IDCases 27 (2022) e01380

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

Case report

Fatal case of disseminated cryptococcal infection and meningoencephalitis in the setting of prolonged glucocorticoid use in a Covid-19 positive patient

Krupa Karnik[b], Yuexiu Wu[b], Samantha Ruddy[b], Bladimir Quijano-Rondan[b], Carl Urban[a,b,c,*], Glenn Turett[a,b], Lok Yung[a,b], Nishant Prasad[a,b], James Yoon[a,b], Sorana Segal-Maurer[a,b,c]

[a] Department of Medicine, NewYork-Presbyterian Queens, 56–45 Main St, Flushing, New York 11355, United States
[b] The Dr. James J. Rahal, Jr. Division of Infectious Diseases, NewYork-Presbyterian Queens, 56–45 Main St, Flushing, New York 11355, United States
[c] Weill Cornell Medicine, Cornell University, New York, New York 10065, United States

ARTICLE INFO

Article history:
Received 30 September 2021
Received in revised form 5 January 2022
Accepted 5 January 2022
Available online xxxx

Keywords:
Cryptococcus neoformans
COVID-19
Glucocorticoids
Fungemia
Meningoencephalitis

ABSTRACT

Based on the RECOVERY trial, glucocorticoids have become the mainstay of treatment for COVID-19, thus increasing the risk of opportunistic infections. We report a case of disseminated *Cryptococcus neoformans* with documented meningoencephalitis in a patient with severe COVID-19 in the setting of prolonged glucocorticoid administration with poor outcome likely due to adrenal involvement.

Introduction

Although glucocorticoids are helpful in the setting of septic shock, their use increases risk of new or reactivated infections including mycobacteria, fungi, viruses, and parasites [1]. Recently, dexamethasone has become instrumental for severe COVID-19 infections [2]. Cases of mucormycosis, aspergillosis, and *Pneumocystis jiroveci* pneumonia have been reported among patients with COVID-19 receiving prolonged glucocorticoid courses [3–5]. In addition, it should be noted that steroids (and not only exclusively glucocorticoids) are used in the treatment of refractory septic shock when vasopressors and inotropes are ineffective. We describe a case of disseminated *Cryptococcus neoformans* with meningoencephalitis, in a patient with severe COVID-19 in the setting of prolonged glucocorticoids administration with poor outcome likely due to adrenal involvement.

Case report

A 57 year old male with a past medical history of hypertension presented to the emergency room in January, 2021 with complaints of fever, chills, shortness of breath, malaise, and poor appetite for nine days. On physical examination, he had an oxygen saturation of 64% on room air and bilateral crackles. Leukocyte count was within normal range (8.17 K/μL, 86.6% neutrophils) and procalcitonin was elevated at 0.41 ng/mL. Nasopharyngeal swab for influenza, blood cultures, *Legionella* urine antigen, *Legionella* sputum culture, streptococcal urine antigen, and urinalysis were all negative; nasopharyngeal swab was positive for SARS-CoV-2. Sputum Gram stain revealed 10–25 WBCs/LPF, and sputum culture was positive for methicillin susceptible *Staphylococcus aureus* and oropharyngeal microbiota. Chest radiograph revealed bilateral patchy airspace disease and increased interstitial opacities consistent with severe COVID-19 disease. He was administered oral dexamethasone 6 mg daily for 10 days, intravenous remdesivir for 5 days, and oxygen support via non-rebreather mask. In addition, he received intravenous azithromycin 500 mg daily and ceftriaxone 1 g daily to cover the *Staphylococcus aureus* found in sputum and other possible community acquired pneumonia organisms including atypical organisms. Due to persistent hypoxia and inability to wean the patient

* Corresponding author at: The Dr. James J. Rahal, Jr. Division of Infectious Diseases, NewYork-Presbyterian Queens, 56–45 Main St, Flushing, New York 11355, United States.
E-mail address: cmurban@nyp.org (C. Urban).

