Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the editor

Invasive pulmonary aspergillosis and candidiasis in a critically ill patient with COVID-19

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To the editor,—Invasive fungal superinfections have been increasingly reported in critically ill patients with coronavirus disease-2019 (COVID-2019) due to the severe immunomodulation and lymphocyte depletion caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the subsequent administration of drugs that target the immune system such as corticosteroids [1]. Among them, pulmonary aspergillosis and invasive candidiasis or candidemia have been widely reported [2–9].

We herein describe one of the first cases in Argentina of combined probable pulmonary aspergillosis and candidemia in a previously immunocompetent, critically ill patient with severe COVID-19 pneumonia.

A 69-year-old insulin-dependent diabetic man as the only underlying disease came to hospital due to pneumonia associated with confirmed diagnosis of SARS-CoV-2 by real time RT-PCR (RealStar® SARS-CoV-2 RT-PCR Kit 1.0, Altona Diagnostics GmbH, Germany). On hospital day (HD) 7, he was admitted to the intensive care unit (ICU) with moderate acute respiratory distress syndrome (ARDS, PaO_2:FiO_2 ratio of 126 mm Hg). Chest X-ray revealed bilateral infiltrates. He received ceftriaxone, clarithromycin, interferon-alpha/remdesivir and dexamethasone (8 mg/day). On HD 9, he was intubated and mechanically ventilated. Tracheal aspirate (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 13. It showed branching hyphae surrounded of yeast cells on direct examination and *Aspergillus fumigatus* and *Candida albicans* colonies in the Sabouraud culture. Both isolates were identified at species level using Matrix Assisted Laser Desorption/Ionization Time-Of-Flight (MALDI-TOF) mass spectrometry (VITEK® MS, bioMérieux). Serum and TA galactomannan (GM) indexes determined using Platelia™ *Aspergillus* (bioMérieux, France) were performed and revealed a positive result (serum GM index of 2.13 and AT GM index of 6.36). Intravenous voriconazole treatment was then initiated (400 mg/12 h first day, then 200 mg/12 h). A new TA sample was obtained on HD 17, whose culture on Sabouraud agar was negative. A serum GM index of 0.78 and a TA GM index of 2.17 were obtained, Due to persistent fever, blood samples were collected for cultures using BacT/ALERT FAN aerobic blood culture bottles (bioMérieux, France) on HD 20. Positive blood culture vials were then subcultured onto blood agar and Sabouraud dextrose agar plates and grown yeast colonies were finally identified as *C. albicans* by MALDI-TOF mass spectrometry.

Antifungal therapy with voriconazole was also discontinued on HD 20 due to severe liver dysfunction (ALT 328 U/L, AST 241 U/L, total bilirubin 3.97 mg/dL) and antifungal therapy with liposomal amphotericin B (5 mg/kg/day) was then commenced. The GM index in sera using Platelia™ *Aspergillus* was 0.27 (HD 20) and 0.16 (HD 22). On HD 26 the patient died due to respiratory instability, sepsis and shock, despite clearance of fungemia during antifungal therapy.

The recent global pandemic of COVID-19 has resulted in more than 6.31 million cases in Argentina with more than 117,000 deaths [10]. A proportion of COVID-19 critically ill patients develop ARDS, requiring admission at ICU and mechanical ventilation, which in turn predisposes them to nosocomial infections due to bacterial and fungal superinfections. The incidence of CAPA in Argentina is almost 10% [11].

Among fungal superinfections, COVID-19-associated pulmonary aspergillosis (CAPA) and invasive candidiasis have been increasingly recognized as secondary complications, especially among critically ill COVID-19 patients at ICU. However, superinfection by multiple fungal species in one individual have rarely been reported.. Herein we described a fatal case of combined probable pulmonary aspergillosis and candidemia in an Argentinean patient with severe COVID-19. This patient has diabetes as the only underlying disease, and was admitted to the ICU where he received broad-spectrum antibiotics, immunosuppressants or corticosteroids (8 mg/day), and required mechanical ventilation due to moderate-severe COVID-19 pneumonia. This patient had a probable diagnosis of CAPA (according to the 2020 ECMM/ISHAM consensus criteria for defining CAPA [12]) during

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the second week of hospitalization, and candidemia during the third week of hospitalization that matches with the middle and latter stages of the COVID-19 disease. He received voriconazole as first line therapy for the therapy of CAPA, and then due to hepatotoxicity, liposomal amphotericin B which also has activity against *C. albicans*.

Regarding the source of *C. albicans* in the bloodstream of this patient, it is well-known that *Candida* species are major constituents of the human mycobiome and the main cause of invasive fungal infections, with a high mortality rate. Despite the marked immune dysregulation in COVID-19, other relevant clinical factors, including prolonged ICU stays, central venous catheters, and broad-spectrum antibiotic use, may be key factors causing COVID-19 patients to invasive candidiasis, thus allowing commensal *Candida* to cells to invade internal organs [13].

Despite catheters are widely recognized as a portal of entry for acquiring nosocomial *Candida* infections, in the case presented herein, blood cultures drawn from central venous catheter from this patient were always negative. Therefore, a potential source of blood stream infection in this case could be *Candida* colonization at multiple sites. On the one hand, in this patient, *C. albicans* was isolated from the upper respiratory tract. According to this, Azoulay et al. reported that *Candida* colonization of the airway was observed in 20% of patients after 48 h of being on mechanical ventilation, and the longer the duration of ventilation, the higher the colonization rate [14]. Furthermore, almost 94% of hospitalized patients with COVID-19 receive antimicrobial agents, which might further heighten the *Candida* colonization rate. On the other hand, patients with sepsis or septic shock, as commonly observed in severe COVID-19 patients in the ICU, as the one presented herein, may develop a leaky gut that facilitates *Candida* translocation from the GI tract into systemic circulation [13]. Understanding the complications of COVID-19 patients, including the potential superinfections and their etiologic agents is paramount for the optimal management of this severally ill group of patients. This knowledge will aid clinicians and mycologists to refine empiric antimicrobial therapy which in turns might have a high impact on patient survival.

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

Declaration of Competing Interest

The authors declare that they do not anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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