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CAPA Case Series

COVID-19 associated pulmonary aspergillosis in ICU patients: Report of five cases from Argentina

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ABSTRACT

Invasive pulmonary aspergillosis is a complication in critically ill patients with acute respiratory distress syndrome, especially those with severe coronavirus disease-associated pneumonia. In this study, five cases of presumed invasive pulmonary aspergillosis in one immunocompromised and four immunocompetent patients with COVID-19 in Buenos Aires are described. In all cases, the underlying conditions, clinical presentation, fungal diagnostic tests used and their results, features of the chest scan images, antifungals used and clinical outcomes are detailed.

1. Introduction

The coronavirus disease 19 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in December 2019 in the Wuhan city, Hubei Province of China. This severe respiratory disease is associated with a high mortality rate, which varies across different countries. Among the causes of morbidity and mortality of patients with COVID-19, invasive pulmonary aspergillosis (IPA) emerged as a bad prognosis complication, especially in critically ill patients such as those with acute respiratory distress syndrome (ARDS) at intensive care units (ICU). In this regard, in many European countries, clinicians reported that patients with ARDS triggered by SARS-CoV-2, are prone to IPA even in absence of prior immunodeficiency. Reports showed that 19–35% of those critically ill patients with COVID-19 have signs of *Aspergillus* co-infections, which is alarmingly high [1–6]. This novel entity, also called CAPA (COVID-19 associated pulmonary aspergillosis), makes *Aspergillus* an agent capable of further compromising the prognosis of these patients, similar to that documented in the Netherlands and Belgium with influenza associated pulmonary aspergillosis (IAPA) in critically ill patients [7,8]. In addition, a study carried out in Toronto in a small autopsy series of patients who died in 2003 from severe acute respiratory syndrome (SARS), reported that 10% of them had a pulmonary pathology suggestive of IPA [9]. As the medical community confronts the ongoing COVID-19 pandemic, determining whether patients infected with SARS-CoV-2 develop fungal complications, especially IPA, is crucial.

Therefore, early detection of CAPA could be a useful tool to optimize the therapy of critically ill patients with COVID-19 by administering the appropriate antifungal treatment [10]. However, diagnosis of CAPA or IPA remains difficult and even underdiagnosed. Bronchoalveolar lavage (BAL) fluid galactomannan (GM) testing and culture, which are the most sensitive diagnostic tests for IPA in the ICU, are hampered by the restricted role of bronchoscopies due to the risk of aerosol generation and disease transmission. In addition, renal tropism and injury caused by SARS-CoV-2 as well as drug-drug interactions, makes CAPA therapy a real challenge. Hence, the use of liposomal amphotericin B should be cautiously considered, and the emergence of azole-resistance is another hazard to take into consideration [11].

In Argentina, the COVID-19 pandemic arrived at the beginning of March, and Buenos Aires emerged as a hotspot for this respiratory disease.

Since respiratory deterioration is usually considered to be mostly associated to bacterial coinfections rather than fungal infection is that appropriate fungal diagnostics are not usually performed and thus CAPA

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may remain undiagnosed. In the present study, we report and describe presumptive invasive aspergillosis in five COVID-19 patients admitted to the ICU of a single medical center of Buenos Aires so as to contribute to the early suspicion, diagnosis and therapeutic management of these aspergillosis diseases in patients with ARDS. Sharing experiences and information, make clinicians and mycologists to be better prepared in the ICU.

2. Case series presentation

All patients reported herein were admitted to the ICU at the Posadas Hospital, Buenos Aires, Argentina, had COVID-19 with pulmonary infiltrates, received broad-spectrum antibiotics, immunosuppressants or corticosteroids (8 mg/day), and required mechanical ventilation due to moderate-severe COVID-19 pneumonia. For the diagnosis of CAPA/IPA, serum GM testing (GM index > 0.5), fungal cultures of sputum, tracheal aspirate (TA), chest computed tomography (CT) scan and GM testing in respiratory samples (GM index ≥ 1.0) were carried out. All these patients had a probable diagnosis of CAPA during the first or second week of hospitalization, that matches with the middle and latter stages of the COVID-19 disease. All patients received voriconazole or liposomal amphotericin B as first-line therapy (Table 1).

2.1. Case 1

A 23-year-old man with B-cell acute lymphoblastic leukemia came to Posadas Hospital on August 2020 to receive block II of salvage chemotherapy. Due to pneumonia associated with febrile neutropenia, a nasal swab sample was taken for diagnosis of SARS-CoV-2 infection, with a positive result. The patient was given antibacterial treatment (meropenem, colistin, amikacin, vancomycin) for 5 days, and stopped because of lack of microbiological documentation. However, he

Table 1
Patients features.