https://doi.org/10.1016/j.idcr.2022.e01380
2214-2509/

from the non-rebreather mask, steroids were continued beyond day 10. His clinical condition continued to worsen and on day 14 he was found to be cyanotic and dyspneic requiring endotracheal intubation. Chest radiograph demonstrated progression of infiltrates. Broader antimicrobial coverage was initiated with vancomycin and meropenem for empiric treatment of possible hospital-acquired pneumonia and oral dexamethasone was changed to intravenous methylprednisolone 40 mg three times per day. His subsequent hospital course was complicated by worsening renal function requiring continuous renal replacement therapy accompanied by periods of hypotension. He was noted to have diarrhea on day 33 and diagnosed with *Candida* colitis and received nystatin 1 million units 6 times a day via gastrostomy tube. On day 36, the patient became hypoxic and hypotensive and methylprednisolone was changed to intravenous hydrocortisone 100 mg three times a day (midodrine 10 mg three times a day was added). Blood cultures revealed yeast, and micafungin 100 mg every 24 hours was administered for presumptive *Candida* fungemia and antibiotics were discontinued. Once the yeast was identified as *Cryptococcus neoformans,* lumbar puncture was performed: opening pressure was 28 cm H_2O, and cerebrospinal fluid revealed 185 WBCs/μL (86% neutrophils), 65,000 RBCs/μL, a positive India ink, and subsequent culture confirmed *Cryptococcus neoformans*. Cerebrospinal fluid cryptococcal antigen was positive with a titer of 1:256. HIV 1/2/P24 combination screen and HIV-1 Real Time PCR test (Hologic Aptima HIV-1 Quant Dx assay™) were both negative. Micafungin was discontinued, and intravenous liposomal amphotericin B 400 mg daily and oral flucytosine 2000 mg via gastrostomy tube every other day (based on renal function) were administered. Lumbar puncture was repeated 10 days later, and daily or every other day until opening pressures were less than 20 cm H_2O, which was attained on the sixth repeat lumbar puncture. He had a prolonged and complicated hospital course and was noted to have new skin nodules on day 40 suspicious for disseminated cryptococcal infection. He died during a hypotensive episode on day 42 of his hospitalization.

Discussion

Cryptococcus neoformans is a fungus found in soil and bird droppings. Human infection occurs following inhalation of basidiospores. *Cryptococcus* may be cleared, become latent, cause local pulmonary infection, or become disseminated to other parts of the body, typically the central nervous system. Immunosuppression due to numerous underlying risk factors has been associated with risk for reactivation and dissemination [6].

Viral replication and host response are responsible for COVID-19 associated acute respiratory distress syndrome (ARDS). Early SARS-CoV-2 infection induces a proinflammatory chemokine production including IL-1B, IL-6, TNF, and IL1RA leading to recruitment of T lymphocytes, monocytes and neutrophils. Over-production or dysfunctional response in some patients (“cytokine storm”) is manifested by pulmonary edema, ARDS, multi-organ failure, and hypercoagulability [7]. Steroids' anti-inflammatory properties are due to multiple signal transduction pathways which activate anti-inflammatory genes, increasing degradation of certain mRNA encoding inflammatory proteins [8]. In the early stages of COVID-19, glucocorticoids reduce systemic inflammation, exudative fluid in the lung tissue, phagocytosis, capillary dilation and alveolar damage, improving oxygen requirements, and decreases risk of respiratory failure [9]. Later, glucocorticoids can inhibit excessive fibroblast proliferation, preventing fibrosis and minimizing organ damage [10]. Based on the RECOVERY trial, the Infectious Diseases Society of America recommended dexamethasone 6 mg IV or PO (or equivalent daily doses of methylprednisolone of 32 mg or prednisone of 40 mg) for 10 days (or until discharge if earlier) for hospitalized patients with either severe COVID-19 (SpO_2 less than or equal to 94% on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal mechanical oxygenation) or for end organ dysfunction (e.g. acute respiratory distress syndrome) [11].

