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Introduction

1.9 million deaths globally have been linked to the COVID-19 pandemic with 88 million cumulative cases reported as of January 12, 2021 [1]. Critically ill patients with COVID-19 are at high risk of developing acute respiratory distress syndrome (ARDS), requiring intensive care and mechanical ventilation, predisposing them to nosocomial bacterial and fungal infections [2,3]. In India, candidemia affected 15 critically ill coronavirus disease patients admitted to an intensive care unit (ICU), with two thirds of cases attributed to multidrug resistant Candida species in COVID-19 patients is scarce, and nonexistent regarding Candida duobushaemulonii superinfections. Candida duobushaemulonii is a yeast that is closely related to Candida auris [4]. Data regarding multidrug resistant (MDR) Candida species in COVID-19 patients has been poorly studied with only a few cases reporting secondary infection, mostly without identifying specific pathogens. Prolonged hospital stays, invasive interventions (central venous catheter, mechanical ventilation), and the use of broad-spectrum antibiotics in COVID-19 infections could carry a high risk of bacterial and/or fungal superinfections.

Case description

A 34-year-old male presented to our tertiary care center in Beirut, Lebanon from Gabon, Central Africa with severe COVID-19 infection and ARDS. He was hospitalized in Gabon and his medical course was complicated by acute pulmonary embolism treated with recombinant tissue plasminogen activator (rtPA), with subarachnoid hemorrhage (SAH) developing as sequela, and a superimposed bacterial pneumonia for which he received levofloxacin and imipenem. Patient presented 16 days post his COVID-19 infection to our institution. He was intubated, sedated and off vasopressors. His labs are reported and summarized in (Table 1) and were significant for elevated inflammatory markers (d-dimer, ferritin, CRP, progressive thrombocytopenia) and neutrophilia (80-90%). SARS-CoV-2 PCR was positive on admission. CT chest showed severe ARDS and is emerging as a rare cause of invasive fungal infections with a multidrug resistant profile [5].

We report a case of Candida duobushaemulonii candidemia in a patient with prolonged ICU stay due to a complicated case of severe COVID-19 infection. To our knowledge, no data exists in the literature in this setting.

Case description

A 34-year-old male without a history of comorbidities presented to our tertiary care center in Beirut, Lebanon from Gabon, Central Africa with severe COVID-19 infection and ARDS. He was hospitalized in Gabon and his medical course was complicated by acute pulmonary embolism treated with recombinant tissue plasminogen activator (rtPA), with subarachnoid hemorrhage (SAH) developing as sequela, and a superimposed bacterial pneumonia for which he received levofloxacin and imipenem.

Patient presented 16 days post his COVID-19 infection to our institution. He was intubated, sedated and off vasopressors. His labs are reported and summarized in (Table 1) and were significant for elevated pro-inflammatory markers (d-dimer, ferritin, CRP, progressive thrombocytopenia) and neutrophilia (80-90%). SARS-CoV-2 PCR was positive on admission. CT chest showed severe ARDS with typical
picture of COVID-19 infection (Fig. 1). Due to the lack of data regarding local resistance in Gabon and the patient’s recent history of multiple antibiotic use and long ICU stay, the decision was made to start meropenem for superimposed pneumonia. Blood, urine, and deep tracheal aspirate (DTA) cultures were taken beforehand. DTA cultures grew *Stenotrophomonas maltophilia* sensitive to levofloxacin and trimethoprim/sulfamethoxazole (TMP-SMX), and patient was subsequently started on levofloxacin. He was shifted to TMP-SMX after a new isolate of *S. maltophilia* from DTA was found to be resistant to levofloxacin. He developed catheter acquired urinary tract infection (CAUTI) and ventilator associated pneumonia (VAP) and progressed into septic shock. He was started on amikacin and tigecycline as his cultures grew carbapenem-resistant *Enterobacteriaceae* (*CRE*) *Enterobacter cloacae* with high minimal inhibitory concentrations (MICs) of ceftazidime/avibactam and carbapenems. Five days later, new DTA and urine cultures were taken and were positive for *Candida* non-albicans, mainly multi-sensitive *Candida parapsilosis* in the urine and *Candida lusitaniae* in the DTA. He was subsequently started on intravenous fluconazole.