Patient	Sex	Age (years)	Medical History	Days after symptom onset to CAPA onset	Days after ICU admission to CAPA onset	CT findings	Microbiological findings	CAPA classification	Antifungal therapy	Outcome
1	M	23	B cell acutelymphoblastic leukemia	13	6	multiple bilateral GGO, CPP, PNC with an air-bronchogram at the level of the right posterior basal segment of the lung	Culture: Negative Serum GM index: 0.9 TA GM index: 4.2	Probable	Voriconazole	Died (HD26)
2	M	57	bronchiectasis	14	3	emphysema, bilateral GGO with small nodular infiltrations with air-bronchogram inside, and an area with diffuse varicose and cystic bronchiectasis in the lower right lobe area.	Culture: *A. fumigatus* (sputum) Serum GM index: 0.92 TA GM index: N/A	Probable	Amphotericin B	Alive
3	M	44	illicit drug abuse, alcoholism, smoking, uncontrolled insulin-dependent type 2 diabetes, arterial hypertension, obesity and recurrent furunculosis.	52	32	multiple bilateral GGO, CPP, PNC with air-bronchograms.	Culture: Negative LFD in serum: positive LFD in TA: positive Serum GM index: 1.01 TA GM index: N/A	Probable	Voriconazole	Alive, but under mechanical ventilation, renal fialure and hemodynamic instability
4	M	69	insuline-dependent diabetes	16	6	N/A	Culture: *A. fumigatus* (TA) LFD in serum: positive LFD in TA: positive Serum GM index: 2.15 TA GM index: 0.25	Probable	Voriconazole	Alive, but under mechanical ventilation
5	F	69	diabetes type 2, arterial hypertension, obesity	15	13	N/A	Culture: *A. fumigatus* (TA) Serum GM index: 0.57 TA GM index: 3.17	Probable	Voriconazole	Alive but under mechanical ventilation

GGO: ground glass opacities; CPP: crazy paving pattern; PNC: peripheral nodular consolidations; N/A: not available; TA: tracheal aspirate.

persisted with refractory hypoxia despite non-invasive positive pressure ventilation. At the contrast-enhanced CT, multiple bilateral ground-glass opacities with a crazy paving pattern and some peripheral nodular consolidations with an air-bronchogram at the level of the right posterior basal segment of the lung, were observed.

On hospital day (HD) 13 he was transferred to the ICU requiring endotracheal intubation and mechanical ventilation for progressive worsening of the radiological picture and moderately severe ARDS with a PaO_2:FiO_2 ratio of 117 mm Hg.

Despite prone positioning, and neuromuscular blockade, refractory hypoxia persisted without response to rescue maneuvers.

TA and serum samples were positive for galactomannan (GM index of 4.2 and 0.9, respectively), and intravenous voriconazole treatment was commenced (400 mg/12 h first day, then 200 mg/12 h).

The patient deceased on HD 26 due to respiratory and hemodynamic instability and sepsis (after having received an initial dose of voriconazole initially unavailable in our pharmacy). Autopsy was not performed due to concerns for the risk of contamination.

2.2. Case 2

A 57-year-old man, whose underlying disease included bronchiectasis presented to Posadas Hospital in June 2020 with productive cough, dyspnea and intermittent fever (>38.5 °C) for two weeks. Clinical examination showed signs of acute respiratory failure, tachypnea and hypoxemia. He was diagnosed with COVID-19 by real time PCR of a nasal swab sample. On HD 2 chest CT showed emphysema, bilateral ground-glass opacities with small nodular infiltrations with air-bronchogram inside, and an area with diffuse varicose and cystic bronchiectasis in the lower right lobe area. The patient was given antibacterial treatment (piperacillin plus tazobactam) without clinical improvement. On HD 3, he was transferred to the ICU requiring endotracheal intubation and mechanical ventilation for progressive worsening of the radiological picture and moderately severe ARDS with a PaO_2:FiO_2 ratio of 148 mm Hg and deterioration of the sensorium. *Aspergillus fumigatus* was cultured from sputum samples. Serum GM turned positive (GM index: 0.92). Due to severe liver dysfunction (ALT 317 U/L, ALT 233 U/L, total bilirubin 4,21 mg/dL) the patient was started with antifungal therapy with liposomal amphotericin B (5 mg/kg/day; HD 11) for 14 days. Due to good clinical evolution, it was decided to go to the general medical clinic room (HD 25). At the time of this report the patient remains well, off anti-fungal therapy, with mild dry cough and improved effort tolerance, and no systemic features.

