Therapeutic Advances in Infectious Disease
Case Report

Missed opportunities to identify cryptococcosis in COVID-19 patients: a case report and literature review

Ther Adv Infectious Dis
2022, Vol. 9: 1–10
DOI: 10.1177/20499361211066363

Daniel B. Chastain, Andrés F. Henao-Martínez, Austin C. Dykes, Gregory M. Steele, Laura Leigh Stoudenmire, Geren M. Thomas, Vanessa Kung and Carlos Franco-Paredes

***Abstract*:** SARS-CoV-2 may activate both innate and adaptive immune responses ultimately leading to a dysregulated immune response prompting the use of immunomodulatory therapy. Although viral pneumonia increases the risk of invasive fungal infections, it remains unclear whether SARS-CoV-2 infection, immunomodulatory therapy, or a combination of both are responsible for the increased recognition of opportunistic infections in COVID-19 patients. Cases of cryptococcosis have previously been reported following treatment with corticosteroids, interleukin (IL)-6 inhibitors, and Janus kinase (JAK) inhibitors, for patients with autoimmune diseases, but their effect on the immunologic response in patients with COVID-19 remains unknown. Herein, we present the case of a patient with COVID-19 who received high-dose corticosteroids and was later found to have cryptococcosis despite no traditional risk factors. As our case and previous cases of cryptococcosis in patients with COVID-19 demonstrate, clinicians must be suspicious of cryptococcosis in COVID-19 patients who clinically deteriorate following treatment with immunomodulatory therapies.

Keywords: COVID-19, Cryptococcus, cytokine release syndrome, immunotherapy, SARS-CoV-2

Received: 6 October 2021; revised manuscript accepted: 24 November 2021.

Correspondence to:
Daniel B. Chastain
Department of Clinical & Administrative Pharmacy, College of Pharmacy, University of Georgia, 1000 Jefferson Street, Albany, GA 31701, USA.
daniel.chastain@uga.edu

Andrés F. Henao-Martínez
Vanessa Kung
Division of Infectious Diseases, University of Colorado, Anschutz Medical Campus, Aurora, CO, USA

Austin C. Dykes
Department of Clinical & Administrative Pharmacy, College of Pharmacy, University of Georgia, Albany, GA, USA

Gregory M. Steele
Infectious Diseases, Phoebe Putney Memorial Hospital, Albany, GA, USA

Laura Leigh Stoudenmire
Department of Pharmacy, Phoebe Putney Memorial Hospital, Albany, GA, USA

Geren M. Thomas
Department of Pharmacy, John D. Archbold Memorial Hospital, Thomasville, GA, USA

Carlos Franco-Paredes
Division of Infectious Diseases, University of Colorado, Anschutz Medical Campus, Aurora, CO, USA

Hospital Infantil de México, Federico Gómez, México City, México

Introduction

SARS-CoV-2 can activate both innate and adaptive immune responses in patients ultimately leading to a dysregulated immune response.[1] Due to the widespread use of immunomodulatory therapy, including high-dose corticosteroids, interleukin (IL)-1 and IL-6 inhibitors, as well as Janus kinase (JAK) inhibitors, as part of the medical management of COVID-19,[2,3] an increasing number of patients may experience an impaired immune response.[4] Consequently, compromising host immunity in COVID-19 patients could provide the perfect opportunity for secondary infections with or reactivation of previously latent diseases, such as latent tuberculosis infections, strongyloidiasis, aspergillosis, mucormycosis, or cryptococcosis.

Specifically, *Cryptococcus neoformans* is frequently associated with advanced HIV disease manifesting as meningoencephalitis, but rates have been decreasing among persons living with HIV (PLH) due to increased uptake of antiretroviral therapy (ART).[5] However, an increasing number of cases of cryptococcosis have been identified among new populations of patients with cell-mediated immunodeficiencies, including solid organ transplant (SOT) recipients and non-HIV-infected, non-transplant patients with malignancies, autoimmune diseases, diabetes mellitus, cirrhosis, as well as those receiving immunosuppressive medications.[6–10] Herein, we present the case of a patient with COVID-19 who received immunomodulatory therapy with high-dose corticosteroids and was later found to have cryptococcosis.

Patient case

A man in his early 70s, who was a nursing home resident, was sent to an outside hospital (OSH) in the Southeastern United States in late November

