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Case Report

Candida dubliniensis fungemia in a patient with severe COVID-19: A case report

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ABSTRACT

Candida dubliniensis phenotypically mimics *Candida albicans* in its microbiological features; thus, its clinical characteristics have yet to be fully elucidated. Here we report the case of a 68-year-old Japanese man who developed *C. dubliniensis* fungemia during treatment for severe coronavirus disease 2019 (COVID-19). The patient was intubated and received a combination of immunosuppressants, including high-dose methylprednisolone and two doses of tocilizumab, as well as remdesivir, intravenous heparin, and ceftriaxone. A blood culture on admission day 11 revealed *Candida* species, which was confirmed as *C. dubliniensis* by mass spectrometry. An additional sequencing analysis of the 26S rDNA and ITS regions confirmed that the organism was 100% identical to the reference strain of *C. dubliniensis* (ATCC MYA-646). Considering the simultaneous isolation of *C. dubliniensis* from a sputum sample, the lower respiratory tract could be an entry point for candidemia. Although treatment with micafungin successfully eradicated the *C. dubliniensis* fungemia, the patient died of COVID-19 progression. In this case, aggressive immunosuppressive therapy could have caused the *C. dubliniensis* fungemia. Due to insufficient clinical reports on *C. dubliniensis* infection based on definitive diagnosis, the whole picture of the cryptic organism is still unknown. Further accumulation of clinical and microbiological data of the pathogen is needed to elucidate their clinical significance.

1. Introduction

Among the various known fungal infections, invasive candidiasis is the most frequent and serious, with candidemia as a representative disease [1]. With progress in medical intervention, *Candida* species have become common pathogens causing bloodstream infections and a high mortality rate among patients in intensive care units [2]. Clinically common *Candida* species include *Candida albicans*, followed by *Candia glabrata, Candia tropicalis, Candia parapsilosis*, *Candia krusei, Candida guilliermondii,* and *Candida lusitaniae* [3].

Candida dubliniensis was first documented in 1995 after its isolation from an oral sample of HIV-infected individuals in Dublin, Ireland [4]. Thereafter, this organism has been isolated from a variety of clinical samples from various countries worldwide. However, *C. dubliniensis* is clinically a less common species among approximately 150 *Candida* species [3], accounting for 0.1–1% of *Candida* species isolated from humans. It is a representative isolate of cryptic *Candida* species, formerly considered *C. albicans* because of its phenotypical similarity in microscopic morphology and production of pseudohyphae, true hyphae, and chlamydospores [5,6]. Previous studies demonstrated that nearly 2–3% of *C. dubliniensis* isolates may be misidentified as *C. albicans* [7–10]. Although rare, *C. dubliniensis* potentially causes invasive infections [11,12]; thus, its clinical features should be documented in greater detail by the accumulation of clinical cases. Here we describe a case of *C. dubliniensis* fungemia in a fatal case of novel coronavirus disease 2019 (COVID-19).

2. Case report

A 68-year-old Japanese man was emergently transferred to our hospital with acute respiratory failure symptoms that had deteriorated over the previous 5 days. His medical history included myocardial infarction and a right lower lung lobe resection for lung cancer. On arrival, he was alert and his vital signs were as follows: body

