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Case report

Aspergillus detection in airways of ICU COVID-19 patients: To treat or not to treat?

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ABSTRACT

It is now well known that patients with severe COVID-19 are at risk for developing invasive pulmonary aspergillosis (IPA). Nevertheless, the symptomatology of IPA is often atypical in mechanically ventilated patients and the radiological aspects of SARS CoV-2 pneumonia and IPA are difficult to differentiate. In this context, the significance of the presence of Aspergillus in respiratory tract samples (detected by culture, galactomannan antigen, or specific PCR) is not yet fully understood. Here we report two cases of intubated and mechanically ventilated ICU patients with SARS-CoV-2 pneumonia, in whom Aspergillus was detected in respiratory samples, who had a favorable outcome in the absence of antifungal treatment. These two cases highlight the difficulty of using the new definitions of COVID-19 associated pulmonary aspergillosis for routine management of patients.

Introduction

After more than one year of the pandemic, secondary Aspergillus infections have emerged as a frequent complication of severe COVID-19 in ICU [1–3]. COVID-19 associated invasive pulmonary aspergillosis (CAPA) is associated with longer hospital stay [4] and increased mortality [5,6]. However, in ICU patients, the presence of Aspergillus in the airway remains difficult to interpret because the symptomology is often atypical and radiological imaging is nonspecific [7,8], despite the new definitions of CAPA recently available [9]. Here we report two cases of patients with SARS-CoV-2 pneumonia, mechanically ventilated in ICU, in whom Aspergillus has been detected in respiratory samples, and who did not receive antifungal treatment and were alive at discharge. These cases raise the question of the significance of Aspergillus detection (by culture, galactomannan antigen (GM), or specific PCR) in intubated COVID-19 patients (colonization or IPA) and thus the indication for antifungal treatment.

Case presentation

Case 1

A 75-year-old man with a history of ischemic heart disease, insulin-requiring diabetes complicated with diabetic nephropathy with moderate creatinine elevation (179 μmol/l) and overweight (BMI = 27) had a positive nasopharyngeal PCR for SARS-CoV-2 on March 23, while hospitalized for Charcot's foot surgery, without any symptomatology. He was discharged from the hospital on March 27. Four days later, on March 31t, he presented to the emergency department with febrile dyspnea. No serious underlying chronic lung disease was known, nor was long-term corticosteroids treatment or immunosuppression. In the emergency room, the patient was hypoxemic at 77 mmHg on arterial blood gasses despite oxygenation of 9 liters/min, C - reactive protein was elevated at 203 mg/L (N < 10 mg/L), and he developed acute renal failure. Chest CT revealed bilateral ground-glass opacities with a crazy paving pattern suggestive of COVID-19 pneumonia. His-condition rapidly deteriorated, requiring transfer to the ICU the next day due to progression of ARDS. Due to increased oxygen requirements, the patient was intubated on April 2.

Evolution was marked by several ventilator-acquired bacterial pneumonias caused by Staphylococcus aureus and Escherichia coli,

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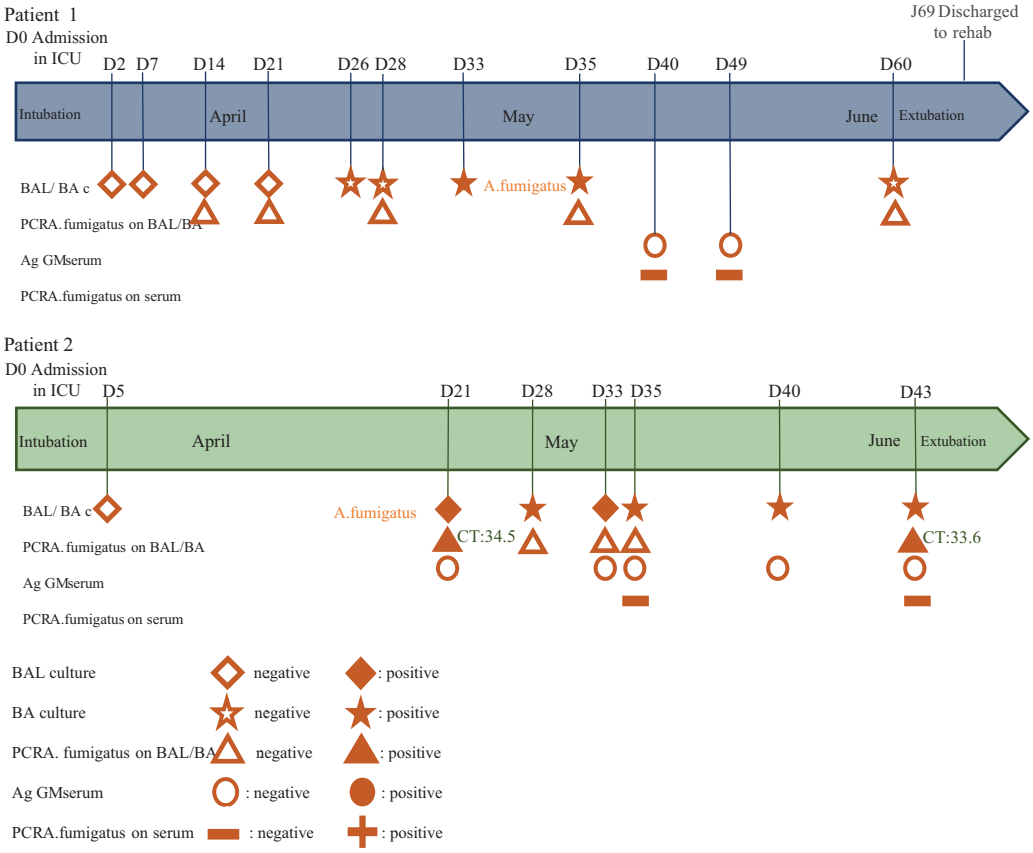

