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Case Report

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A COVID-19 Case Complicated by *Candida dubliniensis* and *Klebsiella pneumoniae*-Carbapenem-Resistant Enterobacteriaceae

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Abstract

There has been increasing evidence of co-infections with coronavirus disease 2019 (COVID-19) pneumonia, which increases the severity of the disease. Organisms such as *Klebsiella pneumoniae* and *Streptococcus pneumoniae* have been previously isolated. We present a case of a COVID-19 patient treated with baricitinib and dexamethasone who later developed *Klebsiella pneumoniae*-carbapenem-resistant Enterobacteriaceae (CRE) and *Candida dubliniensis* bloodstream infections, treated with meropenem/vaborbactam and micafungin, respectively. These infections are exceedingly rare and are mostly reported in immunosuppressed patients. The finding of these bloodstream infections raises concerns on the cause of immunosuppression in this patient infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) treated with baricitinib and dexamethasone. There has been no report so far of COVID-19 associated with these co-infections.

Keywords: COVID-19; Bacteremia; Candidemia; Baricitinib; Dexamethasone

Introduction

Since the start of the coronavirus disease 2019 (COVID-19) pandemic, there has been an increasing need for treatments that can reduce the morbidity, mortality, and length of stay of patients both in the intensive care unit (ICU) and hospital in general [1]. With so many unknown variables involved, it is very unpredictable what further complications are expected, including the management of patients with immunomodulatory treatments and steroids [2-4]. The difficulty, in this case, increased due to the subsequent bacteremia and fungemia that were caused by rare pathogens. These pathogens are *Klebsiella pneumoniae*-carbapenem-resistant Enterobacteriaceae (CRE) and *Candida dubliniensis*. *Klebsiella pneumoniae*-CRE is rapidly emerging around the world with a high case fatality ratio because of the minimal treatment options available [5-7]. *Candida dubliniensis*, on the other hand, has also been reported mostly in immunocompromised patients with oropharyngeal infections and rarely in the bloodstream [8, 9]. In this case report, we present a patient who tested positive for COVID-19, and treated with immunomodulatory therapy, including baricitinib and dexamethasone, who was later found to have *Candida dubliniensis* and *Klebsiella pneumoniae*-CRE in the bloodstream. No other case has been reported so far.

Case Report

A 67-year-old morbidly obese and quadriplegic man who has a very extensive past medical history including chronic obstructive pulmonary disease (COPD), diabetes mellitus, hypertension, chronic kidney disease, peripheral vascular disease, and hepatitis C, who was sent from a skilled nursing facility with respiratory distress, which started about 1 day before admission. On arrival in the emergency room (ER), he had a pulse of 122, respiratory rate of 44, blood pressure of 95/45 mm Hg, temperature of 36.9 °C, and saturating at 78% in room air. On physical exam, his Glasgow coma score was 7, responding only to painful stimuli, he was in severe respiratory distress, using accessory muscles, and had bilateral crackles on auscultation. He was subsequently intubated and placed on mechanical ventilation, and then transferred to the medical ICU. A COVID-19 RNA polymerase chain reaction (PCR) test was done, which came back positive, and he was treated with the standard care at the time for COVID-19 (hydroxychloroquine, azithromycin, vitamin C, and zinc). Two days later, the patient was extubated and placed on a 50% Venturi mask. His evolution was marked by the persistence of hypotension and worsening of respiratory distress with increasing oxygen requirements and worsening imaging exams. Due to the worsening of the respiratory status of the patient and increasing reports on the benefits of dexamethasone and

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Table 1. Evolution of Labs From the Day of Admission to Discharge

	Day 1	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 24	Day 34
WBC (k/µL)	8.7	9.2	18.1	20.0	32.3	35.2	32.1	24.8	10.2	5.3
RBC (m/µL)	3.39	3.79	4.06	3.58	3.52	3.32	3.62	3.62	4.06	3.48
Hgb (g/dL)	9.6	11.0	11.5	10.2	10.4	10.1	10.6	10.9	11.7	10.1
Hct (%)	31.5	36.3	38.7	34.4	34.1	31.3	35.1	35.1	38.6	32.5
MCV (fL)	92.8	95.8	95.4	96.2	97	94.3	97.1	96.8	94.9	93.4
MCH (pg)	28.3	28.3	28.3	28.4	29.5	30.4	29.2	30.1	28.8	29.0
MCHC (g/dL)	30.6	29.8	29.8	29.7	30.3	32.2	30.1	31.2	30.3	31.1
RDW (%)	17.7	18.4	18.4	20.0	19.9	19.8	19.8	19.8	18.9	19.8
Platelet (k/µL)	299	413	413	304	225	203	186	179	176	145

WBC: white blood count; RBC: red blood count; Hgb: hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width.

baricitinib, he was given dexamethasone 15 mg intravenously (IV) for 5 days and baricitinib 2 mg for 5 days. On day 17 of admission, 4 days after completion of baricitinib and dexamethasone, the patient became hypotensive, tachycardic with a blood pressure of 91/52, and heart rate of 115 while on continuous positive airway pressure ventilation (CPAP) saturating at 96%. We noticed a marked increase in his white blood cell count from 9.2 to 18.1 k/µL on this day (Table 1). Blood and urine cultures were done, and he was started on IV fluids and empirical antibiotics, including vancomycin and piperacillin/tazobactam.

