

COVID-19 Associated Pulmonary Aspergillosis

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To the Editor,

Late December 2019, China reported an outbreak of Coronavirus Disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This has become a global threat, with high attack rates, intensive care unit (ICU) admissions, and mortality. Initial cohort studies reported a substantial case fatality rate in patients admitted to the ICU, of which half developed secondary infections.[1] Late February, the South of the Netherlands emerged as a hotspot for COVID-19, and we noticed cases of invasive pulmonary aspergillosis (IPA) occurring in COVID-19 patients admitted to the ICU. Here, we describe the clinical characteristics of COVID-19 associated pulmonary aspergillosis (CAPA) cases and the frequency in our ICU.

In the first three weeks of the outbreak 135 adult patients were admitted to the Amphia Hospital Breda, a 700-bed teaching hospital, with laboratory-confirmed COVID-19. Of these patients 31 (23%) required mechanical ventilation on ICU. Eleven COVID-19 ICU patients developed a secondary infection, of which six (19.4%) presumed invasive pulmonary aspergillosis (IPA). We identified *Aspergillus fumigatus* in five patients, and in three patients the *Aspergillus* antigen galactomannan (GM) (Platelia *Aspergillus*, Biorad) was found positive on bronchoalveolar lavage (BAL) fluid (Table 1). Three patients had pre-existing lung diseases, but none were EORTC/MSGERC host factor positive.[2] Three patients received corticosteroids before ICU admission, however less than 0.3 mg/kg or less than three weeks. No other immunosuppressive medication was given before CAPA diagnosis, and all were treated for COVID-19 with chloroquine and lopinavir/ritonavir. There were no significant differences in clinical characteristics between COVID-19 ICU patients with and without presumed CAPA (Table 2). CAPA occurred after a median of 11.5 days (range 8-42) post COVID-19 symptom onset and at a median of 5 days (3-28) after ICU admission. Chest CT-

scan was performed in one patient, without apparent signs of fungal infection. In one patient bronchoscopy was abnormal, with mucoid white sputum in the left bronchus. Serum GM was tested negative in three patients. Voriconazole and anidulafungin combination therapy was initiated in five patients and one patient received liposomal amphotericin B. Four (66.7%) patients died at median of 12 ICU days (11-20). Autopsies were not performed due to concerns for the risk of contamination.

Discussion

We observed a high incidence (19.4%) of presumed aspergillosis in our cohort of 31 ICU patients, which might indicate that COVID-19 patients are at risk for developing IPA.

Secondary fungal infections are increasingly being reported in COVID-19 patients. Studies from Wuhan, China, reported secondary fungal infections in 3 of 9 (33.3%) patients and in 6 of 17 (35.3%) critically ill patients.[3,4] Subsequent reports from Europe indicate that IPA may be found in association with severe COVID-19. Lescure et al. described a COVID-19 ICU patient with antifungal treatment for *A. flavus*, who died on day 24 post symptom onset.[5] A research letter reports a fatal case of pulmonary aspergillosis co-infection in an immunocompetent patient.[6] Case series from France reported presumed CAPA in 9 of 27 (33.3%) COVID-19 ICU patients and 5 CAPA in 19 (26.3%) ICU patients were reported from Germany. All-cause mortality in the French CAPA series was 3 of 9 (33.3%) and 4 of 5 (80.0%) in the German series.[7,8] This high incidence of secondary aspergillosis in COVID-19 cases resembles the high rates (16% and 23%) of influenza associated pulmonary aspergillosis (IAPA) that has been reported in the ICUs in the Netherlands and Belgium.[9] One problem is that there is no case definition for CAPA. However, recently a case definition for IAPA was proposed by an expert panel, which could be used to classify patients with CAPA.[10]. In the IAPA case definition, host factors are not used to classify patients, as IAPA

may develop in any patient with severe influenza. Diagnostic criteria include proven influenza infection with clinical symptoms and a GM index of ≥ 1 on BAL or of ≥ 0.5 on serum; or *Aspergillus* spp. cultured from BAL.[10] When we apply the IAPA case definition to our cases, three (Table 1) could be classified as probable CAPA based on BAL GM detection. The remaining 3 patients might classify as possible CAPA, with clinical deterioration and *Aspergillus fumigatus* recovered from tracheal aspirates as bronchoscopy was not performed. However, recovery of *Aspergillus* from upper respiratory samples may represent colonization and not invasive pulmonary disease.

Although in a retrospective ICU study 94% of IAPA patients had positive BAL-GM, and 71% had positive serum-GM,[9] the performance of GM in BAL and serum of CAPA patients remains to be further evaluated as it may differ from IAPA. Indeed, in three of our CAPA cases circulating GM was not detected in serum. In patient 1 the serum GM index was 0.4, which is borderline negative. Including our case series, to date 22 ICU patients have been reported with presumed CAPA.[5-8] Only three patients were tested GM-positive in serum. It is important to investigate the diagnostic value of serum GM in CAPA, as there is a general reluctance to perform bronchoscopy in COVID-19 patients due to the risks for the patient and the pulmonologist.

