RESEARCH LETTER

Prevalence of invasive aspergillosis among patients with COVID-19 hospitalized in intensive care units: not a rare problem

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Introduction Fungal infections among patients hospitalized in intensive care units (ICUs) are a considerable diagnostic and therapeutic challenge. *Aspergillus* spp. are very rarely identified as a factor leading to lower respiratory tract infections. So far, they have been recognized as pathogens causing opportunistic infections in immunocompromised patients. Based on data provided in scientific publications, *Aspergillus* spp. were found in only 0.3% to 5.8% of ICU patients. According to the classification introduced by Blot et al,[1] the diagnosis of invasive aspergillosis can be confirmed, probable, or possible. The treatment regimen depends on the classification of the patient into one of these categories. Lesions develop within a few days. The mortality rate of invasive aspergillosis ranges from 40% to 100% (in the case of azole resistance), which primarily depends on the course of the underlying disease that affects the prognosis. However, the number of these infections has recently increased significantly among COVID-19 patients.[2-7] In our hospital, the ICU designated to treat patients with COVID-19 (confirmed with a genetic test) has been operating since November 2020. Already in the first month of its operation, *Aspergillus* spp. were cultured in as many as 7 out of 17 microbiologically diagnosed patients (41%). By comparison, in the previous 5 years there were only 11 cases of patients with pulmonary aspergillosis hospitalized in the ICU. Unlike yeasts of the *Candida* genus which, together with bacteria, form the human intestinal microflora, *Aspergillus* spp. enter from the external environment. On imaging tests, infections caused by *Aspergillus* spp. are very characteristics—there are clear foci of infection, potentially mycelia. However, in patients with SARS-CoV-2 infection, they may be masked by ground-glass opacities, which are characteristic of COVID-19 pneumonia. This significantly complicates the diagnostic imaging of invasive pulmonary aspergillosis. Therefore, it is important to include a microbiological test of material collected from the lower respiratory tract in the diagnostic workup, especially in this group of patients. The aim of the study was to highlight the importance of this issue and its key role in further clinical management of patients.

Patients and methods The study involved an analysis of the results of microbiological tests as well as demographic and clinical data of patients with COVID-19 pneumonia treated in the ICU of the Heliodor Swiecicki University Hospital in Poznan, Poland in the first month of its operation (from November 10 to December 10, 2020). During that time, a total of 19 patients were hospitalized in the ward and aspergillosis was confirmed in 7 individuals (all male).

The microbiological tests were conducted on bronchoalveolar lavage samples collected from patients with severe respiratory tract infections caused by SARS-CoV-2. The samples were collected during bronchial fibroscopy or as tracheal aspirate. Standard microbiological growth media for routine diagnostics of bacteria and fungi were used to analyze the material (for fungi, Sabouraud agar with chloramphenicol and gentamicin). The material tested for fungi was cultured longer than the standard 48 hours, that is, up to the fourteenth day of its collection.

The mean age of the patients was 64 years (range, 44–73 years). The following factors increasing the risk of fungal infections were found: cancer (1 patient), chronic obstructive

TABLE 1 Characteristics of patients with COVID-19 and a coinfection caused by *Aspergillus* spp.

Patient no.	Age, y	Risk factors	VAP	Steroids, mg/24h	BFS	Length of ICU stay, d	Bacterial co-infection	*Candida* co-infection	APACHE II	SAPS	SOFA
1	72	ACS, tumor, HF	No	24	Yes	19	Yes	No	20	55	9
2	72	COPD, AH, AF	Yes	8	Yes	8	Yes	No	19	39	9
3	59	ADS, atherosclerosis	Yes	6	Yes	16	Yes	Yes	26	50	8
4	44	AH, HF, obesity	Yes	8	Yes	29	Yes	Yes	18	29	10
5	57	DM, obesity	Yes	6	Yes	19	Yes	Yes	26	62	12
6	73	obesity, atherosclerosis, ACS	Yes	8	Yes	15	Yes	No	21	50	10
7	71	AH, HF, obesity	Yes	6	Yes	26	Yes	Yes	20	50	12

Abbreviations: ACS, acute coronary syndrome; ADS, alcohol dependence syndrome; AF, atrial fibrillation; AH, arterial hypertension; APACHE II, Acute Physiology and Chronic Health Evaluation II; BFS, bronchial fibroscopy; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HF, heart failure; ICU, intensive care unit; IHD, ischemic heart disease; SAPS, Simplified Acute Physiology Score; SOFA, Sepsis-related Organ Failure Assessment; VAP, ventilator-associated pneumonia

pulmonary disease (1 patient), obesity (3 patients), diabetes (1 patient), renal failure treated with renal replacement therapy (3 patients), and *Candida* yeast infection (4 patients). When aspergillosis was confirmed, all patients were treated with steroids (dexamethasone) at a dose of at least 6 mg per 24 hours (6–24 mg/24 h). Individuals with bacterial coinfection (in some cases even with as many as 5 pathogens) were administered antibiotics. Ventilator-associated pneumonia was diagnosed simultaneously in 6 out of 7 patients with aspergillosis. On admission to the ICU, the average mortality prediction scores of the patients were as follows: Acute Physiology and Chronic Health Evaluation II, 21.4 points (predicted mortality, 40%); Sequential Organ Failure Assessment, 10 points (predicted mortality, 45%); and Simplified Acute Physiology Score, 47.8 points (predicted mortality, 41%). All the patients with a positive *Aspergillus* spp. culture test died during their stay at the ICU. The average length of stay in the ward was 18.8 days and the average duration of ventilation before confirmation of aspergillosis was 8.5 days (range, 2–14 days) (TABLE 1).