The same glucocorticoid pathways reducing inflammation lead to suppression of the microbicidal function of activated macrophages (i.e., suppression of neutrophil adhesion to endothelial cells and impairment of lysosomal enzyme release, respiratory burst, and chemotaxis). Inhibition of T-cell activation leads to negative impact on dendritic cell maturation and function leading to increased risk of new or reactivated opportunistic infections [1]. In addition, impact on interferon gamma production is a further contributing factor [12].

Our patient received the current standard of care for hospitalized COVID-19 with the exception of prolonged steroid use. A systematic review based on case reports demonstrated an increased incidence of mucormycosis in patients with COVID-19 in India in patients with diabetes who were treated with steroids well beyond the recommended 10 day duration [13]. A literature review article based on case reports demonstrated *Aspergillus* co-infection in patients with COVID-19 treated with steroids despite not having traditional risk factors for *Aspergillus* [3]. Also, there are reports of oral candidiasis in patients with COVID-19 who used removable dentures with prosthetic stomatitis related to antibiotics, lack of dental hygiene, and steroid use in intubated patients in the intensive care unit [14]. Recently, a patient with cryptococcemia was presented in the setting of multiple courses of methylprednisolone and hydrocortisone therapy of unknown duration for COVID-19 [15]. Unlike that case, our patient had additional documented central nervous system involvement. There have been other recent cases of cryptococcal meningoencephalitis during convalescent stages of COVID-19 however our patient reactivated cryptococcal infection during the same hospitalization period with a fatal outcome [16,17]. Our patient exhibited multiple episodes of hypotension in spite of a prior history of hypertension. A CT scan demonstrated adrenal gland heterogeneity, raising the possibility of the effect of either *Cryptococcus neoformans* or SARS-CoV-2. Case reports demonstrate a strong association of COVID-19 and adrenal insufficiency, possibly due to molecular resemblance of the antibodies produced against the viral protein to host ACTH leading to decreased ACTH ability to stimulate the adrenal gland to produce stress level corticosteroids [18,19]. We believe that disseminated cryptococcal infection and probable adrenal involvement were major contributing factors for the patient's ultimate demise.

Our aim in reporting this case is to alert clinicians to the possibility of re-activation of latent infections with prolonged glucocorticoid use in COVID-19 patients, including *Cryptococcus neoformans.*

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

All authors have agreed for authorship, read and approved the manuscript, and given consent for publication of the manuscript.

Consent

Consent to publish was not obtained since the case report does not contain any personal identifiers.

CRediT authorship contribution statement

Krupa Karnik, Data curation, Writing – original draft preparation. **Yuexiu Wu**: Writing – review & editing of the manuscript.

Samantha Ruddy: Writing – review & editing of the manuscript. **Bladimir Quijano-Rondan**: Writing – review & editing of the manuscript. **Carl Urban**: Conceptualization, Supervision, Editing and review of the original draft preparation. **Glenn Turett**: Writing – review & editing of the manuscript. **Lok Yung**: Writing – review & editing of the manuscript. **Nishant Prasad**: Writing – review & editing of the manuscript. **James Yoon**: Supervision, Editing and review of the original draft preparation. **Sorana Segal-Maurer**: Supervision, Editing and review of the manuscript.

Declaration of Competing Interest

All authors report no potential conflicts of interest.

References

[1] Youssef J, Novosad SA, Winthrop KL. Infection risk and safety of corticosteroid use. Rheum Dis Clin North Am 2016;42(1):157–76. https://doi.org/10.1016/j.rdc.2015.08.004

[2] RECOVERY Collaborative G, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384(8):693–704. https://doi.org/10.1056/NEJMoa2021436

[3] Lai CC, Yu WL. COVID-19 associated with pulmonary aspergillosis: a literature review. J Microbiol Immunol Infect 2021;54(1):46–53. https://doi.org/10.1016/j.jmii.2020.09.004

