

Isolation of *Rhizopus microsporus* and *Lichtheimia corymbifera* from tracheal aspirates of two immunocompetent critically ill patients with COVID-19

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ABSTRACT

We describe two fatal cases of COVID-19 in which *Rhizopus microsporus* and *Lichtheimia corymbifera* were cultured from endotracheal aspirate samples. Both patients had no underlying comorbidities other than obesity. Despite antifungal therapy, both cases developed septic shock and progressive refractory hypoxemia without evidence of other underlying infections. It is unclear whether isolation of these fungal organisms represents invasive disease or corresponds to an epiphenomenon of critical illness. Yet, patients suffering from COVID-19 may be at risk of superinfection from a broader range of fungal organisms than previously thought.

1. Introduction

Fungal disease complicating viral infections has been observed in patients with severe influenza and SARS-CoV-2 infection [1–3]. Use of dexamethasone as standard of care for COVID-19 may have an impact on the incidence of invasive fungal infections in the intensive care unit (ICU) [3,4]. Diagnosing fungal infection in this context is difficult due to lack of standardized diagnostic algorithms and definitions. Limited access to lung biopsy or bronchoscopy results in an unknown burden of disease.

Though uncommon, infections due to Mucorales among non-immunosuppressed critically ill patients have been reported [5–7]. The unprecedented Mucorales outbreak in India has highlighted COVID-19 as a risk factor for mucormycosis, mainly of the rhino-orbital-cerebral type in patients with uncontrolled diabetes mellitus [8,9].

Although prevalence of Mucormycosis was higher in India before the COVID-19 pandemic, reasons for this outbreak are currently under investigation. COVID-19 results in several immune alterations of which T and NK-cell lymphopenia and expansion of an “exhausted” T lymphocyte phenotype with surface expression of PD-1 are remarkable

features [10]. Diabetes mellitus and glucocorticoids are classical risk factors for mucormycosis [11]. The combination of these factors in a high-prevalence setting may contribute to the remarkably high number of rhino-orbital and rhino-facial mucormycosis cases seen in the Indian subcontinent. In contrast, the disease has not been commonly reported in COVID-19 patients in other settings and until recently, had been considered a sporadic and possibly unrelated phenomenon.

In this report, we describe two fatal cases of COVID-19 in which *Rhizopus microsporus* and *Lichtheimia corymbifera* were cultured from endotracheal aspirate samples.

2. Case presentation

2.1. Case 1

A 62-year-old woman presented to the emergency department (ED) in June 2020 with a 10-day history of fever, anosmia and dry cough. The patient had received a 5-day course of penicillin without improvement. Past medical history was notable for obesity (body mass index: 33 kg/m²).

On physical exam her heart rate was 100 bpm, respiratory rate was

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38 rpm, blood pressure (BP) was 100/70 mmHg and oxygen saturation was 55% on room air. She had cyanosis and bilateral lung crackles. She was admitted (day 0) and placed on oxygen through a non-rebreather mask. Oxygen saturation improved to 94%. Chest computed tomography (CT) revealed bilateral and extensive ground glass opacities (Fig. 1A). Her blood count and chemistry reported mild lymphopenia, 1040 cell/ μ L (normal range 1500–4000); elevation of C reactive protein (CRP), 15.22 mg/dL (normal range 0–1 mg/dL); ferritin, 812 ng/mL (normal range 11–306 ng/mL), D-dimer, 828 ng/mL (normal range <500 ng/mL) and glucose, 89 mg/dL (normal range 70–99 mg/dL). Her serum procalcitonin was 1.0 ng/mL. A nasopharyngeal swab real time PCR for SARS-CoV-2 was positive.

On hospital day +2, she developed acute respiratory distress syndrome (ARDS) (PaO₂/FiO₂ ratio: 108), required invasive mechanical ventilation (IMV) and was admitted to the ICU. Despite prone

positioning, pulmonary distensibility and PaO₂/FiO₂ ratio remained low. She developed distributive shock, leukocytosis, 22800 cell/ μ L, high CRP, 25 mg/dL, and was started on meropenem and vancomycin. Blood and tracheal aspirate (TA) cultures were obtained on days +3 and +4, respectively. The patient was weaned off vasopressors temporarily but presented intermittent fever despite broad antibacterial treatment and her ventilatory status failed to improve.

