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Case report

Exophiala dermatitidis, 'the real black fungus' fungemia in a patient with COVID-19

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ABSTRACT

The second wave of the COVID-19 pandemic in India had brought with it a surge of 'black fungus' co-infection, which is a misnomer for mucormycosis. The present case illustrates the 'real black fungus' infection in a 50-year old male patient with COVID-19 pneumonia, who otherwise had no significant previous medical history. He was admitted on day 8 of COVID-19 illness and was intubated due to persistently low oxygen saturation. Blood cultures were positive for flask-shaped dematiaceous budding yeasts with pseudohyphae formation, which grew as brown-black fuzzy colonies on Sabouraud dextrose agar. The isolate was identified as *Exophiala dermatitidis* based on phenotypic characterization. Despite antifungal therapy with amphotericin B and itraconazole, the patient deteriorated rapidly and succumbed to acute respiratory distress syndrome and multiorgan failure. A review of reported cases of *Exophiala dermatitidis* fungemia over the last 5-years is discussed.

Introduction

Coronavirus disease 2019 (COVID-19), a respiratory infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has been shown to cause immunological dysfunction [1,2]. This predisposes the host to fungal infections including those caused by dematiaceous (melanin producing or black) fungi. *Exophiala dermatitidis*, a dematiaceous fungus, was first isolated from a lesion on the cheek of a Japanese woman [3]. It is a type of black yeast which can be found in many extreme natural habitats, whether in hot or wet environment or in decaying organic matter. Among *Exophiala* species, *Exophiala dermatitidis* is frequently associated with systemic infection and has poorer outcome [4]. To the best of our knowledge, we report the first case of fatal *Exophiala dermatitidis* fungemia in a male patient diagnosed with COVID-19 pneumonia.

Case report

A 50-year old male with no known underlying medical illness was found in his room in a poorly responsive state. He had a history of fever, shortness of breath and lethargy and tested positive for COVID-19 antigen one week prior to presentation. He was brought to the emergency department with a low-grade fever of 37.4 °C, and tachypnea with a respiratory rate of 40 breaths per minute. His capillary blood sugar was 200 mg/dL, blood pressure 110/60 mmHg and pulse rate 105 beats per minute. Since his oxygen saturation was persistently low, he was intubated.

On examination, pulmonary crepitations were heard bilaterally up to the midzone with occasional rhonchi. Abdomen and cardiovascular examinations were unremarkable. ECG showed sinus tachycardia and chest X-ray revealed diffuse lung haziness bilaterally with consolidation. Total WBC was 11,100/μL, C-reactive protein 6.43 mg/dL and D-dimer 1.23 μg/mL. The clinical impression was COVID-19 pneumonia with severe acute respiratory distress syndrome.

Blood drawn on day 2 of admission for culture became positive after 4 days of incubation in the aerobic BACTEC bottle. Gram stain revealed flask-shaped budding yeast with pseudohyphae formation. Hence, an empiric intravenous amphotericin B was started. Culture on Sabouraud dextrose agar grew brown-black, velvety colonies with black pigment on the reverse side of the plate. Microscopic examination of the mould with lactophenol cotton blue dye showed dematiaceous septate hyphae with numerous cylindrical to oval conidiogenous cells produced along the hyphae. Based on the macroscopic and microscopic phenotypic features, the isolate was identified as *Exophiala dermatitidis*.

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Table 1
Summary of cases of *Exophiala dermatitidis* fungemia over the past 5 years (2017–2021).

Reference / Country	Age/sex	Underlying disease	Antifungal susceptibility, MEC or MIC (μg/mL)	Treatment	Outcome
Vasquez et al. 2018 / USA	56–81 / 8 M, 6 F	Outbreak at an outpatient oncology clinic; 14 patients with various types of malignancy. All received contaminated IV flush solution	N/A	CVC removal (n = 14); VOR 42–64 days (n = 11); VOR 7 days then POS 30 days (n = 1); MCF 4 days then VOR 6 days (n = 1); MCF (n = 1)	11 survived, 3 died
Watanabe et al. 2018 / Japan	45/M	*CALR* mutation-positive primary myelofibrosis which progressed to AML	L-AMB (0.5), MCF (> 16), FLC (16)	CVC removal; FLC prophylaxis 200 mg, MCF preventive therapy 150 mg, L-AMB 5 mg/kg	Died
Hagiya et al. 2019 / Japan	29/M	Allogeneic HSCT for chronic active Epstein-Barr virus infection	AMB (0.25), 5FC (> 64), CAS (16), MCF (16), FLC (8), ITR (0.125), VOR (0.06), MCZ (0.25),	CVC removal; L-AMB 50 mg/d for 2 weeks, switched to IV VOR 200 mg/d & intrathoracic AMB	Died
Sato et al. 2019 / Japan	21/F	Chronic GVHD after allogeneic HSCT	N/A	MCF 150 mg/d, changed to L-AMB 5 mg/kg	Died
Vila et al. 2019 / Argentina	75/M	Respiratory failure, treated colonic and prostatic cancers, hypertension, alcoholism, smoking, COPD, cirrhosis	AMB (0.125), ANI (0.008), CAS (0.008)	CVC removal; ANI	Died
Yoshida et al. 2019 / Japan	69/F	Recurrent malignant breast lymphoma on chemotherapy, febrile neutropaenia	N/A	CVC removal; MCF 150 mg/d; then combined with L-AMB 5 mg/kg/day, then switched to VOR	Survived
Kumar et al. 2020 / India	2-month /F	Mitochondriopathy, inborn errors of metabolism	FLC (4), ITR (0.03), VOR (0.03), POS (0.06)	CVC removal; FLC for 3 weeks	Survived
Yurtsever et al. 2020 / USA	77/M	COPD complicated with pneumonia and UTI	N/A	Thought to be contaminant as the patient improved with antibiotics. No antifungal agent given	Survived
Itoh et al. 2021 / Japan	75/M	Stage IVb thoracic oesophageal cancer and early gastric cancer, hypertension, hyperlipidaemia, TPN	AMB (0.25), 5FC (2); CAS (8), MCF (4), FLC (16); ITR (0.5), VOR (2), MCZ (0.25)	CVC removal; MFG & VOR until dead	Died
Present case 2021 / Malaysia	50/M	COVID-19 positive (category 4 A), otherwise, no known medical illness.	N/A	AMB 80 mg/d, changed to ITR 200 mg q12h	Died