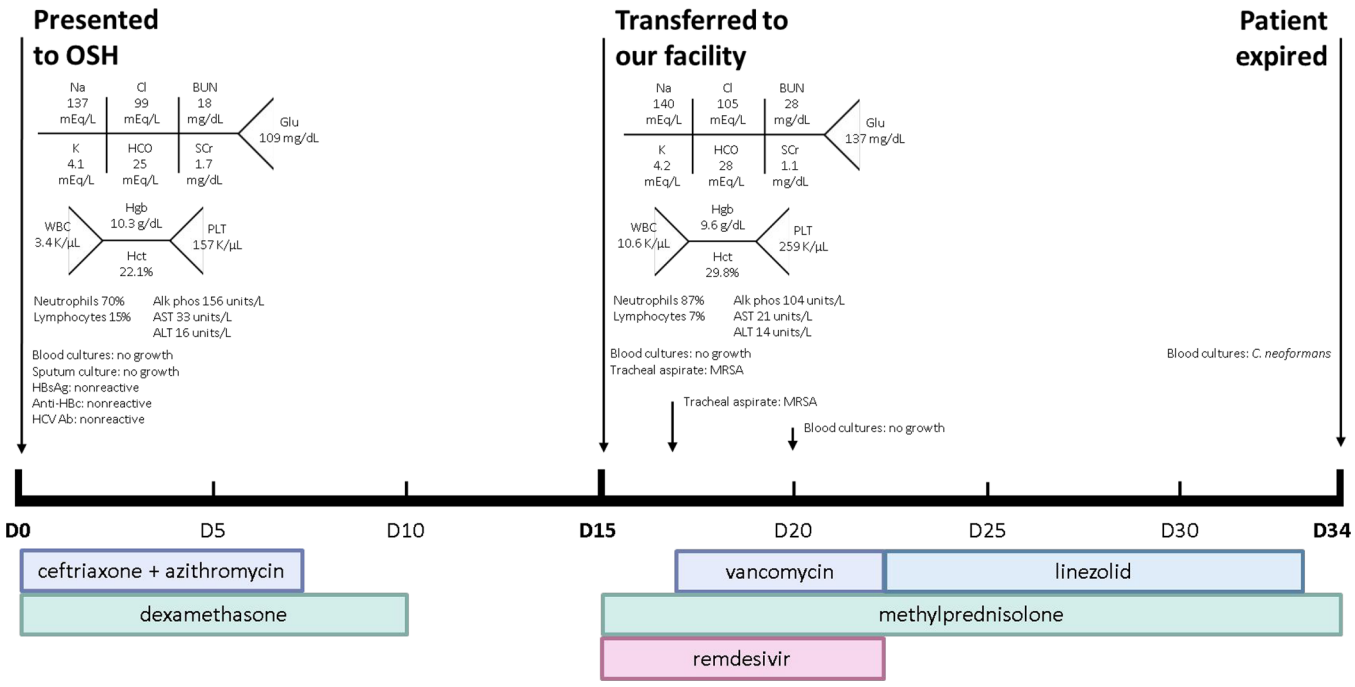

Figure 1. Timeline of hospitalization.
Figure depicts daily (D) timeline of hospitalization at the outside hospital (OSH) and subsequent transfer to our facility. Baseline laboratory data are presented upon admission to both facilities and include the following: Alk phos, alkaline phosphatase (range: 30–120 units/L); ALT, alanine transferase (10–40 units/L); Anti-HBc, hepatitis B virus core antibody (range: nonreactive); AST, aspartate transferase (10–40 units/L); BUN, blood urea nitrogen (range: 8–20 mg/dL); Cl, chloride (range: 98–106 mEq/L); Glu, glucose (range: 77–99 mg/dL); HBsAg, hepatitis B virus surface antigen (range: nonreactive); HCO, bicarbonate (range: 23–28 mEq/L); Hct, hematocrit (range: 42–50%); HCV Ab, hepatitis C virus antibody (range: nonreactive); Hgb, hemoglobin (range: 14–18 g/dL); K, potassium (range: 3.5–5 mEq/L); Lymphocytes (range: 30–45%); Na, sodium (range: 135–145 mEq/L); Neutrophils (range: 50–70%); PLT, platelet (range: 150–450 K/µL); SCr, serum creatinine (range: 0.70–1.30 mg/dL); WBC, white blood cell (range: 3.5–10 K/mm^3).

2020, due to hypoxia following a recent diagnosis of SARS-CoV-2 infection. His past medical history included a cerebrovascular accident resulting in left hemiplegia and hemiparesis, idiopathic peripheral autonomic neuropathy, spinal stenosis with bilateral lower extremity radiculopathy, atrial fibrillation, hypertension, coronary artery disease, dyslipidemia, chronic obstructive pulmonary disease, gastroesophageal reflux disease, stage 3 chronic kidney disease (CKD), benign prostatic hypertrophy, obesity, major depressive disorder, and vascular dementia for which he took amlodipine, aspirin, atorvastatin, dabigatran, donepezil, famotidine, memantine, metoprolol tartrate, omeprazole, pregabalin, tamsulosin, and valproic acid. On admission, he complained of fevers, shortness of breath, nonproductive cough, loose stools, and anorexia, but denied headache, visual disturbance, hemoptysis, arthralgia, myalgia, nausea, vomiting, or rashes. His O_2 saturation was 91% on room air and computed tomography (CT) of the chest revealed multifocal infiltrates with a ground-glass appearance consistent with COVID-19. Baseline chemistry and hematology laboratory values revealed leukopenia and lymphopenia but were otherwise unremarkable and reflected his underlying CKD (Figure 1). He was provided supplemental oxygen via nasal cannula and treated with ceftriaxone and azithromycin for 7 days. Although he was deemed not to be a candidate for remdesivir at that time due to CKD, he received dexamethasone for 10 days in combination with convalescent plasma. Blood cultures and sputum cultures were collected on admission but remained sterile.