[4] Choy CY, Wong CS. It's not all about COVID-19: pneumocystis pneumonia in the era of a respiratory outbreak. J Int AIDS Soc 2020;23(6):e25533https://doi.org/10.1002/jia2.25533

[5] Pal R, Singh B, Bhadada SK, Banerjee M, Bhogal RS, Hage N, et al. COVID-19-associated mucormycosis: An updated systematic review of literature [published online ahead of print, 2021 Jun 16]. Mycoses 2021;64:1452–9. https://doi.org/10.1111/myc.13338

[6] Li SS, Mody CH. Cryptococcus. Proc Am Thorac Soc 2010;7(3):186–96. https://doi.org/10.1513/pats.200907-063AL

[7] García LF. Immune response, inflammation, and the clinical spectrum of COVID-19. Front Immunol 2020;11:1441. https://doi.org/10.3389/fimmu.2020.01441

[8] Barnes PJ. How corticosteroids control inflammation: Quintiles Prize Lecture 2005. Br J Pharm 2006;148(3):245–54. https://doi.org/10.1038/sj.bjp.0706736

[9] Singh AK, Majumdar S, Singh R, Misra A. Role of corticosteroid in the management of COVID-19: A systemic review and a clinician's perspective. Diabetes Metab Syndr 2020;14(5):971–8. https://doi.org/10.1016/j.dsx.2020.06.054

[10] Ahmed MH, Hassan A. Dexamethasone for the treatment of coronavirus disease (COVID-19): a review [published online ahead of print, 2020 Oct 31]. SN Compr Clin Med 2020:1–10. https://doi.org/10.1007/s42399-020-00610-8

[11] Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, Edwards KM, Gandhi R, Muller WJ, O'Horo JC, Shoham S, Murad MH, Mustafa RA, Sultan S, Falck-Ytter Y. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19 [published online ahead of print, 2020 Apr 27]. Clin Infect Dis 2020:ciaa478. https://doi.org/10.1093/cid/ciaa478

[12] Cesario TC, Slater L, Poo WJ, Spindler B, Walter B, Gorse G, Carandang G. The effect of hydrocortisone on the production of gamma-interferon and other lymphokines by human peripheral blood mononuclear cells. J Interferon Res 1986;6(4):337–47. https://doi.org/10.1089/jir.1986.6.337

[13] Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr 2021;15(4):102146https://doi.org/10.1016/j.dsx.2021.05.019

[14] Jerônimo LS, Esteves Lima RP, Suzuki TYU, Discacciati JAC, Bhering CLB. Oral candidiasis and COVID-19 in users of removable dentures: is special oral care needed? [published online ahead of print, 2021 Apr 14]. Gerontology 2021:1–6. https://doi.org/10.1159/000515214

[15] Khatib MY, Ahmed AA, Shaat SB, Mohamed AS, Nashwan AJ. Cryptococcemia in a patient with COVID-19: A case report. Clin Case Rep 2020;9(2):853–5. https://doi.org/10.1002/ccr3.3668

[16] Thota DR, Ray B, Hasan M, Sharma K. Cryptococcal meningoencephalitis during convalescence from severe COVID-19 pneumonia. Neurohospitalist 2021;12:1–4. https://doi.org/10.1177/19418744211009766

[17] Ghanem H, Sivasubramanian G. *Cryptococcus neoformans* meningoencephalitis in an immunocompetent patient after COVID-19 infection. Case Rep Infect Dis 2021;2021:5597473https://doi.org/10.1155/2021/5597473

[18] Hashim M, Athar S, Gaba WH. New onset adrenal insufficiency in a patient with COVID-19. BMJ Case Rep 2021;14(1):e237690https://doi.org/10.1136/bcr-2020-237690

[19] Wheatland R. Molecular mimicry of ACTH in SARS - implications for corticosteroid treatment and prophylaxis. Med Hyp 2004;63(5):855–62. https://doi.org/10.1016/j.mehy.2004.04.009