2.3. Case 3

A 44-year-old man with a history of illicit drug abuse, chronic alcoholism and smoking was admitted to the ICU because of ARDS with a PaO2:FiO2 ratio of 164 mm Hg. Among his underlying diseases were uncontrolled insulin-dependent type 2 diabetes, arterial hypertension, obesity (body mass index: 37 kg/m^2) and recurrent furunculosis.

Real time PCR on AT was tested positive for SARS-CoV-2. On HD 20, the patient required endotracheal intubation and mechanical ventilation for progressive clinical deterioration and hypoxemia. Chest CT-scan was performed and showed multiple bilateral ground-glass opacities with a crazy paving appearance with many peripheric nodular consolidations with air-bronchograms.

On HD 31, the patient presented bacteremia by *Staphylococcus epidermidis* and antibiotic therapy with vancomycin was introduced for 14 days and stopped because he had no more findings of septic embolil. On HD 36, he received fluconazole (200-mg loading dose followed by 100 mg/day for four days) due to urinary candidiasis caused by *Candida albicans*. Then he had daily febrile records without hemodynamic decompensation. Due to a novel episode of bacteremia by *S. epidermidis* thirteen days later (HD 49), empirical antibiotic therapy with meropenem and colistin commenced.

Due to persistence of fever, a new TA was obtained. TA culture on Sabouraud agar remained sterile. However, *Aspergillus* LFD was performed from this respiratory sample and from serum and revealed a positive result, for which voriconazole was added to the treatment (400 mg/12 h first day, then 200 mg/12 h) on HD 52. Due to acute renal failure with refractory metabolic acidosis and hyperkalemia, the patient required slow low-efficient daily dialysis. Noradrenaline therapy was started due to hemodynamic decompensation. At the time of this report the patient remains with hemodynamic and respiratory instability and with a serum GM index of 1.01.

2.4. Case 4

A 69-year-old insulin-dependent diabetic man came to Posadas Hospital due to pneumonia associated with confirmed diagnosis of SARS-CoV-2. Chest X-ray revealed bilateral infiltrates. He received ceftriaxone, clarithromycin, and interferon alpha/remdesivir (HD 1, 2 and 4). On HD 10, he was admitted to the ICU with moderate ARDS (PaO2:FiO2 ratio of 126 mm Hg). He was intubated and mechanically ventilated. TA cultures were negative. Due to persistence of fever, progressive clinical deterioration and worsening of the radiological picture a new endotracheal aspiration was obtained on HD 16. TA revealed *A. fumigatus* in culture and showed branching hyphae on direct examination. *Aspergillus* LFD was performed from the TA and serum and revealed a positive result. Intravenous voriconazole treatment was initiated (400 mg/12 h first day, then 200 mg/12 h). At the time of this report the patient remains with hemodynamic and respiratory instability and with a serum GM index of 2.15 and an AT GM index of 0.25.

2.5. Case 5

A 69-year-old insulin-dependent diabetic woman with arterial hypertension and obesity came to hospital due to pneumonia associated with confirmed diagnosis of SARS-CoV-2. On HD 2, she was admitted to the ICU with moderate ARDS (PaO_2:FiO_2 ratio of 132 mm Hg). She received ceftriaxone, clarithromycin, and dexamethasone 8 mg/day. Chest X-ray revealed bilateral infiltrates. She was intubated and mechanically ventilated. TA cultures were negative. Due to persistence of fever, progressive clinical deterioration and worsening of the radiological picture a new TA was obtained on HD 15 and showed *A. fumigatus* in culture. Serum GM index determined using Platelia™ *Aspergillus* was performed and revealed a positive result. Intravenous voriconazole treatment was initiated (400 mg/12 h first day, then 200 mg/12 h). At the time of this report the patient remains with hemodynamic and respiratory instability and with a serum GM index of 0.57 and a TA GM index of 3.17.

All described cases fulfilled the IAPA case definitions for the diagnosis of CAPA [12], the oncohematologic patient fulfilled the EORTC/MSGERC criteria of probable IPA and the remaining four patients fulfilled the criteria of putative invasive aspergillosis according to the AspICU classification defined by Blot et al. for the diagnosis of invasive pulmonary aspergillosis in critically ill patients [13].