On day +14 a mold was observed on the TA culture. Microscopy revealed wide, non-septate hyphae with round sporangioophores and rhizoids (Fig. 2). The organism was identified as *Rhizopus* sp. by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) and as *Rhizopus microsporus* by Internal transcribed spacer (ITS) sequencing. The patient was started on amphotericin-B lipid complex (ABLC) (5 mg/kg). Head and chest CT did not reveal sinusitis, the pulmonary parenchyma showed widespread infiltrates without

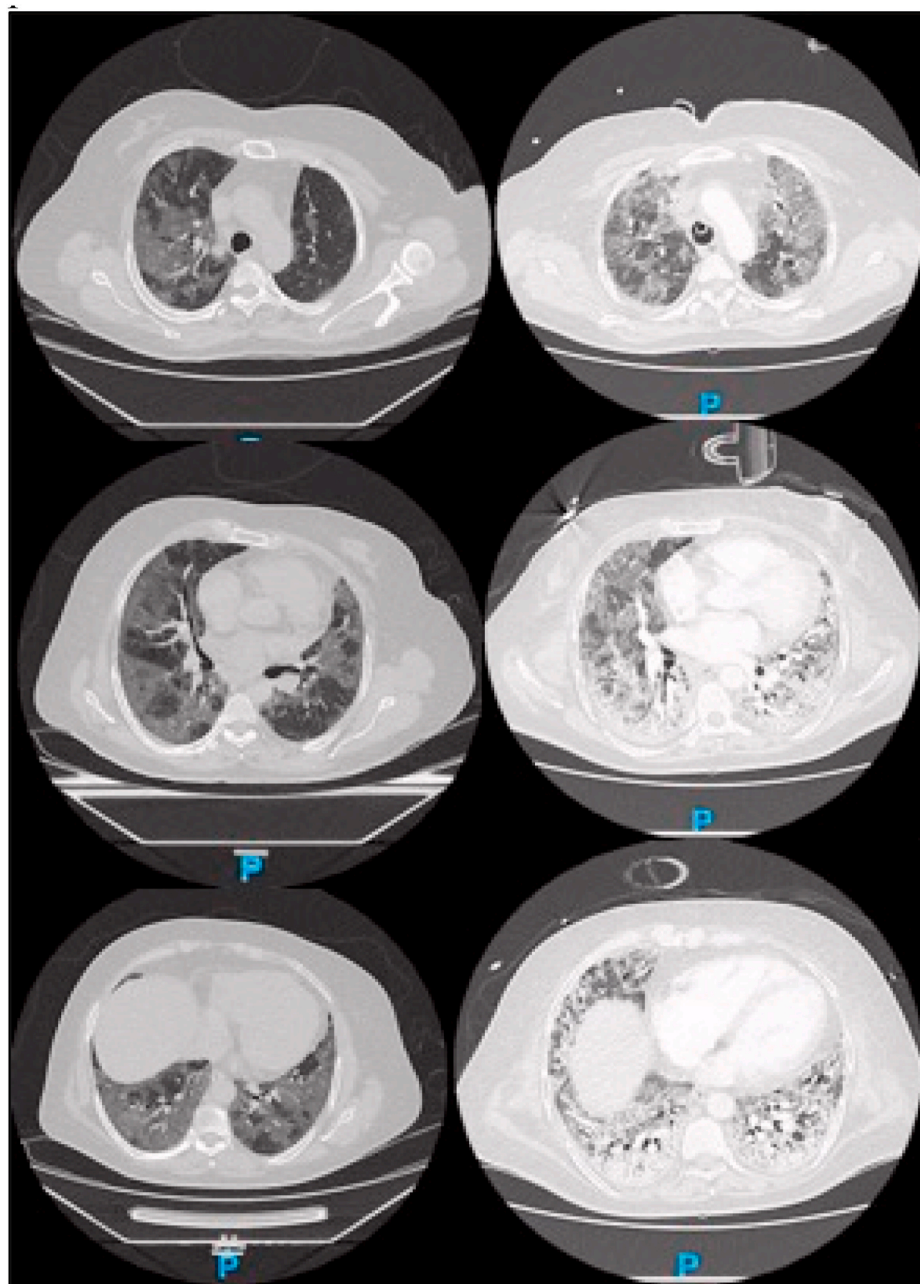


Fig. 1. Chest CT of patient #1.