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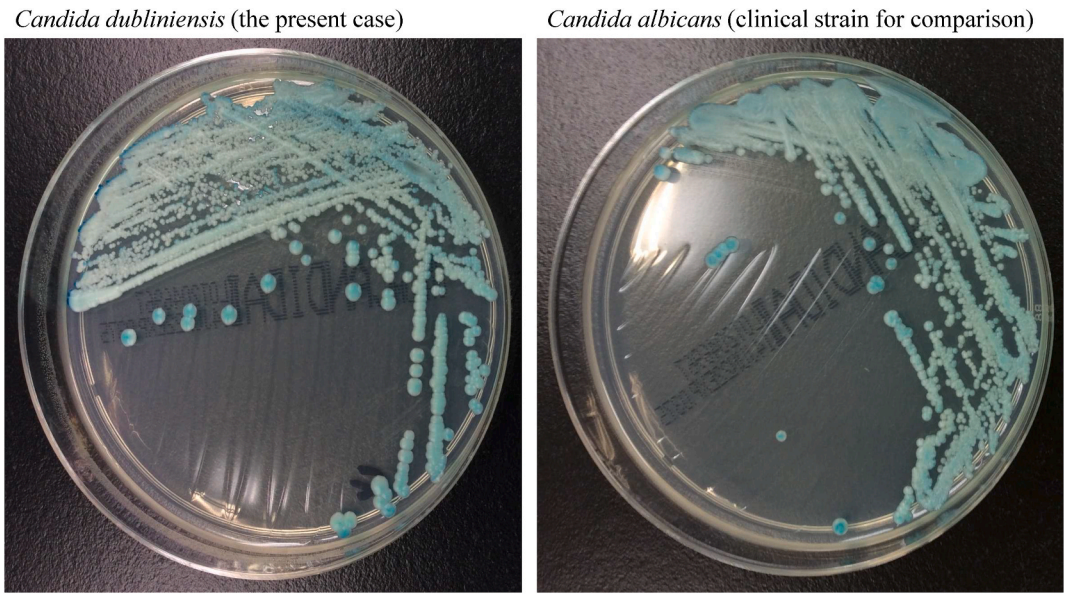

Fig. 1. Morphological comparison of *Candida dubliniensis* and *Candida albicans*.
Candida species were cultured on BBL™ CHROMagar™ Candida II medium (BBL, Beckton Dickinson GmbH, Heidelberg, Germany) for 2 days at 35 °C.

temperature, 37.0 °C; blood pressure, 138/107 mmHg; pulse, 85 beats/min; respiratory rate, 30/min; and oxygen saturation, 92% on 6 L/min of oxygen. In the physical examination, lung auscultation revealed bilateral course crackles, while laboratory testing showed elevated levels of C-reactive protein (7.03 mg/dL; normal, <0.14 mg/dL) and D-dimer (19.2 μg/mL; normal, <1.0 μg/mL). Lung computed tomography detected bilateral non-segmental ground-glass opacity. The patient was positive for PCR testing of severe acute respiratory syndrome coronavirus-2 and was hospitalized with a diagnosis of severe COVID-19.

He immediately received combination treatment consisting of methylprednisolone (250 mg/day for 3 consecutive days), remdesivir, tocilizumab (8 mg/kg), anticoagulant therapy with intravenous heparin, and ceftriaxone (2 g/day). However, his respiratory condition progressively deteriorated, and he was moved to an intensive care unit on admission day 2 and intubated the following day. On day 4, an additional dose of tocilizumab (8 mg/kg) was administered, and corticosteroid therapy was continued prednisolone (80 mg/day). On day 8, the antimicrobial therapy was empirically changed to meropenem and micafungin (150 mg/day).

A blood culture on day 11 was positive for a yeast-like fungus. We sub-cultured the organism on BBL™ CHROMagar™ Candida II Medium (BBL, Beckton Dickinson GmbH, Heidelberg, Germany) and found that its morphological appearance was indistinguishable from that of *C. albicans* (Fig. 1). However, mass spectrometry (MALDI Biotyper; Bruker Daltonics Inc., Billerica, MA, USA) identified the organism as *C. dubliniensis,* with score values of 1.561 on incubation day 1, 1.740 on day 2, and 1.990 on day 3. *C. dubliniensis* was also isolated from a sputum sample on the same day. The central venous line was removed, which was negative for the pathogen, and the administration of micafungin was continued. Two weeks of antifungal therapy successfully eradicated the infection without persistent candidemia; however, his general condition progressively deteriorated, and he passed away after 5 weeks of hospitalization.

2.1. Fungal identification

During the clinical course, we detected *C. dubliniensis* in blood and sputum samples. Minimum inhibitory concentrations of antifungal agents were as follows: amphotericin, 0.5 μg/mL; fluconazole, 0.06 μg/mL; itraconazole, 0.03 μg/mL; voriconazole, ≤0.015 μg/mL; micafungin, 0.03 μg/mL; and caspofungin, 0.25 μg/mL by the microdilution method using Dry Plate 'Eiken' (Eiken Chemical Co., Ltd, Tokyo, Japan). The blood-origin isolate was transferred for further in-depth analysis.