For CAPA, some clinical characteristics are similar to IAPA, including early symptom onset after ICU admission, absence of EORTC/MSGERC host factors, and a high ICU mortality. Invasive *Aspergillus* tracheobronchitis (with plaque formation), which is a common manifestation of IAPA, was however not registered in these patients. Three patients were known with chronic lung disease which makes differentiation between IPA and *Aspergillus* colonization challenging.

The diagnosis IAPA has controversies as varying frequencies of the infection have been reported in ICU influenza studies. Geographical differences may explain the observed variations, while differences in diagnostic approaches are also likely to contribute. IAPA may remain undiagnosed since respiratory deterioration is considered to be caused by bacterial coinfection rather than fungal infection and appropriate fungal diagnostics are not performed.[11]

SARS-CoV-2 infection might be a risk factor for IPA and early diagnosis and prompt treatment for CAPA in ICU patients seems warranted as high mortality rates have been reported. In our center, on suspicion of CAPA, a diagnostic work-up is performed that includes serum GM and, if feasible, bronchoscopy with BAL for fungal culture and GM. Antifungal therapy is started in patients highly suspected for CAPA, while awaiting results of fungal diagnostics. Until the risk of IPA in severe COVID-19 is better understood, infectious disease specialists, ICU physicians, pulmonologists, and clinical microbiologists should be aware of this secondary infection.

We declare no competing interests. AvA and RGB contributed equally to this work. Patient consent was obtained.

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Patient	Sex, age in years	Medical history	Days post symptom onset to onset CAPA	APACHE-II at ICU admission	Days post ICU admission to onset CAPA	Bronchoscopy findings	Microbiological findings (days post symptom onset of sample acquisition)	CAPA classification [8]	Outcome (days post symptom onset)
1	Male, 83	Cardiomyopathy Prednisolon 0·13 mg/kg/day for 28 days pre-admission	10 days	16	3 days	Not performed	Tracheal aspirate cultured <i>Aspergillus fumigatus</i> (day 7) Serum GM index 0·4 (day 8)	Possible	Died (day 12)
2	Male, 67	COPD Gold III Post RTx NSCLC 2014 Prednisolon 0·37 mg/kg/day for 2 days pre-admission	10 days	16	3 days	Not performed	Tracheal aspirate cultured <i>Aspergillus fumigatus</i> (day 5)	Possible	Died (day 11)
3	Male, 75	COPD Gold IIa	8 days	15	5 days	Mucoid white sputum left bronchus	BAL cultured <i>Aspergillus fumigatus</i> (day 8) BAL GM index 4·0 (day 8)	Probable	Died (day 12)
4	Male, 43	None	21 days	10	14 days	Unrevealing	BAL GM index 3·8 (day 18) Serum GM index 0·1 (day 16)	Probable	Survived
5	Male, 57	Bronchial asthma Fluticason 1·94 mcg/kg/day for 1 month pre-admission	13 days	15	5 days	Unrevealing	BAL cultured <i>Aspergillus fumigatus</i> (day 11) BAL GM index 1·6 (day 11) Serum GM index 0·1 (day 13)	Probable	Died (day 20)
6	Male, 58	None	42 days	15	28 days	Not performed	Sputum cultured <i>Aspergillus</i> (day 36, 40, 43, 47, and 50)	Possible	Survived
Median			11·5 days	15	5 days				12 days

APACHE-II, Acute Physiology and Chronic Health Evaluation II; BAL, bronchoalveolar lavage; CAPA, COVID-19 associated pulmonary aspergillosis; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ICU, intensive care unit; NSCLC, non-small-cell lung carcinoma; RTx, radio therapy;

Table 1: Patient characteristics, clinical course and outcome.

Parameter	Presumed CAPA (n=6)	Non-CAPA (n=25)	p
Age in years [range]	62·5 [43-83]	67·0 [16-79]	0·942
Male sex (ratio)	6/6 (100·0%)	20/25 (80·0%)	0·553
EORTC/MSGERC host risk factors (ratio)	0/6 (0·0%)	3/25 (12·0%)	1·000
Interval from symptom onset to ICU admission	7·0 [3-14]	9·0 [3-15]	0·268
Interval from ICU admission to ICU discharge	10·5 [4-47]	14·0 [2-42]	1·000
Interval from symptom onset to death	12 [11-20]	17·5 [9-37]	0·570
Systemic corticosteroid use	2/6 (33·3%)	3/25 (12·0%)	0·241
BAL performed	1/6 (16·7%)	6/25 (24·0%)	1·000
Mortality (%)	4/6 (66·7%)	8/25 (32·0%)	0·174

Table 2: Characteristics of CAPA versus non-CAPA patients, clinical course and outcome. Medians with range and percentages are visualized. We used the Mann-Whitney U test or Fisher's exact test to compare differences between CAPA and Non-CAPA where appropriate.

BAL, bronchoalveolar lavage; CAPA, COVID-19 associated pulmonary aspergillosis; ICU, intensive care unit.