than that of a previous Korean nationwide multicenter cohort study (7.5 mg/day of dexamethasone equivalent for the first 10 days)[13], but less than that of another multicenter cohort study in Korea (22.4 mg/day of dexamethasone equivalent)[14]. Comparing the use of corticosteroids in different studies is difficult because it depends on the severity and comorbidities of patients. However, it might be considered in clinical practice because many previous studies suggested high-dose corticosteroids as a risk factor for CAPA development[9-14].

All individuals in this study showed deterioration on simple radiography upon the initial diagnosis. Abnormal radiographic findings alone were insufficient to suspect CAPA because most chest X-ray findings are nonspecific. CT scanning is a more sensitive imaging modality, but the risks of transmission and clinical deterioration during intrahospital transport were considered. Bronchoscopy was more frequently performed in our hospital because it can be performed at the bedside. Additionally, bronchoscopy has been reported safe for medical personnel who use personal protective equipment[21,22]. However, invasive procedures, such as biopsy and BAL, were not routinely performed due to the risk of complications such as bleeding and respiratory deterioration. Bronchoscopy findings of tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar are required for a CAPA tracheobronchitis diagnosis[1], with only 2 of the 11 patients in the present study showing significant findings.

Mycologic evidence has a crucial role in CAPA diagnosis in practice because radiologic and bronchoscopic abnormalities are often nonspecific. The presence of GM in serum played a pivotal role in CAPA diagnosis because the ability to obtain BAL samples from isolated COVID-19 patients was limited in our hospital. This might result in CAPA underestimation, as <20% of patients with CAPA were reported to have sera positive for GM[23,24]. Moreover, the high serum GM positivity rate in the present study may explain the high mortality rate (81.1%) among these patients because serum GM positivity has been associated with more angioinvasive disease and poor outcomes[23].

The treatments of choice for CAPA consist of antifungal agents, including voriconazole and isavuconazole[1-3]. The present study revealed that 8 of 11 patients received voriconazole-based antifungal therapy. Isavuconazole was not available in our center during the study period because it was approved in January 2020 in Korea although isavuconazole has comparable efficacy but fewer toxicities than voriconazole[25]. Of the 8 patients who received voriconazole, 2 (25%) survived;

these patients have a longer antifungal therapy duration than those who did not survive. A minimum of 6~12 weeks of antifungal treatment has been recommended[1], but the optimal treatment duration has not been determined, and few studies to date have evaluated long-term outcomes.

In conclusion, *Aspergillus* infection can be complicated in critically ill patients with COVID-19. Clinical suspicion and mycologic evidence from optimal specimens are key to early diagnosis because of its atypical presentation. An antifungal drug that targets *Aspergillus* should be initiated upon CAPA suspicion, as a lack of treatment is associated with poor outcomes.

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CONFLICT OF INTEREST

Wan Beom Park is the associate editor of the *Journal of Mycology and Infection*; however, he was not involved in peer reviewer selection, evaluation, or the decision to publish this article. All other authors have no competing interests to report.

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ETHICAL APPROVAL STATEMENT

The study was approved by the Institutional Review Board of (IRB No. H-2108-172-1248). This study was conducted in accordance with the principles of the Declaration of Helsinki.

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