Over the next 10 days, he remained afebrile, but his respiratory function continued to deteriorate on nasal cannula, and he was transitioned to nonrebreather (NRB) mask. The previously identified multifocal infiltrates persisted on follow-up chest radiography (CXR). Due to decreased O_2 saturation to 70% and bluish-gray appearance, the patient required intubation, mechanical

ventilation, and initiation of vasopressors, which prompted a transfer to our institution.

Upon arrival, he was admitted to the intensive care unit (ICU), where he remained sedated, mechanically ventilated, and on vasopressors. He was subsequently started on remdesivir for 5 days, in addition to IV methylprednisolone 60 mg IV every 8 h for 2 days followed by a gradual taper throughout his hospitalization. His initial blood and urine cultures were sterile, but multiple tracheal aspirate cultures revealed methicillin-resistant *Staphylococcus aureus*. Despite an unchanged CXR and successful extubation, he was started on IV vancomycin on day 3, but was transitioned to linezolid after experiencing an acute kidney injury for a combined total of 16 days.

The patient continued to improve and was transferred out of the ICU on a high-flow nasal cannula over the next 4 days, but became febrile and experienced hypoxia, lethargy, as well as hypotension requiring intubation and mechanical ventilation with a subsequent transfer back to ICU. Blood cultures revealed yeast on Gram stain, and he was started on micafungin. Unfortunately, the patient's blood pressure and respiratory function continued to deteriorate over the next 24 h, and he expired. Post-mortem, the previously detected yeasts grew on Sabouraud Dextrose Agar (Emmons modification) which were identified via Thermo Scientific™ RapID™ Yeast Plus System (RapID; Thermo Fisher Scientific, Lenexa, Kansas) as *C. neoformans*. Molecular identification and antifungal susceptibility testing were not performed due to limited capabilities in the local microbiology laboratory. Serum cryptococcal antigen (CrAg) lateral flow assay (LFA) was also not performed due to low suspicion of cryptococcosis in this patient and limited data describing cryptococcosis in patients with COVID-19 at the time of this patient's care.

Discussion

There is increasing recognition of opportunistic infections (OIs) in COVID-19 patients with underlying medical conditions such as uncontrolled diabetes mellitus.[11,12] Although the precise mechanism remains unknown, the most likely pathophysiology is multifactorial involving cytokine dysregulation and impaired cell-mediated immunity due to SARS-CoV-2 combined with receipt of immunomodulatory therapies as part of the therapeutic armamentarium for COVID-19. The most frequently identified OIs include invasive pulmonary aspergillosis and mucormycosis. Clinical presentation varies depending on organ involvement and overlap with COVID-19, but often develops 1 to 2 weeks after hospitalization.[13,14] Advanced age, chronic pulmonary disease, and treatment with antimicrobial therapy were identified as risk factors for coronavirus disease-associated pulmonary aspergillosis (CAPA),[13,15] whereas diabetes mellitus was the most common risk factor among patients with COVID-19-associated mucormycosis (CAM).[14] In addition, many of these patients received immunomodulatory therapies for COVID-19, specifically corticosteroids and IL-6 inhibitors, which likely contributes to the increasing incidence of CAPA and CAM.[13–15] As our case demonstrates, cryptococcosis is yet another important opportunistic pathogen that should be considered by clinicians caring for patients with COVID-19 who received immunomodulatory agents.

While cryptococcosis primarily affects immunodeficient patients, an increasing number of cases have been reported in immunocompetent patients, in which some of these patients do not have identifiable risk factors.[9] In most situations, immunocompetent hosts can eradicate *C. neoformans* after inhalation, but *C. neoformans* may survive by evading the host immune response and forming a cryptococcal granuloma or residing in phagocytic cells, thereby establishing a latent infection.[16,17] Following the development of disease state- (e.g. diabetes mellitus, cirrhosis, sarcoidosis, etc.)[6–8,10,18] or medication- (e.g. corticosteroids, chemotherapy, etc.)[19,20] induced immune defects in these previously immunocompetent patients, the latent *C. neoformans* infection can reactivate resulting in detectable cryptococcosis.[21]

Indeed, eight previous cases of cryptococcosis in patients with COVID-19 have been reported (Table 1)[22–29] based on a PubMed literature search on 14 September 2021, using 'Cryptococcus' and 'COVID-19'. Of those reports, the median age was 74 (range: 24–78) years and 80% were men. Seventy-five percent had chronic comorbidities,[22,25–29] of which hypertension (83%)[22,25–27,29] and diabetes mellitus (33%)[25,27] were most common. In addition, two patients were receiving immunosuppressive medications: prednisone for autoimmune hemolytic anemia[28] and tacrolimus in combination with prednisone due to renal

Table 1. Reports of cryptococcosis in patients with COVID-19.

