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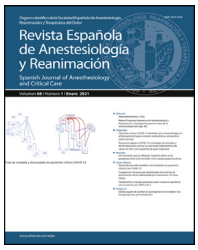

CASE REPORT

Invasive pulmonary aspergillosis in patients with acute respiratory syndrome by COVID-19☆

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Abstract Patients with COVID-19 who are admitted to intensive care unit (ICU) are at high risk of developing secondary infections, including invasive fungal infections such as invasive pulmonary aspergillosis (IPA). The main purpose was to analyse the putative COVID-19 Associated Pulmonary Aspergillosis (CAPA) patients in our setting. In these patients, we performed mycological culture in bronchoalveolar lavage (BAL) for isolation of *Aspergillus* sp. We followed the *Aspl*CU algorithm to diagnose putative IPA. Moreover, we considered relevant the positivity of Galactomannan in BAL. We diagnosed putative IPA in 3 patients. The common features of these 3 patients were: more than 21 days of stay in ICU, severe acute respiratory distress syndrome (ARDS) and treatment with steroids (1 mg/kg per day). Therefore, CAPA has to be systematically considered although a new algorithm to diagnose it is needed to treat patients in early stages in order to avoid catastrophic outcomes.

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PALABRAS CLAVE
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Aspergilosis pulmonar invasiva en pacientes con síndrome de distrés respiratorio por COVID-19

Resumen Los pacientes con COVID-19 que ingresan en una unidad de cuidados intensivos (UCI), tienen un alto riesgo de desarrollar infecciones secundarias, incluyendo infecciones fúngicas invasivas como Aspergilosis pulmonar invasiva (API). El objetivo principal fue el análisis de los casos con sospecha de COVID-19 Associated Pulmonary Aspergillosis (CAPA) en nuestra unidad. En estos pacientes realizamos cultivo micológico en el lavado broncoalveolar como métodos de aislamiento de *Aspergillus* sp. Se siguió el algoritmo *Asp*ICU para establecer el diagnóstico de API probable. Además, considerando también relevante la positividad de antígeno de Galactomanano. Se confirmó API probable en 3 de ellos. Los tres pacientes permanecieron ingresados más de 21 días por SDRA grave y recibieron corticoterapia (1 mg/kg/día). Por tanto, la CAPA se debe considerar de forma sistemática, aunque se necesita un nuevo algoritmo diagnóstico que permita tratamiento precoz por las consecuencias deletéreas que puede implicar en los pacientes críticos.

Introduction

Between 5%–30% of patients with COVID-19 require admission to the intensive care unit (ICU)[1], and present a high risk of developing secondary infections, including invasive fungal infections such as invasive pulmonary aspergillosis (IPA)[2]. In 2012, the association of severe infection by the influenza A (H1N1) virus and IPA led to an increase in mortality of up to 40%–60%[3]. COVID-19 has characteristics similar to severe forms of influenza A virus; therefore, it is reasonable to suspect that critical COVID-19 patients may be susceptible to IPA[4]. In addition, corticosteroid therapy is an immunosuppressive factor related to IPA, and has been used in up to 46% of critical COVID-19 patients[5].

We found several case series in the literature that describe the association between IPA and COVID-19, forming a new entity known as COVID-19 Associated Pulmonary Aspergillosis (CAPA). The earliest studies included 1 in 9 patients in France (33% of the 27 admitted to the ICU with COVID-19), and another with 5 patients in Germany (26% of the 19 admitted)[2,6] - rates similar to those observed in influenza A-associated IPA[3]. This was a red flag for the medical community. Several prospective studies were then published, such as the one performed in Lyon, France where 19 of the 106 patients with COVID-19 analysed presented putative IPA (17.9%)[7]. Another prospective study was performed in Bologna, Italy[8] in 108 patients, of which 30 (27.7%) presented putative CAPA, a rate consistent with the aforementioned studies. This study also analysed the Kaplan-Meier survival curve, which showed an increase in 30-day mortality in patients with putative CAPA compared with no CAPA (44 vs. 19%; $p = 0.002$). The lack of uniformity in diagnostic criteria for putative CAPA prevents us from determining the exact prevalence of the disease and, therefore, its mortality. However, data from the review article published by Pemán et al.[1] show that the mortality rate for CAPA could be as high as 59.1%, and could justify taking samples from the lower respiratory tract in all critically ill COVID-19 patients to perform systematic aspergillosis screening, and even starting empirical treatment before definitive diagnosis[5].