Antibiotics were discontinued following completion of fourteen days of therapy and clinical improvement. Antifungal therapy with fluconazole was kept. Patient initially improved clinically but he developed hypotension a week later with elevation of his inflammatory markers (Table 1). Blood cultures were taken from his central line and peripheral lines. He was started on inhaled colistin and tigecycline. Central line blood cultures grew *Candida* non-albicans, and caspofungin was started. Speciation and susceptibility testing revealed *Candida duobushaemulonii*, susceptible to fluocytosine (Table 2). Susceptibility data for other anti-fungals is not available. His stay was again complicated by recurrent pneumothoraces leading to respiratory failure followed by cardiac arrest and death.

### Discussion

Bacterial and fungal infections are common complications of viral pneumonia, especially in critically ill patients, leading to increased mortality rate [6]. Nosocomial fungal infections, particularly Candidiasis and Aspergillosis, are frequently seen in immunocompromised patients that exhibit predisposing risk factors such as neutropenia, compromised neutrophil function, cell-mediated immune dysfunction, and disruption of mucosal integrity [7,8]. In 2017, a team in France analyzed the proportion of fungemia associated with uncommon yeast species and the predisposing factors in 338 cases. The study demonstrated the existence of 35 species with different susceptibility profiles to antifungal drugs and a predisposition to patients who are immunocompromised or have received prior antifungal therapy [9]. COVID-19 has been found to cause immune dysregulation and hyperinflammation in severe cases potentially contributing to the development of nosocomial infections in severely ill patients [10–12]. Nevertheless, limited data regarding bacterial and fungal infections in COVID-19 patients has been published [6].

**Table 1**

| Date       | WBC (/cu.mm) | Neutrophils (%) | Hb (g/dl) | Platelets (/cu.mm) | Cr (mg/l) | Na (mmol/L) | K (mmol/L) | Chloride (mmol/L) | SGPT (IU/L) | SGOT (IU/L) | ALP (IU/L) | Bilirubin (mg/dl) | Ferritin (ng/ml) | D dimer (ng/ml) | CRP (mg/L) | Procalcitonin (ng/ml) | INR | PTT (seconds) | Procalcitonin (ng/ml) | COVID-19 PCR |
|------------|--------------|-----------------|-----------|-------------------|----------|-------------|------------|----------------|--------------|-------------|-----------|----------------|----------------|----------------|-----------|---------------------|-----|--------------|---------------------|-------------|
| 16/6/2020  | 8,600        | 93%             | 10.6      | 164,000           | 1        | 144         | 4.8        | 100             | 61           | 86          | 96        | 0.7            | 2.207            | 3,862          | 1.9        | 29.6                | 6.9 | 0.16         | 0.06                | Positive     |
| 20/6/2020  | 12,100       | 91%             | 10.8      | 194,000           | 0.6      | 141         | 5          | 102             | 86           | 96          | 96        | 0.7            | 1109            | 3,862          | 1.2        | 27.1                | 0.7 | 1.2          | 0.06                | Negative     |
| 26/6/2020  | 11,900       | 85%             | 10.3      | 366,000           | 0.6      | 146         | 5.3        | 106             | 92           | 96          | 96        | 0.7            | 820             | 2,160          | 1.2        | 27.1                | 0.7 | 0.16         | 0.06                | Negative     |
| 4/7/2020   | 10,300       | 79%             | 9.5       | 360,000           | 0.4      | 138         | 4.4        | 92              | 90           | 92          | 92        | 0.7            | 667             | 2,160          | 0.8        | 27.1                | 0.06| 0.16         | 0.06                | Positive     |
| 16/7/2020  | 7,600        | 82%             | 8.5       | 355,000           | 0.3      | 136         | 4.1        | 92              | 90           | 92          | 92        | 0.7            | 85              | 2,160          | 0.6        | 27.1                | 0.06| 0.16         | 0.06                | Positive     |
| 26/7/2020  | 9,200        | 90%             | 8.5       | 352,000           | 0.2      | 135         | 4.8        | 92              | 90           | 92          | 92        | 0.7            | 84              | 2,160          | 0.2        | 27.1                | 0.06| 0.16         | 0.06                | Positive     |
| 2/8/2020   | 9,200        | 90%             | 8.4       | 401,000           | 0.2      | 137         | 4.5        | 93              | 93           | 93          | 93        | 0.7            | 9.4             | 2,160          | 0.2        | 27.1                | 0.06| 0.16         | 0.06                | Positive     |
| 10/8/2020  | 13,000       | 88%             | 9.4       | 562,000           | 0.2      | 93          | 4.5        | 93              | 93           | 93          | 93        | 0.7            | 9.4             | 2,160          | 0.2        | 27.1                | 0.06| 0.16         | 0.06                | Positive     |

