



Case report

Cryptococcus neoformans blood stream infection in severe COVID-19 pneumonia



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ABSTRACT

Severe coronavirus disease (COVID-19) associated pneumonia leads to acute respiratory distress syndrome and emerging data suggest fungal coinfections also contribute to mortality in this patient population. *Aspergillus* ventilator associated pneumonia is increasingly recognized. We describe a case of likely re-activation of community acquired *Cryptococcus neoformans* in a patient with severe COVID-19.

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As the pandemic continues, global deaths due to COVID-19 have surpassed four million [1]. Lansbury et al. completed a meta-analysis of 3834 COVID-19 patients between January and April 2020 and found 14% of patients in intensive care units (ICU) had bacterial coinfections and 3% had coinfections with other viruses [2]. While invasive aspergillus infections (IAI) have been well described in severe influenza with acute respiratory syndrome, in (SARS-CoV-1) infections, only a handful of fungal coinfections were reported [3,4]. Since that publication, fungal coinfections, especially Aspergillosis, have been increasingly reported in the setting of COVID-19 and mortality contributing to IAI are emerging in case reports and larger cohorts [5,6].

We report the case of a 75-year old, immunocompetent male who died of *Cryptococcus neoformans* fungemia in the setting of severe COVID-19 associated pneumonia and acute respiratory distress syndrome (ARDS).

A Hispanic male with a history of diabetes mellitus, hypertension, obesity, osteoarthritis presented with a 4-day history of fever, difficulty breathing and was diagnosed with COVID-19 by reverse transcription polymerase chain reaction (RT PCR) (Abbott ID NOW

SARS CoV RNA). His oxygen saturation was 50% on room air in the emergency department (ED) prompting intubation and intensive care unit (ICU) admission. Social and travel history was unremarkable.

Admission labs were unremarkable including a negative HIV test. His lymphocyte percentage was 3.0–8.1% throughout his hospitalization, with an absolute lymphocyte nadir of 400 on day eight of hospitalization. HgBA1C was 9%, blood and sputum cultures were negative. He was treated with remdesivir for 5 days, convalescent plasma, and dexamethasone 6 mg IV daily for 10 days starting on day two of hospitalization. Due to persistent fevers starting on day 11, increasing oxygen requirements, and bilateral airspace disease on chest x-ray, sputum cultures were obtained and grew methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA was also documented from sputum on day 17 and 22. He received vancomycin, which was eventually switched to linezolid for possible treatment failure with worsening ARDS. His hospital course was complicated by acute kidney injury and bilateral cerebral infarcts.

In the last week of hospitalization, he was oxygenating adequately on 50% FiO₂. He acutely worsened and FIO₂ use increased to 90% and did not improve despite proning, neuromuscular agents, and inhaled nitric oxide. Due to persistent fevers and eosinophilia, and concern of drug fever, he received prednisone for 8 days, which ended 2 days before his death. Due to his age, multiple strokes, inability to oxygenate despite using multiple methods, and prolonged ICU stay, he transitioned to comfort measures. On day 26 of

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hospitalization, bacterial blood cultures were obtained. The patient expired the following day. Four days later *Cryptococcus neoformans* resulted in both sets.

Studies to date have demonstrated that COVID-19 can invoke a severe inflammatory response resulting in significant damage to lung tissue, allowing fungal species that would otherwise be colonizers in normal hosts to invade lung tissue and disseminate [6]. Previous studies have shown that pulmonary epithelial and alveolar cells, often destroyed in severe COVID-19 pneumonia, are otherwise critical in the initial immune and inflammatory response to *Cryptococcus* [7]. These patients are also frequently lymphopenic and have been noted to have specific decreases in CD4⁺ and CD8⁺ T cell counts, as well as suppressed IFN- γ production by CD4⁺ T cells [8]. This relative deficiency in cell-mediated immunity would also be a risk factor for invasive Cryptococcal disease.

Although we hypothesize that this patient's infection was a result of direct fungal invasion into damaged lung tissue, we cannot completely rule out the possibility of reactivation of latent/asymptomatic cryptococcal infection or potential nosocomial acquisition (i.e. airborne or central venous catheter acquisition). *Cryptococcus* can remain latent and asymptomatic for many years following initial airway acquisition [9]. Clinical disease and dissemination later occur when the host immune system is suppressed. However, if this was the predominant pathogenesis then one would expect more reported cases of other reactivated endemic mycoses (e.g., histoplasmosis, coccidioidomycosis), and fewer cases of *Aspergillus* (which typically does not exist in a latent phase). In review of the literature, there have also been rare reported cases of possible nosocomial spread of *Cryptococcus*, but only in the setting of case clusters within a single facility [10]. No other recent cases of *Cryptococcus* in our hospital have been reported, thus nosocomial spread would be highly unlikely.

Based on this case and reports of other fungal infections with concurrent severe COVID-19 associated pneumonia, providers may need to consider adding serum cryptococcal antigen testing to other routine diagnostics in the work-up for invasive fungal disease, especially in patients with prolonged fever, mechanical ventilation

for ARDS, and receipt of steroids. A high clinical suspicion and early diagnosis of all fungal infections including cryptococcal disease is critical. *Cryptococcus neoformans* and other fungal coinfections should be considered early in patients with severe COVID-19 pneumonia in the ICU regardless of presence of other risk factors as timely, effective therapy can be life-saving.

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Conflicts of Interest

All authors declare no relevant conflict of interest

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