We present a series of 4 patients out of a total of 15 admitted for COVID-19 to the Anaesthesiology ICU of the Doctor Peset University Hospital, Valencia between March 22 and May 22 in which IPA was suspected. Our objective was to compare our results with those reported in the medical literature.

Methods

All patients were treated according to the COVID-19 protocol in place in our hospital, namely hydroxychloroquine 200 mg/12 h and lopinavir/ritonavir 400/100 mg/12 h (for the first 7 days of admission). Patients with established pneumonia were also given ceftriaxone (2 g/24 h) and azithromycin (500 mg/24 h), and those with moderate to severe respiratory distress syndrome (ARDS) were also given corticosteroid therapy with intravenous methylprednisolone (0.5 mg/kg/12 h) for 5 days. Patients with elevated IL-6 (>40 pg/m) received immunosuppressive therapy with tocilizumab 600 mg (single dose) and/or anakinra 100 mg when supplies of tocilizumab became depleted. Interferon β1b (0.25 mg sc/48 h) was used in the pulmonology ward.

Bronchoalveolar lavage (BAL) was performed in patients presenting clinical and radiological deterioration, characterized by increased alveolar infiltrates with appearance of fever and/or progressive respiratory failure despite broad-spectrum antibiotic treatment and ventilatory support. We obtained samples for mycological culture and galactomannan antigen assay (Ag).

Respiratory samples were processed for mycological study, seeded onto Sabouraud plates (Difco® Sabouraud Dextrose Agar Ref.: 210950) and introduced into Sabouraud-Chloramphenicol tubes (Difco® Sabouraud Dextrose W/Chlor Ref.: 771212). Growth was identified both macroscopically

Table 1 Characteristics of patients with suspected invasive pulmonary aspergillosis.

Patient	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Male	Male	Female	Female
Age	71	73	67	70
History	High blood pressure DL	High blood pressure DM 2 Dyslipidaemia	Thalassemia minor	High blood pressure DM2 DL Obesity ML lobectomy ACD
IPA risk factors prior to admission				
COPD	No	No	No	No
Steroid therapy	No	No	No	No
Transplant	No	No	No	No
Liver disease	No	No	No	No
Solid organ tumour	No	No	No	Yes (lung)
HIV	No	No	No	No
Risk factors during admission				
Steroid therapy	Yes	Yes	Yes	No
ARDS	Severe	Severe	Severe	Severe
Immunomodulators	Tocilizumab 600 mg, single dose Anakinra 100 mg, single dose	No		Interferon beta 0.25 mg/48 h
Superinfection H1N1	No	No	No	No
ARDS				
PaO_2/FiO_2 (mmHg)	At admission: 79	At admission: 119	At admission: 71	At admission: 139
Specific treatment				
Methylprednisolone	UCI - 40 mg/12 h/5 days - 40 mg/24 h/5 days	Hospital ward: 250 mg, dose UCI: - 40 mg/12 h/5 days - 40 mg/24 h/5 days	UCI - 40 mg/12 h/5 days - 40 mg/24 h/5 days	No
Hydroxychloroquine 200 mg/12 h/7 days	Yes	Yes	Yes	Yes
Lopinavir/ritonavir 400/100 mg/12 h/7 days	Yes	Yes	Yes	Yes

ACD: Anaemia of chronic disease; ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; DL: dyslipidaemia; DM 2: type 2 diabetes mellitus; HIV: human immunodeficiency virus; ICU: intensive care unit; IFN: interferon.

Table 2 Diagnostic characteristics, therapeutic and mycological characteristics of patients with suspected invasive pulmonary aspergillosis.