Case	Age (years)	Sex	Medical, surgical, or social history	Clinical course	Outcome
Heller *et al.*[24]	24	M	Born in Central America, but immigrated to the United States 3 months prior to admission, otherwise unremarkable	• Complained of headaches, shortness of breath, pleuritic pain, myalgias, nausea, vomiting for approximately 3 weeks prior to hospitalization • SARS-CoV-2 RNA detected 1 week prior to hospitalization • On admission, underwent lumbar puncture due to signs of meningeal inflammation upon admission which revealed increased opening pressure (55 cm H_2O), colorless CSF with 108 WBC/μL (81% lymphocytes), 47 mg/dL protein, and 42 mg/dL glucose • *C. neoformans* isolated from CSF cultures and treated with amphotericin B and flucytosine • Subsequently diagnosed with HIV (VL 138,000 copies/mL, CD4 16 cells/μL) and started on B/F/TAF	No neurologic deficits at 2.5-month follow-up
Passarelli *et al.*[26]	75	M	Hypertension, deceased donor kidney transplant 3 years ago (tacrolimus 4 mg/day and prednisone 5 mg/day), cirrhosis	• Presented with cough and progressive dyspnea × 4 days with SARS-CoV-2 detected upon admission • Chest CT revealed bilateral ground-glass opacities for which ceftriaxone and clindamycin were started while prednisone was increased to 30 mg/day and tacrolimus was discontinued • After 4 days, required mechanical ventilation and started on IV hydrocortisone 50 mg every 6 h • Developed septic shock on day 12 despite treatment with meropenem, vancomycin, and fluconazole • *C. neoformans* isolated from blood cultures on day 12 and 16	Died on day 18
Woldie *et al.*[28]	24	M	Autoimmune hemolytic anemia (prednisone 20 mg/day)	• Presented with fevers, myalgias, cough with SARS-CoV-2 detected upon admission • His prednisone dose was increased to 1.5 mg/kg/day and cyclophosphamide 50 mg every 12 h was started • Discharged after 13 days, but readmitted 1 week later due to persistent headache which then progressed to decreased consciousness and new onset seizures • MRI brain revealed necrotizing encephalitis for which IV methylprednisolone 1 g/day and IVIG 1 g/kg were initiated • Sustained a cardiac arrest prior to undergoing LP • *C. neoformans* was isolated from blood cultures obtained on the second hospitalization	Died prior to identification of cryptococcosis

(Continued)

Table 1. (Continued)

Case	Age (years)	Sex	Medical, surgical, or social history	Clinical course	Outcome
Cafardi *et al.*[22]	78	M	Hypertension, COPD	• Presented with fever, myalgia, hypoxia, dyspnea, headache, and diarrhea with SARS-CoV-2 detected upon admission • Remdesivir × 5 days, IV methylprednisolone 40 mg every 12 h, and inhaled recombinant sialidase† × 10 days were initiated • After 16 days, clinically improved but then deteriorated with onset of fevers and respiratory failure requiring mechanical ventilation and bronchoscopy • *C. neoformans* was isolated from respiratory cultures, whereas serum CrAg was not detected • Received LAMB × 6 days but sustained AKI and was transitioned to isavuconazole	Died approximately 20 days after identification of cryptococcosis
Ghanem and Sivasubramanian[23]	73	F	R THA 2 weeks prior to admission, otherwise unremarkable	• Febrile and hypoxic with patchy bilateral infiltrates on CXR postoperatively • SARS-CoV-2 detected and received azithromycin × 5 days and dexamethasone × 10 days • After 7 days of therapy, developed new onset gait instability, falls, and aphasia with CT head demonstrating hydrocephalus • Underwent EVD placement and CSF analysis revealed 25 WBC/μL, 173 mg/dL protein, and <10 mg/dL glucose • *C. neoformans* isolated from CSF cultures and treated with amphotericin and flucytosine	Discharged to a rehabilitation facility
Khatib *et al.*[25]	60	M	Hypertension, diabetes mellitus, ischemic heart disease	• Required ICU admission and MV due to COVID-19, received three doses of tocilizumab, multiple doses of methylprednisolone, and hydrocortisone • Required HD for AKI • Developed candidemia (*Candida parapsilosis*) and received anidulafungin • *C. neoformans* isolated from blood cultures while receiving anidulafungin so switched to amphotericin and flucytosine	Died 10 days after identification of cryptococcosis

(Continued)

Table 1. (Continued)