**Table 2**

| Antifungals | Interpretation |
|-------------|----------------|
| Amphotericin B | 8 ug/mL | Resistant |
| Flucytosine | ≤ 1 ug/mL | Susceptible |
| Voriconazole | 4 ug/mL | Resistant |
Although the mechanism is still unclear, patients with severe COVID-19 are at high risk of developing nosocomial infections associated with mechanical ventilation and the use of broad-spectrum antibiotics. Medical and invasive procedures are potential routes of bacterial and fungal infections, with the latter being of particular concern due to the emergence of drug-resistant fungi. A meta-analysis found that four out of five COVID-19 ICU patients were colonized with Candida auris and four of them developed candidemia. The increasing reports of Candida auris co-infection in severely ill COVID-19 patients and the close phylogenetic relation between Candida auris and Candida duboisheunlonii could signify that Candida duboisheunlonii superinfection is underdiagnosed. In fact, in a study done by Jurado-Martin et al., 150 isolates were reanalyzed using novel PCR approaches to identify multidrug-resistant complex of uncommon Candida species that were missed by regular phenotypic testing. The study found that the prevalence of C. duboisheunlonii was likely underestimated and that the species was initially associated with superficial infections before emerging as a cause of invasive candidiasis. The identified isolates also showed reduced susceptibility to fluconazole, itraconazole, and amphotericin B. Risk factors for invasive candidemia include prolonged hospital stay, invasive interventions (central venous catheter, mechanical ventilation), and the use of broad-spectrum antibiotics. The widespread use of empirical antibiotics in COVID-19 ICU patients could be a major cause of both bacterial and fungal superinfections and warrants additional evaluation. The reliance on clinical presentation, inflammatory markers, and radiological findings is insufficient to confirm secondary infections and may lead to overuse of antibiotics empirically, while current data on co-infections is limited.

Antimicrobial stewardship programs aim to optimize antimicrobial use, improve patient outcomes, and reduce harms from excessive use, such as antimicrobial resistance. However, due to the lack of stewardship programs targeted at pandemics such as COVID-19, inpatient antibiotic use may have proceeded unchecked for several months, potentially contributing to antimicrobial resistance and the development of secondary bacterial and/or fungal infections from unnecessary empirical use of broad-spectrum antibiotics.

**Conclusion**

Severely ill COVID-19 are at high risk of developing nosocomial infections associated with mechanical ventilation and the use of broad-spectrum antibiotics. Medical and invasive procedures are potential routes of bacterial and fungal infections, with the latter though rare, is associated with considerable mortality in critically ill patients. Strategies to improve outcome in COVID-19 ICU patients should, therefore, include early recognition of candidemia and appropriate antifungal therapy.

**Authors’ contribution**

Dr. Bassem Awada contributed to the investigation and writing the original draft.

Dr. Walid Alam contributed to the investigation, writing the original draft, and review and editing.

Maria Chalfoun contributed to writing the original draft.

Dr. George Araj contributed to the investigation and formal analysis.

Dr. Abdul Rahman Bizri was responsible for conceptualization and contributed to the review and editing.

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**Ethics and patient consent**

We acknowledge that approval from the American University of Beirut ethical committee was sought where necessary, and guidelines on consent were followed. Informed consent was obtained from the patient’s family.

**Conflict of Interest**

The authors have no conflict of interest.

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None

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