Ethics The study did not require approval of the bioethics committee or written consent of the patients.

Results and discussion The present study underscores the problem of invasive aspergillosis in patients treated in the ICU due to COVID-19 pneumonia. The physicians and microbiologists collaborated to obtain fungal cultures in 7 out of 17 patients (41%). When conducting microbiological tests for mold infections it is important that the material collected from patients be cultured for at least 7 days. Until recently, the diagnostics focused mainly on the macroscopic assessment of fungal colonies and microscopic analysis of the isolated strain, based on the atlas of pathogenic fungi. Currently, our microbiological laboratory is capable of identifying the species of molds by means of mass spectrometry. The identification lasts only several minutes; however, the culturing of clinical material may take up to 14 days. At present it is the best and most reliable testing method. Matrix-assisted laser desorption/ionization–time of flight mass spectometry enables correct identification of 127 species of molds.[8,9] The method is based on the measurement of specific proteins. The spectra of proteins are compared with the current library (microbial database). There were high scores for the *Aspergillus* genus, particularly the *A. flavus* and *A. fumigatus* species among the study patients.

Pulmonary aspergillosis is a complication of a severe viral infection. The risk factors include chronic obstructive pulmonary disease, nonhematological malignancies, diabetes, cirrhosis, chronic alcohol abuse, HIV infection, and malnutrition. These concomitant diseases are usually observed in ICU patients. Other risk factors of invasive aspergillosis are steroid therapy, male sex, influenza complications, immunodeficiency, autoimmune disorders, and a higher Acute Physiology and Chronic Health Evaluation II score. Long-term and broad-spectrum antibiotic therapy favors fungal infection because it eliminates the patient's microbiota, which is responsible for individual immunity.[10-12] In 3 out of the 7 patients analyzed in our study, molds were cultured as early as 1 to 2 days after the start of incubation due to the very large numbers of these microorganisms in the patients' bodies. In the remaining cases, *Aspergillus* spp. were cultured after 7 to 14 days from the collection of the biomaterial. Most of the patients who developed severe forms of COVID-19 pneumonia had at least 1 concomitant disease and presented with immunity disorders resulting from their stay and treatment in the ICU, although these were not definite risk factors predisposing to fungal infection. It seems that the SARS-CoV-2 infection itself, accompanied by additional risk factors for fungal infection, may cause invasive aspergillosis. The diagnosis and treatment of the infected patients require a close cooperation between physicians and laboratory diagnosticians who specialize in microbiology. SARS-CoV-2 infection increases the risk of fungal infections in

patients hospitalized in the ICU. Therefore, our center routinely tests material from the lower respiratory tract of SARS-CoV-2–positive patients in the course of COVID-19. So far, no guidelines for a routine testing have been set in this regard, even though the analysis of material collected from the lower respiratory tract for fungal infections seems to be of key importance for proper management of patients. The aim of this report is to draw the readers' attention to the problem of aspergillosis in patients with COVID-19 pneumonia, because this coinfection has a very high mortality. The lack of reports from other centers on confirmed infections caused by *Aspergillus* spp. in patients with COVID-19 may result from incorrect collection of biomaterial for microbial tests or too short culturing time. The coinfection caused by *Aspergillus* spp. in COVID-19 patients has been recognized as a new clinical entity, that is, COVID-19–associated pulmonary aspergillosis. According to some reports, its incidence is estimated at 19% to 35%.[3,11] Due to the current epidemiological situation and increasingly frequent reports from ICUs designated to treat patients with a severe course of COVID-19, it is necessary to confirm or exclude *Aspergillus* infection during the diagnostic procedure. Further multi-center studies assessing the incidence of *Aspergillus* co-infections among patients with COVID-19 are warranted. The pathogenesis of such a rapid onset of invasive pulmonary aspergillosis needs to be examined thoroughly, particularly with regard to the etiology of this infection in the course of COVID-19. It is also necessary to determine the population of patients at high risk of this fatal co-infection, develop a strategy for rapid diagnosis and treatment, and create guidelines for the prevention of aspergillosis.

Conclusions Microbiological analysis of material collected from the lower respiratory tract is of key importance for effective diagnosis and treatment of patients with COVID-19. The characteristic image of pulmonary aspergillosis may not always be visible on a computed tomography scan of the lungs, as it may be masked by ground-glass opacities.

It is necessary to incubate the cultured biomaterial for at least 7 to 14 days to effectively diagnose the molds in this group of patients.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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