Case	Age (years)	Sex	Medical, surgical, or social history	Clinical course	Outcome
Thota *et al.*[29]	76	F	Hypertension, osteoarthritis, gastroesophageal reflux disease	• Presented with diarrhea, confusion, and weakness with SARS-CoV-2 detected upon admission • Cefepime, ampicillin, vancomycin, and IV methylprednisolone 40 mg every 12 h were initiated due to fevers and lactic acidosis • On day 3, required mechanical ventilation and then received convalescent plasma, remdesivir, tocilizumab, and inhaled budesonide • Clinically improved and discharged to a SNF, but readmitted with fever and encephalopathy after 14 days • MRI brain demonstrated numerous acute and subacute infarcts in the cerebral and cerebellar hemispheres without enhancement • CSF analysis revealed 87 WBC/μL, 3530 RBC/μL, 193 mg/dL protein, and <5 mg/dL glucose, and CrAg titer > 1:2560 • *C. neoformans* was isolated from CSF and blood cultures and treated with amphotericin and flucytosine × 3 weeks • Transitioned to fluconazole after CSF sterilized	Discharged to LTCF but remained comatose
Thyagarajan *et al.*[27]	75	M	Diabetes mellitus, hypertension, obesity, osteoarthritis	• Presented with fever and difficulty breathing with SARS-CoV-2 detected upon admission requiring ICU admission and MV • Remdesivir × 5 days, IV dexamethasone 6 mg daily × 10 days, and convalescent plasma • Developed VAP due to MRSA on day 17 and was treated with vancomycin then linezolid • Continued to clinically deteriorate and was transitioned to comfort measures • *C. neoformans* isolated from blood cultures on day 26	Died prior to identification of cryptococcosis

[†]A phase III randomized placebo-controlled study to examine the efficacy and safety of DAS181 for the treatment of lower respiratory tract parainfluenza infection in immunocompromised subjects (https://clinicaltrials.gov/ct2/show/NCT03808922).
AKI, acute kidney injury; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CrAg, cryptococcal antigen; CSF, cerebrospinal fluid; CT, computed tomography; CXR, chest radiography; EVD, external ventricular drain; F, female; HD, hemodialysis; ICU, intensive care unit; IV, intravenous; LAMB, liposomal amphotericin B; LP, lumbar puncture; LTCF, long term care facility; M, male; MRSA, methicillin resistant *Staphylococcus aureus*; MV, mechanical ventilation; R, right; RBC, red blood cell; SNF, skilled nursing facility; THA, total hip arthroplasty; VAP, ventilator acquired pneumonia; VL, viral load; WBC, white blood cell.

transplantation.[30] Characterization of symptoms caused by cryptococcosis was challenging due to overlap with COVID-19. However, due to low suspicion for cryptococcosis many patients clinically deteriorated, some of which died prior to detection of cryptococcosis.

During hospitalization, 25% of patients received tocilizumab, and 88% received corticosteroids. In the only case where corticosteroids were not administered for COVID-19, diagnosis of cryptococcosis subsequently led to a new diagnosis of HIV,[24] whereas *C. neoformans* was most commonly identified after receiving immunomodulatory therapy in all other cases; *C. neoformans* was isolated from blood cultures in 63% ($n = 5$) of patients. Of the 38% ($n = 3$) of patients who underwent cerebrospinal fluid (CSF) evaluation, *C. neoformans* was detected in all CSF cultures. Overall mortality was 63%, of which two patients died before identification of cryptococcosis.[27,28]

In four cases,[22,23,29] including our patient, no traditional risk factors for cryptococcosis were identified.[9] Notably, our patient had a glycated hemoglobin (A1C) of 5.6% (A1C $\geqslant$ 6.5% diagnostic for diabetes),[31] but did not undergo HIV testing. While viral pneumonia increases the risk of invasive fungal infections, it remains unclear whether SARS-CoV-2 infection, immunomodulatory therapy, or a combination of both were responsible for increased susceptibility to acute infection with or reactivation of *C. neoformans* in these patients with COVID-19. Although much of the pathogenesis of cryptococcosis in COVID-19 patients is poorly defined due to limited details in other case reports, we suspect our patient had latent cryptococcosis which reactivated because of SARS-CoV-2 infection–induced lymphopenia and corticosteroid treatment. Blood cultures obtained on admission at the OSH were sterile. Based on a rat model of pulmonary cryptococcosis which mirrors human infection, *C. neoformans* persists as a granuloma within the lung despite initial containment and no clinical symptoms.[17,21] Following receipt of corticosteroid therapy, increased fungal burden and extrapulmonary dissemination were observed to a greater extent when corticosteroid therapy was administered within 4 weeks of initial infection with *C. neoformans*. However, similar findings were not observed with late stages of latent cryptococcosis suggesting multiple mechanisms might be necessary for reactivation, which in this case include SARS-CoV-2 infection–induced lymphopenia combined with prolonged high-dose corticosteroid treatment. Mechanisms to predict and prevent reactivation of latent cryptococcosis are needed given the increasing incidence of immunosuppressive diseases and widespread use of immunosuppressive medications.