Fig. 1. Timelines for two ICU patients with Aspergillus reported with severe COVID-19 pneumonia. BAL: bronchioalveolar lavage; BA: bronchial aspiration; ICU: Intensive Care Unit, CT: Threshold cycle.

both of which resolved after antibiotic treatments. Respiratory samples (5 broncho-alveolar lavages [BAL] and 2 bronchial aspirates [BA] between April 4 and 30) remained sterile for fungi at that time (Fig. 1, Table 1). On May 5 (day 33), a BA culture on Sabouraud agar grew Aspergillus fumigatus, and a positive Aspergillus culture was confirmed on a second BA, on May 7 (day 35) (Fig. 1). However, PCR for Aspergillus fumigatus on these respiratory samples remained negative [10]. Galactomannan testing was not performed on respiratory samples (including BAL) due to biosafety issues [11]. Investigations were completed by determination of the galactomannan index in blood on May 12 and 21, and by blood PCR for A. fumigatus, both of which were negative. Unexpectedly, the patient improved his ventilatory parameters, and no antifungal treatment was initiated. An initial extubation was attempted on May 10 with success, but later, on June 1, the patient was re-intubated due to new nosocomial bacterial pneumonia, which quickly regressed, allowing final extubation on June 4. Subsequent BA cultures as well as PCR for A. fumigatus and fungal markers remained negative until discharge from the ICU. Of note, due to multiple nocturnal desaturations, the patient was subsequently explored and diagnosed with sleep apnea syndrome, ultimately demonstrating an underlying pulmonary pathology. Eventually, the patient was discharged to a rehabilitation unit on July 8.

Case 2

A 66-year-old man, with insulin-requiring diabetes and class 1 obesity (BMI= 33), was brought to the emergency department on April 2 for rapidly worsening febrile dyspnea with major hypoxemia, requiring 12 L/min oxygen therapy with high concentration mask and signs of acute respiratory distress. Nasopharyngeal PCR was positive for SARS-CoV-2 and CT scan showed bilateral ground-glass opacities with subpleural linear opacities strongly suggestive of COVID-19 pneumonia. The patient's condition rapidly worsened, and he was transferred directly to ICU and intubated due to hemodynamic failure and severe hypoxemia refractory to oxygen therapy. The patient then presented several septic shocks due to ventilator-acquired pneumonias on April 12 (oropharyngeal flora), again on April 23 (Staphylococcus aureus and Pseudomonas aeruginosa) and finally on May 5 (Pseudomonas aeruginosa), all of which were treated with antibiotics.

From April 23 (day 21) to May 15 (day 43) 4 BAs and 2 BALs revealed the presence of A. fumigatus by direct examination and or by culture (Fig. 1). Only two PCR for A. fumigatus were positive on day 21 (Ct: 34.5) and on day 43 (Ct: 33.6) (Table 1). Of note, GM assay on BA and BALs were not performed. However, PCR for A. fumigatus on blood and serum GM antigen remained negative on May 10 and 17. No antifungal treatment was initiated. The patient had no concomitant respiratory or hemodynamic degradation and was extubated on May 15. He was transferred to an internal medicine unit on May 17 and then transferred to rehabilitation a few days later.

These two clinical observations questioned the positive predictive value of Aspergillus detection in respiratory samples.

Discussion

Here we report two interesting and yet different cases that highlight the difficulty of interpretation of a positive culture for Aspergillus in respiratory samples from COVID-19 patients, as previously reported [12]. Indeed, the first case illustrates a probable transient colonization of the respiratory tract by A. fumigatus (identified on BA only), while the second case shows sustained colonization (on BA and BAL) with two positive A. fumigatus PCR on BAL. None of them

Table 1
Characteristics of two COVID-19 patients in ICU for whom presence of Aspergillus has been detected.