We performed direct polymerase chain reaction of the 26S rDNA and ITS regions. The primers for the targeted genes were as follows: NL1 (5′-GCATATCAATAAGCGGAGGAAAAG -3′) and NL4 (5′-GGTCCGTGTTTCAAGACGG-3′) for 26S rDNA; and forward (5′-TCCGTAGGTGAACCTGCGG-3′) and reverse (5′-TCCTCCGCTTATTGATATGC-3′) for the ITS region [13]. The sequence data were analyzed using the Basic Local Alignment Search Tool (BLAST). The concordance rates for 26S ribosomal DNA (577 bp) and ITS (480 bp) were both 100% of the reference strains of *C. dubliniensis* (ATCC MYA-646). Therefore, the organism was identified as *C. dubliniensis*.

3. Discussion

Here we reported a clinical case of *C. dubliniensis* fungemia in a patient with severe COVID-19 who received two doses of tocilizumab in combination with high-dose corticosteroids. Although the infectious focus was unclear in the present case, considering the isolation of *C. dubliniensis* from the sputum, a lower respiratory tract infection was possible. Aggressive immunosuppressive treatment is recommended for patients with severe COVID-19 [14], and opportunistic infections, including candidemia, are increasingly reported in such cases [15,16].

C. dubliniensis is an infrequent and cryptic pathogen; thus, its clinical features remain to be elucidated. Most *C. dubliniensis* isolates have been isolated from the respiratory tract [10], especially oral samples [17,18]; however, recent reports have suggested that rare fungi can cause invasive infections as well [11,12]. Although rare, one case of *C. dubliniensis* fungemia during the treatment of COVID-19 has been described in the literature [19]. Similar to our case, that patient received immunosuppressive therapy consisting of dexamethasone and baricitinib, which was assumed to have contributed to the development of the *C. dubliniensis* fungemia. Unfortunately, the details of the fungal identification in that case were not fully discussed.

We identified the causative organism as *C. dubliniensis* based on a genetic investigation of the 26S rDNA and ITS regions. More specifically, the hyphal wall protein 1 gene polymorphism is currently available for species differentiation [20,21]. However, these methods are not accessible everywhere. A recent study corroborated that colony color on

HiCrome candida differential agar after 72 h of incubation or growth on xylose-based agar medium after 48 h incubation is an easy, accurate, and cost-effective method of differentiating *C. dubliniensis* from *C. albicans* [22]. A mass spectrometry identification approach of *C. dubliniensis* appears reliable [23,24]; however, more database reviews are warranted [25,26]. Notably, nearly one-fifth of *C. dubliniensis* isolates showed mass spectrometry scores of <1.7 [10]. However, our data suggest that an inadequate incubation period may result in lower score values.

C. dubliniensis was previously considered an azole-resistant fungus. However, recent studies reported a good susceptibility of *C. dubliniensis* to azole-class antifungal drugs [21,27,28]. In fact, the COIVD-19–associated *C. dubliniensis* fungemia case was successfully treated with fluconazole [19]. However, an *in vitro* experiment suggested that fluconazole resistance may be induced in *C. dubliniensis* [29].

In conclusion, we herein presented a rare case of *C. dubliniensis* fungemia in a patient with severe COVID-19 in which the causative pathogen was genetically identified. *C. dubliniensis* is relatively new species and possibly overlooked in the laboratory because of its microbiological similarity to *C. albicans*. Thus, clinical features of *C. dubliniensis* infection do not appear to be fully elucidated. More clinical and microbiological data are required to increase our understanding of the cryptic pathogen.

Authorship statement

All authors met the ICMJE authorship criteria. AK and HH wrote the first draft of the manuscript. AK and IK analyzed the pathogens. YN and KH contributed to the clinical management of the patients. AH and FO supervised the study. All authors approved the final manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work in this paper.

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