Asymptomatic treatment-naïve PLH with CD4 cell counts $\leqslant$100 to 200 cells/μL undergo screening for cryptococcosis using serum cryptococcal antigen (CrAg) testing.[32,33] Among those with detectable CrAg, CSF should be evaluated to determine whether the cryptococci have disseminated to the central nervous system (CNS). Early identification and treatment of cryptococcus in PLH with low CD4 cell counts has led to decreased mortality attributable to cryptococcal meningoencephalitis.[34–36] Unfortunately, similar recommendations to detect cryptococcal antigenemia and ultimately identify localized pulmonary cryptococcosis or disseminated cryptococcosis do not exist in HIV-uninfected immunodeficient patients nor immunocompetent patients. Diagnosis of cryptococcosis in non-HIV non-transplant patients is often missed or significantly delayed compared to PLH or organ transplant recipients resulting in lower survival rates,[37,38] as the sensitivity of CrAg LFA to detect CrAg in serum, while still relatively high, is lower than that in PLH.[39] Unfortunately, the sensitivity of serum CrAg is unknown in COVID-19 patients with an impaired immune response. As such, the risk of dissemination is increased compared to immunocompetent patients, therefore necessitating an evaluation for meningoencephalitis in COVID-19 patients with serologic or microbiologic evidence of cryptococcosis.

An optimal treatment regimen for cryptococcosis has not been identified in non-HIV nontransplant patients due to limited data.[40,41] As a result, most treatment regimens are based on efficacy data from PLH and SOT recipients, but depend on the extent of disease. A combination of lipid-associated formulations of amphotericin B (LFAB), such as liposomal amphotericin B (LAmB) or amphotericin B lipid complex (ABLC), plus flucytosine is most effective due to rapid fungicidal activity and is considered first line for induction therapy among patients with meningoencephalitis, disseminated (e.g. involvement of two or more noncontiguous

sites), or severe pulmonary disease (e.g. diffuse pulmonary infiltrates). In cases of meningoencephalitis, antifungal therapy should be combined with daily therapeutic lumbar punctures or placement of a lumbar drain or ventriculostomy to reduce intracranial pressure (ICP). Indeed, most patients who were still alive after identification of cryptococcosis received an LFAB in combination with flucytosine,[23–25,29] though few patients underwent CSF examination.[23,24,29]

While LFABs are preferred due to lower risk of nephrotoxicity, amphotericin b deoxycholate (AmBd) can be used if LAmB or ABLC are unavailable.[42] Many resource-limited countries are unable to access flucytosine due to limited availability and prohibitive costs,[43,44] requiring use of less efficacious regimens such as high dose fluconazole with or without AmBd.[40,41] A prolonged duration of induction therapy of 4 weeks, or longer in the presence of neurologic complications, is required in non-HIV nontransplant patients. After clinical improvement with induction therapy, fluconazole 800 mg per day should be initiated as consolidation therapy for at least 8 weeks followed by 200 to 400 mg per day as maintenance therapy for at least 1 year. However, the duration of antifungal therapy is somewhat dependent on resolution of the underlying immunodeficiency allowing for gradual restoration of immune function.

Conclusion

Cases of cryptococcosis have previously been reported following short- or long-term initiation of corticosteroids, IL-6 inhibitors, and JAK inhibitors for patients with autoimmune diseases, but it remains unknown how the use of one or a combination of these therapies will directly or indirectly alter immunologic response in patients with COVID-19. Clinicians must be suspicious of cryptococcosis in COVID-19 patients who clinically deteriorate following treatment with immunomodulatory therapies as signs and symptoms of cryptococcosis may overlap with COVID-19. Given the utility of CrAg LFA to detect CrAg in serum coupled with the high rate of missed opportunities to identify cryptococcosis and dire outcomes in non-HIV nontransplant patients, early recognition, perhaps through the use of a CrAg screen-and-treat strategy, prior to administration of immunomodulatory therapies in COVID-19 patients will result in prompt administration of antifungal therapy, most often a combination of LFAB plus flucytosine, thereby halting or eliminating further dissemination and improve overall mortality.

Author contributions

Daniel B. Chastain: Conceptualization; Data curation; Visualization; Writing – original draft; Writing – review & editing.
Andrés F. Henao-Martínez: Conceptualization; Supervision; Writing – review & editing.
Austin C. Dykes: Writing – original draft; Writing – review & editing.
Gregory M. Steele: Writing – review & editing.
Laura Leigh G. Stoudenmire: Writing – review & editing.
Geren M. Thomas: Writing – review & editing.
Vanessa Kung: Writing – review & editing.
Carlos Franco-Paredes: Conceptualization; Supervision; Writing – review & editing.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Ethics approval

Our report did not require ethical board approval as it described the treatment of a single patient which does not meet the federal definition of human subjects research. This case was documented in the context of routine care and the information presented was anonymized in accordance with the Declaration of Helsinki.