Abbreviations: MEC, minimum effective concentration; MIC, minimum inhibitory concentration; F, female; M, male; IV, intravenous; CVC, central venous catheter; CALR, calreticulin gene; AML, acute myeloid leukaemia; HSCT, haematopoietic stem cell transplantation; GVHD, graft-versus-host disease; COPD, chronic obstructive pulmonary disease; UTI, urinary tract infection; MALDI-TOF, matrix-assisted laser desorption ionization time-of-flight; ITS, internal transcribed spacer; LSU, large ribosomal subunit; AMB, amphotericin B; L-AMB, liposomal-amphotericin B; 5FC, 5-fluorocytosine; ANI, anidulafungin; CAS, caspofungin; MCF, micafungin; FLC, fluconazole; ITR, itraconazole; VOR, voriconazole; POS, posaconazole; MCZ, miconazole

In view of poor response to amphotericin B, the antifungal agent was changed to itraconazole 200 mg 12-hourly. Unfortunately, the patient condition continued to deteriorate and after 12 days of intensive care therapy, the patient eventually succumbed due to severe COVID-19 pneumonia with fungemia and multiorgan failure.

Discussion

COVID-19 infection has been shown to induce some degree of immunological dysfunction, such as diffuse alveolar damage with severe inflammatory exudates and reduced amount of absolute T lymphocytes, CD4 + T cells and CD8 + T cells [1]. The surviving T cells among patients with severe COVID-19 were also showed to be functionally exhausted [2]. During severe active COVID-19 infection, markedly increased level of cytokines such as IL-2R, IL-6, IL-10, and TNF-alpha further result in an immunosuppressed state [5]. Highly aggressive features of SARS-CoV-2 virus on the lung tissue give rise to large bilateral alveolo-interstitial lesions, making the occurrence of fungal infection very likely, especially infection through inhalation including *Exophiala dermatitidis* [6].

Our case is the first reported case of *Exophiala dermatitidis* fungemia co-infection in COVID-19 pneumonia in a previously healthy individual. Review of reported cases of *Exophiala dermatitidis* fungemia over the last five years (2017–2021) found one reported outbreak at an outpatient oncology clinic in New York, USA [7] and eight other individual cases throughout the world; mainly from Japan (5 cases) [8–12] and one case each from Argentina [13], India [14] and the United States [15]. For cases that were reported between 2019 and 2021, none of the authors mentioned any association of SARS CoV-2 or COVID-19 disease with *Exophiala dermatitidis* fungemia (Table 1).

In terms of management of *Exophiala dermatitidis* fungemia, all patients in the New York outbreak had their central venous catheters (CVCs) removed and antifungal agents started. Despite being in immunocompromised states, the majority of patients (11/14, 78.6%) who received voriconazole during this outbreak survived [7]. This is in stark contrast to other individual cases reported later including the present case, where only three out of nine (33.3%) patients survived (Table 1). Six of these nine patients had documented removal of their CVCs. However, what is striking about these nine cases is that none of them received voriconazole as the first line antifungal therapy. Only three patients did receive voriconazole later in their management but only one of them survived (Table 1).

Pooled 5-year data on antifungal susceptibility testing performed on *Exophiala dermatitidis* isolates (Table 1) showed the following minimum inhibitory concentrations (MICs): liposomal amphotericin B 0.5 μg/mL, conventional amphotericin B 0.125 – 0.25 μg/mL, anidulafungin 0.008 μg/mL, caspofungin 0.008–16 μg/mL, micafungin 4 -> 16 μg/mL, fluconazole 4–16 μg/mL, flucytosine 2 -> 64 μg/mL, itraconazole 0.03–0.5 μg/mL, voriconazole 0.03–2 μg/mL, posaconazole 0.06 μg/mL, and miconazole 0.25 μg/mL. Although amphotericin B (whether liposomal or conventional) appeared to have low MICs, patients treated with them did not fare well as compared to patients treated with voriconazole. Twelve out of 16 (75%) patients who received either voriconazole alone (10/11) or voriconazole with other antifungal agent/s (2/5) survived. In comparison, only 1/5 (20%) patients who received amphotericin B formulations survived. Similarly, only 1/6 (16.7%) patients who received micafungin survived (Table 1). Even though these observations are intriguing,

clearly there were other factors at play that could influence the outcomes in these patients. Therefore, more studies are needed to better correlate in vitro antifungal susceptibility with clinical response, especially for moulds.

Conclusions

Severe COVID-19 pneumonia can lead to immunosuppression which increases the risk for infection by inhaled fungi including invasive *Exophiala dermatitidis*. Review of previous cases of *Exophiala dermatitidis* fungemia suggests that complete removal of CVC and voriconazole therapy seemed to produce the best survival outcome.

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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 appeared to influence the work reported in this paper.

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