3. Discussion

Patients infected with SARS-CoV-2 might develop major lung damage due to viral replication, cytokine storm and the exacerbated inflammatory responses [10]. It was reported that the severe damage to the lung tissue may lead to secondary infections within a median of 17 days post COVID-10 symptom onset. Some clinicians reported that CAPA occurred after a median of 11.5 days (range 8–42) after onset of COVID-19 and at a median of 5 days (3–28) after ICU admission [2]. Notable most immunocompetent patients who suffer from severe forms of COVID-19 have ≥1 underlying comorbidities, such as hypertension, diabetes, chronic obstructive pulmonary disease, obesity, chronic renal disease, liver disease, pulmonary fibrosis, smoking [14], such as those

described in the four immunocompetent patients studied herein. However, none of these predisposing factors are frequently associated with an increased risk for developing fungal infections. The immunocompromised patient included in this study was treated for B-cell acute lymphocytic leukemia 6 months ago and developed CAPA during chemotherapy.

Among the pathophysiological factors that may be associated with IPA in critically ill patients with COVID-19, are included: damage to the respiratory epithelium, defective mucociliary activity, and dysfunctional or "paralyzed" local immune response [15]. Furthermore, in the case of influenza, which is also associated to IPA in critically ill patients, this virus has been documented to produce an immunomodulatory effect by inhibiting the formation of the NADPH oxidase complex, inducing a temporary situation similar to that of a patient with chronic granulomatous disease [16]. Something similar could be happening with critical patients with COVID-19 who develop CAPA, although further studies are needed.

In the present study, we report presumptive invasive aspergillosis in five COVID-19 patients with moderate to severe ARDS without underlying immunocompromising disease in four patients. Ground-glass opacities that characterize COVID-19 as well as IPA were observed in all patients that have undergone chest CT scan. To prevent missing IPA, a microbiological evaluation at the mycology laboratory is mandatory (i.e. testing for the presence of *Aspergillus* sp. or other fungi in lower respiratory secretions and galactomannan in consecutive serum samples in COVID-19 ICU patients).

We identified *A. fumigatus* in three patients (patients 2, 4 and 5), in four patients the *Aspergillus*

antigen GM was found positive on TA (patient 1, 3, 4 and 5) and in all patients the GM antigen was positive in serum samples. One patient had a pre-existing lung disease, one was EORTC/MSGERC host factor positive [2] and three exhibited $\geq$ 1 underlying comorbidities (diabetes, obesity, arterial hypertension). All patients received corticosteroids before ICU admission, however less than 0.3 mg/kg during a short period of time (<three weeks).

No other immunosuppressive medication was given before CAPA diagnosis, except to the oncohematologic patient. CAPA occurred after a median of 22 days (range 13–52) post COVID-19 symptoms onset and at a median of 12 days (2–32) after ICU admission. Chest scan was performed in all patients, with apparent signs of fungal infection. It is noteworthy that all patients except one, were male with a median age of 52.4 years (range 23–69), a younger median age than that reported in the literature [17–19].

Because all patients with clinical features of probable CAPA were suffering from moderate-to-severe respiratory failure and hemodynamic instability, antifungal therapy was initiated as soon as cultures or GM assays were positive.

Voriconazole was initiated in four patients and the remaining one received liposomal amphotericin B because of severe liver dysfunction. One patient (20%) died on treatment at 13 ICU days.

The diagnosis of IPA in critically ill patients with COVID-19 in ICUs still remains a challenge. A decade ago, the H1N1 pandemic showed that patients with ARDS triggered by this viral infection were prone to IPA and that mortality rates were significantly higher for influenza patients who are co-infected with *Aspergillus* sp. Diagnostic algorithms for patients admitted to the ICU with and without influenza infection have been proposed and are indeed of value in the patient with CAPA [12]. However, the limited use of bronchoscopy, makes that diagnosis of CAPA usually relies on detection of *Aspergillus* in upper respiratory tract specimens such as sputum or TAs, which may represent airway colonization rather than IPA. Diagnostic uncertainty is further increased by frequent negative serum GM, even in patients with proven CAPA as well as the observation of survival of *Aspergillus* positive patients who did not receive antifungal therapy [20].

Finally, SARS-CoV-2 infection should be considered a risk factor for IPA and early diagnosis and prompt treatment for CAPA in ICU patients could help to improve patients' outcomes due to the high mortality rates associated to this invasive fungal disease.

Ethical considerations

Publication of this case series was approved by the institutional review committee "Dr Vicente Federico Del Giúdice" at Hospital Nacional Alejandro Posadas, Buenos Aires, Argentina (Ref. 395 EMnPES0/20).

Consent

Written informed consent was obtained from the patient or legal guardian(s) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Declaration of competing interest

None to declare.

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