Patient consent

Consent was unable to be obtained as the patient is deceased and their relatives were not contactable. As such, details have been removed from the case description to ensure anonymity.

ORCID iDs

Daniel B. Chastain https://orcid.org/0000-0002-4018-0195

Andrés F. Henao-Martínez https://orcid.org/0000-0001-7363-8652

Carlos Franco-Paredes https://orcid.org/0000-0001-8757-643X

References

1. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, *et al*. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host Microbe* 2020; 27: 992–1000.e3.
2. NIH. COVID-19 treatment guidelines panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. https://www.covid19treatmentguidelines.nih.gov/ (2021, accessed 14 September 2021).
3. Chastain DB, Stitt TM, Ly PT, *et al*. Countermeasures to coronavirus disease 2019: are immunomodulators rational treatment options-a critical review of the evidence. *Open Forum Infect Dis* 2020; 7: ofaa219.
4. Hall MW, Joshi I, Leal L, *et al*. Immune immunomodulation in coronavirus disease 2019 (COVID-19): strategic considerations for personalized therapeutic intervention. *Clin Infect Dis*. Epub ahead of print 1 July 2020. DOI: 10.1093/cid/ciaa904.
5. Rajasingham R, Smith RM, Park BJ, *et al*. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet Infect Dis* 2017; 17: 873–881.
6. Chamilos G, Lionakis MS and Kontoyiannis DP. Call for action: invasive fungal infections associated with ibrutinib and other small molecule kinase inhibitors targeting immune signaling pathways. *Clin Infect Dis* 2018; 66: 140–148.
7. George IA, Spec A, Powderly WG, *et al*. Comparative epidemiology and outcomes of human immunodeficiency virus (HIV), non-HIV non-transplant, and solid organ transplant associated cryptococcosis: a population-based study. *Clin Infect Dis* 2018; 66: 608–611.
8. Marr KA, Sun Y, Spec A, *et al*. A multicenter, longitudinal cohort study of cryptococcosis in human immunodeficiency virus-negative people in the United States. *Clin Infect Dis* 2020; 70: 252–261.
9. Pappas PG, Perfect JR, Cloud GA, *et al*. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. *Clin Infect Dis* 2001; 33: 690–699.
10. Yoon HA, Felsen U, Wang T, *et al*. Cryptococcus neoformans infection in Human Immunodeficiency Virus (HIV)-infected and HIV-uninfected patients at an inner-city tertiary care hospital in the Bronx. *Med Mycol* 2020; 58: 434–443.
11. Rodriguez-Morales AJ, Sah R, Millan-Oñate J, *et al*. COVID-19 associated mucormycosis: the urgent need to reconsider the indiscriminate use of immunosuppressive drugs. *Ther Adv Infect Dis*. Epub ahead of print 18 June 2021. DOI: 10.1177/20499361211027065.
12. Salehi M, Ahmadikia K, Badali H, *et al*. Opportunistic fungal infections in the epidemic area of COVID-19: a clinical and diagnostic perspective from Iran. *Mycopathologia* 2020; 185: 607–611.
13. Marr KA, Platt A, Tornheim JA, *et al*. Aspergillosis complicating severe coronavirus disease. *Emerg Infect Dis* 2021; 27: 18–25.
14. Garg D, Muthu V, Sehgal IS, *et al*. Coronavirus disease (Covid-19) associated mucormycosis (CAM): case report and systematic review of literature. *Mycopathologia* 2021; 186: 289–298.
15. Koehler P, Bassetti M, Chakrabarti A, *et al*. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. *Lancet Infect Dis* 2021; 21: e149–e162.
16. Elsegeiny W, Marr KA and Williamson PR. Immunology of cryptococcal infections: developing a rational approach to patient therapy. *Front Immunol* 2018; 9: 651.
17. Ristow LC and Davis JM. The granuloma in cryptococcal disease. *PLoS Pathog* 2021; 17: e1009342.
18. Hevey MA, George IA, Raval K, *et al*. Presentation and mortality of cryptococcal infection varies by predisposing illness: a retrospective cohort study. *Am J Med* 2019; 132: 977–983.e1.
19. Bratton EW, El Husseini N, Chastain CA, *et al*. Comparison and temporal trends of three groups with cryptococcosis: HIV-infected, solid organ transplant, and HIV-negative/non-transplant. *PLoS ONE* 2012; 7: e43582.
20. Schmalzle SA, Buchwald UK, Gilliam BL, *et al*. Cryptococcus neoformans infection in malignancy. *Mycoses* 2016; 59: 542–552.
21. Goldman DL, Lee SC, Mednick AJ, *et al*. Persistent cryptococcus neoformans pulmonary infection in the rat is associated with intracellular parasitism, decreased inducible nitric oxide synthase expression, and altered antibody responsiveness to cryptococcal polysaccharide. *Infect Immun* 2000; 68: 832–838.

22. Cafardi J, Haas D, Lamarre T, *et al*. Opportunistic fungal infection associated with COVID-19. *Open Forum Infect Dis* 2021; 8: ofab016.