A. Admission chest CT (left column) showing bilateral ground-glass opacities. B. Follow-up chest CT 18 days after admission (right column) showing bilateral consolidations and ground-glass opacities.

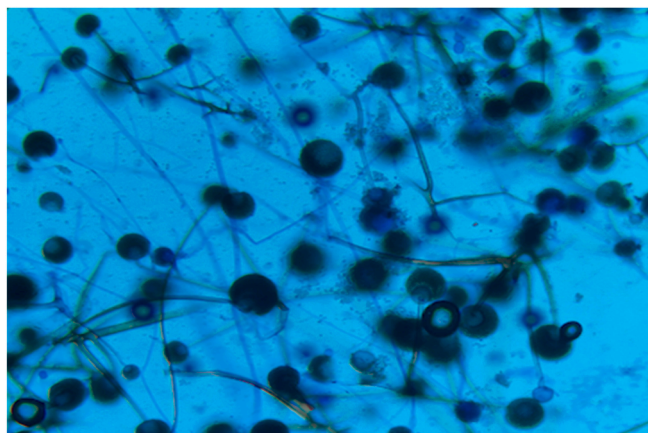


Fig. 2. *Rhizopus microsporus* on lactophenol-cotton blue stain
Lactophenol-cotton blue stain of the tracheal aspirate fungal culture showing round sporangia. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

nodules or masses (Fig. 1B). The patient's ventilatory status improved slightly and respiratory acidosis resolved.

After two weeks of ABLC without further improvement, posaconazole suspension through nasogastric tube was added. The patient presented intermittent episodes of fever and hypotension despite broad spectrum antibiotics and antifungal treatment. No additional microorganisms were isolated on repeated blood, urine or TA cultures. The patient died on day +43 due to refractory respiratory failure. Autopsy was not performed due to SARS-CoV-2 infection.

2.2. Case 2

A 50-year-old man, with history of obesity (body mass index: 30 kg/m²) presented to the ED in January 2021 with a 15-day history of headache, fever, myalgias, arthralgias, nonproductive cough and progressive dyspnea. He received 5 days of azithromycin, oseltamivir and ivermectin without improvement.

On examination, his heart rate was 132 bpm, respiratory rate was 60 rpm, BP was 109/80 mmHg, temperature was 36.7 °C and oxygen saturation was 45% on room air. His blood-cell count was 9500 with 91.4% neutrophils and lymphopenia (351 cell/μL), CRP was 26.6 mg/dL, ferritin was 2229 ng/mL, D-dimer 4953 ng/mL, creatinine was 2.09