Characteristics	Patient 1	Patient 2
Gender	Male	Male
Age (years)	75	66
Comorbidities	Insulin-requiring diabetes, overweight (BMI= 27), chronic kidney disease	Insulin-requiring diabetes, obesity (BMI=33)
Host factors	None	None
Chest CT scan	Typical COVID-19 pneumonia moderate to severe	Typical COVID-19 pneumonia
Days on invasive mechanical ventilation prior to detection of Aspergillus	34 days	21 days
Culture of A. fumigatus in respiratory samples, n/N	BAL 0/4, BA 2/5	BAL 2/3, BA 4/4
positive serum sample (PCR or GM), n/N	0/2	0/5
clinical outcome	Improvement	Stability
Antifungal therapy	None	None
Total days of intubation	70 days	43 days
Total days in ICU	69 days	53 days
Final outcome	Discharged (rehabilitation)	Discharged (rehabilitation)
EORTC definition [14]	Colonization	Colonization
AspICU definition [18]	Colonization	Putative IPA
Modified AspICU definition [13]	Colonization	Putative IPA
ECMM/ISHAM definition [9]	Possible CAPA	Probable CAPA

BAL: bronchioalveolar lavage, BA: bronchial aspiration, GM: galactomannan.

had a positive blood biomarker for IPA (A. fumigatus PCR or GM). The observed discrepancies between the results of culture and PCR on respiratory samples may be explained by the used of small volume for the PCR, as the PCR was performed on remaining samples that were primarily used for cultures. Therefore, the volume used for PCR (100 μl) was probably not optimal.

Patient 2 would have been classified as putative IPA according the (modified) AspICU classification [13]. Therefore, an antifungal treatment could have been introduced. However, the patient's outcome was favorable in the absence of antifungal treatment. In the most recent definitions [9], new criteria such as PCR and the possibility to use non-BAL respiratory samples have been introduced to help diagnose CAPA in ICU patients.

Using this new classification, Patient #1 would have been classified with possible CAPA (two BAs with positive A. fumigatus culture) and Patient #2 with probable CAPA (two BALs and 4 BAs with positive A. fumigatus culture or PCR). Given the favorable outcome without antifungal treatment, we could assume that these two patients were more likely colonized with Aspergillus, but did not develop an invasive pulmonary infection. It should be highlighted that guidelines for definition of cases are primarily intended for clinical trials and epidemiological studies but not to direct or guide patient care [14].

The presence of Aspergillus in the respiratory tract may not be sufficient to diagnose IPA in a COVID-19 patient with a non-specific pulmonary imaging. Nevertheless, isolation of Aspergillus from a non-sterile respiratory specimen cannot be disregarded and should be used as a trigger to further evaluate patients for invasive pulmonary aspergillosis. In this context, the detection of GM in BAL in these non-neutropenic patients is important. A lung biopsy (CT guided/transbronchial) to reach a diagnosis of proven CAPA in such clinical situation may also be of interest, also there are currently few data that evaluate this procedure [15]. The difficulty to differentiate colonization from invasive infection among putative CAPA cases has been reviewed previously [7,8]. Absence of fever and typical radiology of IA should make one think of colonization rather than infection. Moreover, routine detection of Aspergillus markers (culture, GM, or PCR) from BAL/BA may not be helpful and may confuse clinicians as in described cases. Ideally, such tests should be performed in patients with high pre-test probability for invasive fungal infection (CAPA) as suspected because of appropriate clinical scenario like new onset fever, or progressive worsening respiratory status despite adequate antibiotic treatment.

In the case of Aspergillus tracheobronchitis in COVID-19 patients, it has been proposed that different factors contribute to the progression from Aspergillus colonization to invasive infection and local angioinvasion [16]. A similar pathophysiology can be hypothesized for invasive pulmonary aspergillosis. The thresholds between the different stages of disease progression are important but difficult to assess during the management of the patients. In this context, a management on a case-by-case basis seems necessary. If antifungal treatment is not started at this stage, close monitoring of the patient should be performed. Starting an antifungal prophylaxis could be an option as it has been proposed for influenza associated invasive aspergillosis [17]. Nevertheless, there are currently no data available to support this choice in COVID-19 patients. Clinical studies are urgently needed to address these issues. In summary, the presence of Aspergillus in a respiratory sample in a severe COVID-19 patient with ARDS and non-specific pulmonary imaging remains difficult to interpret despite the new CAPA definitions.

Declarations

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Authors' contributions

Conceptualization, ED, MEB; data curation, GP and AB; Formal analysis, GP and AB; writing - original draft , GP, AB, ED, MEB; writing - review and editing, all authors.

Consent to participate

Informed consent has been obtained

Declaration of Competing Interest

During the past 5 years, Eric Dannaoui has received research grants from MSD and Gilead, travel grants from Gilead, MSD, Pfizer, and Astellas, and speaker's fee from Gilead, MSD, and Astellas. Marie-Elisabeth Bougnoux has received research grants from Astellas, and speaker's fee from Pfizer, MSD, Astellas, and Gilead. Other authors have no conflict of interests.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.mycmed.2022.101290.

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