Case report

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

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A R T I C L E   I N F O

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
Fungi
Meningoencephalitis

A B S T R A C T

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/LP, 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...
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. His subsequent hospital course was complicated by worsening renal function requiring continuous renal replacement therapy accompanied by episodes 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 yeasts, 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 H₂O, 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 fluconazole 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 H₂O, 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 badiospores. 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-1β, 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 (SpO₂ 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 cryptococemia 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. Yuxiu 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.

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