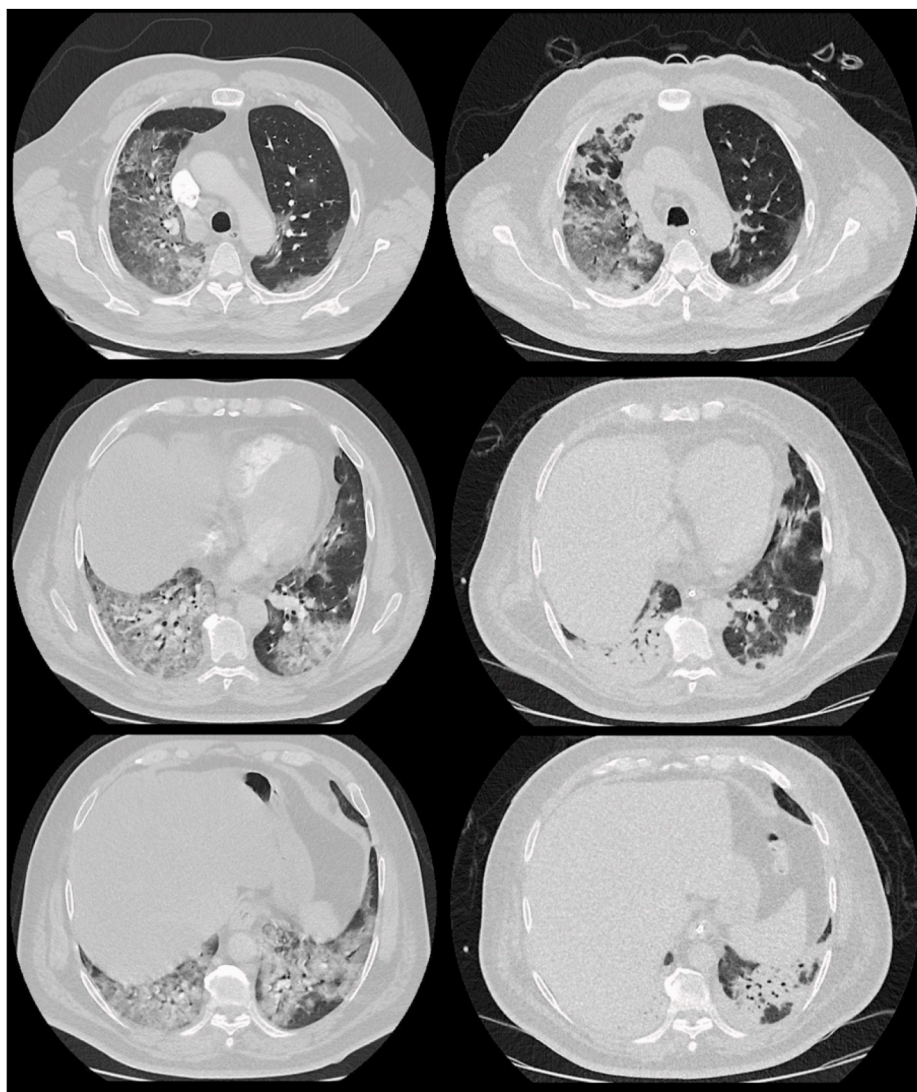


Fig. 3. Chest CT of patient #2A
Admission chest CT (left column) revealing ground-glass opacities and areas of consolidation. B. Follow-up chest CT 10 days after admission (right column) revealing progression of bilateral consolidations.

mg/dL and glucose was 235 mg/dL. Angio CT showed diffuse bilateral alveolar infiltrates with confluent ground glass opacities involving more than 50% of lung volume and some consolidations (Fig. 3A) without pulmonary embolism. A real time PCR of a nasopharyngeal swab was positive for SARS-CoV-2.

The patient was admitted (day 0) to the ICU requiring endotracheal intubation and IMV due to severe ARDS with a PaO₂:FiO₂ ratio of 74. He was started on dexamethasone.

On day +5, he was diagnosed with ventilator acquired pneumonia (VAP) due to *Klebsiella pneumoniae* and methicillin-susceptible *Staphylococcus aureus*, and ceftriaxone was added. On day +8, due to VAP progression, he was switched to imipenem and vancomycin. A new TA culture on day +10 grew a mold. Lactophenol-cotton blue stain showed smooth, hyaline hyphae with ellipsoidal sporangiospores and columella (Fig. 4). The mold was identified as *Lichtheimia corymbifera* by MALDI-TOF MS and ITS sequencing. Isavuconazole was started, and imipenem and vancomycin were stopped. Chest CT revealed progressive pneumonia with new infiltrates (Fig. 3B).

Due to hypotension and persistent fever, isavuconazole was switched to amphotericin B deoxycholate (AmBd) on day +15. *L. corymbifera* was repeatedly obtained on TA cultures sent on days +13 and +24. CT revealed acute pansinusitis without bone involvement. A nasal swab culture was negative. Repeated Chest CT showed unilateral pleural effusion. Hemodynamic instability and high oxygen demand hindered further workup. Despite AmBd and vasopressor support, he died on day +28 due to refractory hypoxemia. Autopsy was not performed.

Table 1 depicts clinical and microbiological characteristics of both patients.

3. Discussion

Viral infection is not among the usual risk factors for mucormycosis (diabetes mellitus, trauma, intravenous drug use, prolonged neutropenia and immunosuppression) [5]. However, severe respiratory viral infection is associated with a complex phenotype of immune dysregulation and propensity for secondary pulmonary infections. Severe influenza infection is associated with low circulating CD4-T cells, NK-cells and aberrant CD8-T cell activation. Along with epithelial damage, these derangements may explain enhanced susceptibility to fungal infection [12]. Immune dysregulation is also a hallmark of severe respiratory disease due to SARS-CoV-2; patients develop T and NK cell lymphopenia associated with elevated inflammatory cytokine blood levels [10,12,13]. An autopsy series from the United Kingdom reported T-CD8 lymphocyte depletion in primary and secondary lymphoid organs [14].