Patient	Patient 1	Patient 2	Patient 3	Patient 4
Mycological study of BAL fluid				
Days from ICU admission to performance of test:	19°	25°	27°	27°
Fungal culture: Seeded on Difco® Sabouraud Dextrose Agar and Difco® Sabouraud Dextrose W/Chlor Confirmed with MALDI-TOF MS (Bruker)	*Aspergillus fumigatus*	*Aspergillus fumigatus*	*Aspergillus fumigatus*	Negative
Sensitivity	Multisensitive (sensitive to voriconazole and amphotericin B)	Multisensitive (sensitive to voriconazole and amphotericin B)	Multisensitive (sensitive to voriconazole and amphotericin B)	Not applicable.
Galactomannan Ag: Platelia *Aspergillus* test®	Galactomannan Ag^+ (Index 1.4)	Galactomannan Ag^+ (Index 1.4)	Galactomannan Ag^+ (Index 1.5)	Galactomannan Ag^-
Imaging				
Chest X-ray	Day 19 of ICU admission: Appearance of new bilateral infiltrates	Day 25 of ICU admission: Appearance of new bilateral infiltrates	Day 26 of ICU admission: Appearance of new bilateral infiltrates	Day 26 of ICU admission: No significant changes from previous studies
CT				Day 26 of ICU admission: Consolidations in LLLs
IPA diagnosis				
Absolute criterion	No	No	No	No
Putative criteria	1. Positive culture 2. Sign and symptoms: fever, respiratory distress 3. Compatible image 4. IPS risk factors: Yes	1. Positive culture 2. Compatible signs and symptoms: haemoptysis, progression of respiratory distress, fever 3. Compatible image 4. IPS risk factors: Yes	1. Positive culture 2. Signs and symptoms: haemoptysis, progression of respiratory distress, fever 3. Imaging 4. IPS risk factors: Yes	1. Negative culture 2. Sign and symptoms: progression of respiratory deterioration, haemoptysis, fever 3. Compatible image 4. IPS risk factors: No
Antifungal treatment				
Prior to diagnosis	Anidulafungin (day 1 200 mg IV, day 2 and thereafter 100 mg IV)	No	Amphotericin B (3 mg/kg/day due to evidence of candidemia)	No
Targeted	Isavuconazole sulphate (200 mg/8 h for 48 h followed by 200 mg thereafter)	Isavuconazole sulphate (200 mg/8 h for 48 h followed by 200 mg thereafter)	Isavuconazole sulphate (200 mg/8 h for 48 h followed by 200 mg thereafter)	
Destination/outcome	Discharge to ward 50 days after admission to the ICU	Discharge to ward 38 days after admission to the ICU	Died 37 days after admission to the ICU	Discharge to ward 60 days after admission to the ICU

Ag: antigen; BAL: bronchoalveolar lavage; CT: computed tomography; ICU: intensive care unit; IPA: invasive pulmonary aspergillosis; LLL: left lower lobe.

and microscopically, and the results were confirmed by mass spectrometry (MALDI-TOF MS, Bruker). Galactomannan Ag was determined by the Platelia test® *Aspergillus* (Bio-Rad Ref.: 62794), with index of >1 being positive.

We followed the *Asp*ICU[9] algorithm to establish a diagnosis of putative IPA - the EORT-MSC algorithm[10] was not applicable because the patients had no previous immunodeficiency. We believe the recently published influenza-associated pulmonary aspergillosis (IAPA) diagnostic algorithm[3], which experts claim can be extrapolated, requires more validation studies.

Results

Only 1 of our study patients had a previous risk factor for IPA (history of solid organ neoplasia). All study patients presented moderate-to-severe ARDS requiring orotracheal intubation at some point in their evolution, 10 received corticosteroid therapy with doses equivalent to more than 20 mg of prednisone and 2 were treated with immunomodulators. None of the patients presented H1N1 superinfection.

Out of a total of 15 patients, BAL was performed in 4 (2 men and 2 women with a mean age of 67 years) due to radiological and clinical deterioration. Three of the 4 patients had 1 or more cardiovascular risk factors (arterial hypertension, dyslipidaemia, obesity and/or diabetes). Only 1 of the patients (patient 3) had no cardiovascular risk factors - his only history of interest being thalassemia minor. All study patients were treated according to the COVID-19 protocol in place in our hospital. The characteristics of these patients are shown in Table 1.