Blood cultures grew *Klebsiella pneumoniae*-CRE (sensitivity patterns are shown in Table 2). Because meropenem showed an intermediate sensitivity, antibiotics were switched to meropenem/vaborbactam. Subsequent blood cultures still grew *Klebsiella pneumoniae*-CRE on three consecutive cultures drawn on three different days. Seven days after starting meropenem/vaborbactam, the blood cultures became positive to *Candida dubliniensis* twice on two consecutive blood cultures drawn on two different days. He was then started on IV micafungin 100 mg, which he received for 10 days and then switched to oral fluconazole for 14 days. Meropenem/vaborbactam was discontinued 14 days after the first negative blood culture. His repeat blood cultures and COVID-19 were negative and he was discharged back to his skilled nursing facility.

Discussion

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, single-stranded positive-sense RNA virus that affects human cells by spike glycoprotein binding to its cellular receptor, angiotensin-converting enzyme 2 (ACE2) [10]. With over 20,000,000 confirmed cases and 736,000 deaths, COVID-19 is wreaking havoc across the globe. The incubation period of the virus ranges from 3 to 21 days [11], after which most patients present with either mild non-specific

Table 2. Sensitivity Profile of *Klebsiella pneumoniae*-CRE Isolated in the Patient

Antibiotic	Minimal inhibitory concentration (mg/L)	Susceptibilities
Ampicillin	≥ 32	R
Ampicillin/sulbactam	≥ 32	R
Aztreonam	≥ 64	R
Cefazolin	≥ 64	R
Cefepime	≥ 64	R
Ceftazidime	≥ 64	R
Ceftriaxone	≥ 64	R
Gentamycin	≥ 16	R
Levofloxacin	≥ 8	R
Meropenem	8	I
Piperacillin/tazobactam	≥ 128	R
Tobramycin	≥ 16	R
Trimethoprim/sulfamethoxazole	≥ 320	R

R: resistant; I: intermediate; CRE: carbapenem-resistant Enterobacteriaceae.

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symptoms or severe pneumonia with multiorgan dysfunction [12-14].

With the surge of COVID-19 patients in March 2020, New York, the epitome of the disease at that time, also observed a surge in blood cultures [15]. However, this surge of blood cultures showed that those infected with COVID-19 had lower rates of bacteremia. But respiratory co-infections were high and often a significant cause of mortality [16]. Commonly isolated respiratory co-infection organisms were *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa*, and *Hemophilus influenzae*. Due to the increased mortality with concomitant bacterial infections with the previous influenza pandemic, a systematic review found about 7% of COVID-19 patients had co-infections and mostly patients in the ICU [17]. Our case had a positive blood culture to a very resistant bacteria called *Klebsiella pneumoniae*-CRE and *Candida dubliniensis*, which is the only case associated with COVID-19 reported so far. CRE in particular was labeled an "urgent threat" in the 2013 and 2019 antibiotic resistance threats in the USA reports by the US Centers for Disease Control and Prevention (CDC) [18, 19].

Candida dubliniensis is also a very rare organism, mostly found in oropharyngeal infections in immunosuppressed individuals [8, 9]. The presence of this organism in the blood culture of our patient suggests underlying immunosuppression, which needs to be explored. This immunosuppression could be due to the use of baricitinib and dexamethasone in our patient [20], or it could suggest immunosuppression caused by COVID-19 not yet demonstrated.

With the increasing evidence of the presence of hyperinflammation and cytokine storm and high levels of IL-6 being associated with increased mortality in COVID-19 patients, treatment with immunomodulatory therapies like baricitinib and steroids like dexamethasone has been shown to reduce mortality [3, 4, 21]. The use of baricitinib in the treatment of rheumatoid arthritis was proven to cause immunosuppression; the most frequent infection associated with this was herpes zoster [20]. With the use of baricitinib and dexamethasone in combination in the management of COVID-19 patients, they tend to become more immunosuppressed, and therefore, susceptible to many infections.

Klebsiella pneumoniae-CRE has a very low sensitivity profile to most antibiotic categories and is very challenging to treat [22]. One drug combination that shows universal coverage against beta-lactamase-producing Enterobacteriaceae, including those with extensive drug resistance, is aztreonam and ceftazidime/avibactam [22]. However, our patient had resistance to aztreonam and ceftazidime, which made it even more challenging to treat. Even though it had intermediate sensitivity to meropenem alone, we used it in the combination of meropenem/vaborbactam as the only available choice of treatment. The high case fatality ratio of this organism is due to the very resistant properties.

It is very rare to have fungemia due to *Candida dubliniensis* without any immunosuppression. This is why, despite the short period of immunomodulatory treatment in our patient, the discovery of *Candida dubliniensis* in two consecutive blood cultures is most likely because of the relative immunosuppression. For the treatment of *Candida dubliniensis*, treatment options vary per Infectious Disease Society guidelines. Currently, it is recommended to use echinocandin with fluconazole being an appropriate alternative [9]. However, some reports have shown resistance to fluconazole and must be taken into consideration [23]. Follow-up blood cultures should be taken until a negative result is achieved, and at this point, treatment should subside 2 weeks later. Our patient was treated with micafungin for 10 days, with repeat blood cultures which came back negative, and he was then discharged with an additional 2 weeks of oral fluconazole.

Conclusions

In this case, we were able to present a patient with multiple comorbidities infected with COVID-19 whom we treated with baricitinib and dexamethasone for 5 days, who developed *Klebsiella pneumoniae*-CRE and *Candida dubliniensis* in blood cultures. The use of immunomodulators might have caused relative immunosuppression, hence increasing the susceptibility of the patient developing rare bloodstream infections, therefore, increasing the complexity of the management of COVID-19.

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None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

HA collected the data, guided the literature search, wrote the manuscript, and is the research guarantor. FA, SSB, FMK and KD helped with data collection and writing of the article. JN reviewed and supervised the study.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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