Criteria for the diagnosis of COVID-19 Associated Pulmonary Aspergillosis (CAPA) have been published [2]. Yet, there are no other

definitions to aid in the diagnosis of other invasive mold infections. Histopathological evidence of fungal invasion by broad, pauci-septate hyphae branching at right angles or culture from tissue biopsy are commonly used for a definite mucormycosis diagnosis. Molecular tests targeting the Mucorales are being increasingly described and may help expedite diagnosis but are not widely available [15].

Before the surge of cases in India, few cases of mucormycosis in COVID-19 patients had been reported worldwide. A series of cases of COVID-19 and mucormycosis from Bangalore, India, included 16 patients with rhinocerebral mucormycosis, of whom 6 died. Most of them had underlying diabetes mellitus and received steroids during COVID-19 treatment. This case series occurred during the first wave of the pandemic, was the largest at the time of its publication and seems to be the first to raise the alarm of the association between COVID-19 and mucormycosis [16]. It is unknown if it is as strongly associated with diabetes mellitus as rhino-orbito-cerebral disease and how much the environment or geographical location of the patient influences its development.

In general, mucormycosis in the ICU is described mostly in case series or individual reports in patients with hematological neoplasia, transplant recipients, immunosuppression, or trauma. Salient features include non-resolving pulmonary infiltrates and fever despite broad-spectrum antibiotics [6,17]. Concern about dangerous exposure to SARS-CoV-2 and the difficulty of invasive sampling in patients with respiratory failure have hindered our ability to identify invasive fungal infections in COVID-19 patients. After 18 months of the COVID-19 pandemic, only few cases of pulmonary mucormycosis associated with COVID-19 have been reported [14,18]. An autopsy study of a young man with critical COVID-19 reported disseminated mucormycosis affecting the lung, brain and pericardium [14]. A patient who received tocilizumab treatment for severe COVID-19 necrotizing pulmonary infection with bronchopleural fistula succumbed despite surgery and antifungal treatment [18].

Herein, we report two new cases of critical COVID-19 with isolation of *Rhizopus microsporus* and *Lichtheimia corymbifera*, respectively, in tracheal aspirate culture of patients with no previous underlying comorbidities other than obesity. At our center, all respiratory samples are inoculated in Sabouraud-dextrose medium and cultured at 30 °C. Further description of the microbiological methodology performed at our center can be found in the supplemental file 1. The isolate of *Rhizopus microsporus* in patient number one took an unusually long time to grow on culture media. It may be possible that organism inoculum on non-invasive respiratory sample was lower and resulted in longer culture turnaround times. It is notable that this patient did not receive anti-inflammatory treatment with corticosteroids or anti-cytokine antibodies, as she was admitted before publication of the beneficial effect of

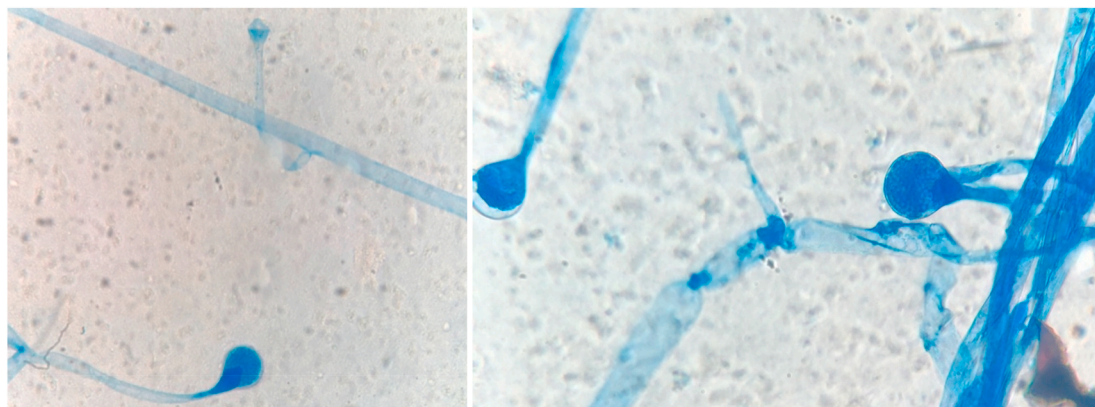


Fig. 4. *Lichtheimia corymbifera* on lactophenol-cotton blue stain

Lactophenol-cotton blue stain of the tracheal aspirate fungal culture showing hyaline hyphae, ellipsoidal sporangiospore and columella. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1

Patient characteristics, clinical course, microbiological findings, treatment, and outcome.