The mycological diagnostic and therapeutic characterization of study patients with putative IPA is described in Table 2 and below:

- Patient 1: we performed BAL with samples obtained on day 19 of admission to the anaesthesiology ICU due to clinical and radiological deterioration on that day (new bilateral infiltrates on chest X-ray). The patient was receiving echinocandin (anidulafungin 100 mg/day) for suspected invasive candidiasis. Aspergillus fumigatus with a galactomannan Ag index of 1.4 was isolated from BAL samples. The diagnosis of putative API was established after 4 criteria were met. Targeted treatment began with isavuconazonium sulphate (200 mg/8 h for 48 h and 200 mg/day thereafter). The patient was discharged to the ward on day 50 of admission to the ICU.
- Patient 2: BAL samples were obtained on day 25 of admission to the anaesthesiology ICU due to clinical and radiological deterioration on that day (new bilateral infiltrates on chest X-ray). Aspergillus fumigatus with a galactomannan Ag index of 1.4 was isolated from BAL samples. The diagnosis of putative API was established after 4 criteria were met. Targeted treatment began with isavuconazonium sulphate, and the patient was discharged to the ward on day 38 of admission to the ICU.
- Patient 3: BAL samples were obtained on day 27 of admission to the anaesthesiology ICU due to clinical and radiological deterioration on day 26 (new bilateral infiltrates on chest X-ray). The patient was receiving liposomal amphotericin B (3 mg/kg/day) for candidemia. Aspergillus fumigatus with a galactomannan Ag index of 1.5 was isolated from BAL samples. The diagnosis of putative API was established after 4 criteria were met. We decided to switch to isavuconazonium sulphate given the failure of liposomal amphotericin B. Despite this, the patient died on day 37 of admission to the ICU.
- Patient 4: BAL samples were obtained on day 27 of admission to the anaesthesiology ICU due to clinical and radiological deterioration on day 26 (chest CT scan showing consolidations in lower left lobes). The mycological culture was negative, so IPA was ruled out. The patient was discharged to the ward on day 60 of admission to the ICU.

Putative IPA was diagnosed in 3 study patients (20% of the total of 15 patients). Lung histopathological samples were not obtained by autopsy or post mortem lung biopsy.

Discussion

The SARS-CoV-2 pandemic challenged healthcare systems around the world in 2020. Around 5%–30% of patients with COVID-19 have required admission to critical care units[1], and secondary superinfection such as IPA are a possible cause of increased morbidity and mortality in these patients, particularly in those requiring invasive mechanical ventilation[2].

The literature describes various methods for diagnosing CAPA. Some studies consider COVID-19 to be a prior immunodeficiency and use the EORT-MSC algorithm[10], while others follow the more complex *Asp*ICU algorithm, in which the entry criterion is a BAL fluid sample positive for *Aspergillus*[9]. We diagnosed CAPA following the *Asp*ICU algorithm in 3 patients (20% of the total), which is somewhat lower than the series of 9 patients in France (33% of the total)[2], the series of 5 patients in Germany (26% of the total)[6], and the prospective studies performed in Italy and France in which diagnosis was obtained in 30 (27.7% of the total) and 19 (17.9%) patients, respectively[7,8].

Aside from differences in the diagnostic method, there is increasing evidence that COVID-19 may be associated with serious nosocomial superinfections, such as IPA[1,2,5–8]. Similarly, some authors claim that the mere isolation of *Aspergillus* in respiratory samples in critically ill patients with COVID-19 should be considered putative aspergillosis, and should prompt clinicians to start antifungal therapy[1]. Therefore, patients admitted to ICUs for COVID-19 should be systematically screened for fungal superinfections in order to reduce the negative consequences of such colonisation.

The main limitation of this study is the small sample size and our failure to initially perform BAL due to the risk of aerosolization and a shortage of protective material during the pandemic. Likewise, strict adherence to the *Asp*ICU diagnostic algorithm and the high rate of early mortality in our patients could have led us to underestimate the presence of CAPA.

Conclusion

IPA superinfection should be systematically considered in COVID-19 patients admitted to the ICU. Given the difficulty involved in diagnosing this type of colonisation using tradi-

tional diagnostic algorithms, there is a clear need for a new common CAPA diagnostic algorithm that can give prompt diagnosis leading to early treatment to mitigate the negative outcomes that can be associated with *Aspergillus* superinfection in critically ill patients with SARS-CoV-2.

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Authorship

All authors made a significant contribution to the design, development and review of this study.

Conflict of interests

The authors have no conflict of interest to declare.

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