23. Ghanem H and Sivasubramanian G. Cryptococcus neoformans meningoencephalitis in an immunocompetent patient after COVID-19 infection. *Case Rep Infect Dis* 2021; 2021: 5597473.

24. Heller HM, Gonzalez RG, Edlow BL, *et al*. Case 40-2020: a 24-year-old man with headache and Covid-19. *N Engl J Med* 2020; 383: 2572–2580.

25. Khatib MY, Ahmed AA, Shaat SB, *et al*. Cryptococcemia in a patient with COVID-19: a case report. *Clin Case Rep* 2021; 9: 853–855.

26. Passarelli VC, Perosa AH, de Souza Luna LK, *et al*. Detected SARS-CoV-2 in ascitic fluid followed by cryptococcemia: a case report. *SN Compr Clin Med* 2020. DOI: 10.1007/s42399-020-00574-9.

27. Thyagarajan RV, Mondy KE and Rose DT. Cryptococcus neoformans blood stream infection in severe COVID-19 pneumonia. *IDCases* 2021; 26: e01274.

28. Woldie IL, Brown IG, Nwadiaro NF, *et al*. Autoimmune hemolytic anemia in a 24-year-old patient with COVID-19 complicated by secondary cryptococcemia and acute necrotizing encephalitis: a case report and review of literature. *J Med Cases* 2020; 11: 362–365.

29. Thota DR, Ray B, Hasan M, *et al*. Cryptococcal meningoencephalitis during convalescence from severe COVID-19 pneumonia. *Neurohospitalist*. Epub ahead of print 3 May 2021. DOI: 10.1177/19418744211009766.

30. Passerini M, Terzi R, Piscaglia M, *et al*. Disseminated cryptococcosis in a patient with metastatic prostate cancer who died in the coronavirus disease 2019 (COVID-19) outbreak. *Cureus* 2020; 12: e8254.

31. 2.Classification and diagnosis of diabetes: standards of medical care in diabetes-2021. *Diabetes Care* 2021; 44: S15–S33.

32. Mfinanga S, Chanda D, Kivuyo SL, *et al*. Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial. *Lancet* 2015; 385: 2173–2182.

33. Ford N, Shubber Z, Jarvis JN, *et al*. CD4 cell count threshold for cryptococcal antigen screening of HIV-infected individuals: a systematic review and meta-analysis. *Clin Infect Dis* 2018; 66: S152–S159.

34. Ssekitoleko R, Kamya MR and Reingold AL. Primary prophylaxis for cryptococcal meningitis and impact on mortality in HIV: a systematic review and meta-analysis. *Future Virol* 2013; 8. DOI: 10.2217/fvl.13.71.

35. Hakim J, Musiime V, Szubert AJ, *et al*. Enhanced prophylaxis plus antiretroviral therapy for advanced HIV infection in Africa. *N Engl J Med* 2017; 377: 233–245.

36. Awotiwon AA, Johnson S, Rutherford GW, *et al*. Primary antifungal prophylaxis for cryptococcal disease in HIV-positive people. *Cochrane Database Syst Rev* 2018; 8: Cd004773.

37. Brizendine KD, Baddley JW and Pappas PG. Predictors of mortality and differences in clinical features among patients with cryptococcosis according to immune status. *PLoS ONE* 2013; 8: e60431.

38. Salazar AS, Keller MR, Olsen MA, *et al*. Potential missed opportunities for diagnosis of cryptococcosis and the association with mortality: a cohort study. *EClinicalMedicine* 2020; 27: 100563.

39. Jitmuang A, Panackal AA, Williamson PR, *et al*. Performance of the cryptococcal antigen lateral flow assay in non-HIV-related cryptococcosis. *J Clin Microbiol* 2016; 54: 460–463.

40. Henao-Martínez AF, Chastain DB and Franco-Paredes C. Treatment of cryptococcosis in non-HIV immunocompromised patients. *Curr Opin Infect Dis* 2018; 31: 278–285.

41. Perfect JR, Dismukes WE, Dromer F, *et al*. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of America. *Clin Infect Dis* 2010; 50: 291–322.

42. Hamill RJ, Sobel JD, El-Sadr W, *et al*. Comparison of 2 doses of liposomal amphotericin B and conventional amphotericin B deoxycholate for treatment of AIDS-associated acute cryptococcal meningitis: a randomized, double-blind clinical trial of efficacy and safety. *Clin Infect Dis* 2010; 51: 225–232.

43. Merry M and Boulware DR. Cryptococcal meningitis treatment strategies affected by the explosive cost of flucytosine in the United States: a cost-effectiveness analysis. *Clin Infect Dis* 2016; 62: 1564–1568.

44. Kneale M, Bartholomew JS, Davies E, *et al*. Global access to antifungal therapy and its variable cost. *J Antimicrob Chemother* 2016; 71: 3599–3606.