Patient	Age/ Sex	Underlying conditions	COVID-19 Drugs	Microbiological investigation (days after admission of sample acquisition)	Susceptibility Profile ^a (µg/mL)	Radiologic findings at IFI diagnosis	Treatment (days)	Outcome (days after admission)
1	62/F	Obesity	None	<u>Positive:</u> TA (4): <i>R. microsporus</i> <u>Negative:</u> BC (3, 8, 14, 27, 34, 38) GM (14) TA (6, 14, 32, 38, 41)	AMB 0.25 VOR 2 ITC 0.5 PSC 0.25 ISV 0.38	Bilateral consolidations and ground-glass opacities	ABLC (29) → + PSC (15)	Refractory hypoxemia Septic shock Death (43)
2	50/ M	Obesity	Dexamethasone IV 6 mg once daily from hospital day 1–10	<u>Positive:</u> TA (3): KPN & MSSA TA (8, 13, 24): <i>L. corymbifera</i> <u>Negative:</u> BC (3, 8, 11, 14, 16, 21, 25) CVC tip (12, 25) Nasal swab (14) Skin biopsy (20) TA (21)	AMB 0.25 VOR >16 ITC 1 PSC 0.5 ISV 1.5	Bilateral consolidations and unilateral pleural effusion	ISV (5) → AMBD (13)	Refractory hypoxemia Septic shock Death (28)

^a Antifungal susceptibility testing isolates are reported according to CLSI recommendations (Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi M38 3Ed). AMB: Amphotericin B; ABL: Amphotericin B lipid complex; AMBD: Amphotericin B deoxycholate; BC: Blood cultures; CVC: Central venous catheter; GM: Galactomannan antigen testing in serum; IFI: Invasive Fungal Infection; ISV: Isavuconazole; ITC: Itraconazole; KPN: *Klebsiella pneumoniae*; MSSA: *Staphylococcus aureus* methicillin-susceptible; PSC: Posaconazole; TA: Tracheal aspirate culture; VOR: Voriconazole.

dexamethasone on COVID-19 patients requiring supplemental oxygen or ventilatory support [4].

In the case of patient number two, hyperglycemia was found upon admission. Though this could represent undiagnosed diabetes, stress response due to severe infection could also cause this abnormality. Regardless of the etiology, hyperglycemia promotes an ideal environment that enables mucor to thrive [9,11]. Typical radiographic signs of mucormycosis (halo, reversed halo, vascular occlusion sign) were absent. However, follow-up Chest CT of patient number two exhibited pleural effusion, which is also described in patients with mucormycosis [19]. Confirmation of pulmonary mucormycosis through biopsy or bronchioalveolar lavage culture was not possible due to the hemodynamic and ventilatory instability of patients.

Treatment of mucormycosis is complex. Optimal results usually require a combination of surgery and prolonged antifungal therapy. Active agents against Mucorales species have the inconvenience of being expensive (liposomal formulations of amphotericin B, posaconazole and isavuconazole), ridden with poorly tolerated adverse effects (amphotericin B deoxycholate) or have relevant pharmacological interactions (posaconazole and isavuconazole) [19]. Both patients received different antifungal regimens due to the availability of specific agents during their period of presentation. Patient 1 was treated with liposomal amphotericin-B and eventually had posaconazole added to her treatment due to lack of improvement. Patient 2 was started on isavuconazole as liposomal amphotericin B was not available at the time of diagnosis and eventually switched to amphotericin B deoxycholate due to lack of improvement. In both cases, patients developed septic shock and progressive refractory hypoxemia despite antifungal treatment and no evidence of other bacterial organisms. No further SARS-CoV-2 tests were performed after diagnosis.

At the beginning of the pandemic isolation of fungal species was regarded as unusual. We now appreciate that COVID-19, anti-inflammatory medications, and the critically ill state of many patients seem to act synergistically to render subjects vulnerable to infections usually associated states of profound immunosuppression. Though aspergillosis and mucormycosis have received most of the attention, critically ill COVID-19 patients are also at increased risk of invasive candidiasis [20]. The diagnostic difficulties, complex treatment and the acuity of COVID-19 patients make management of fungal infections a formidable challenge even for the most robust healthcare systems. Further research on the pathogenesis, diagnosis, and management of fungal infection in

COVID-19 patients is needed.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mmcr.2021.07.001>.

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