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Case Report

Disseminated Cryptococcosis Complicating Severe SARS-CoV-2 Infection

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Abstract: Opportunistic invasive fungal infections (IFI) have been described in severe SARS-CoV-2 infection. COVID-19-related cytokine storm, immune dysregulation and lymphopenia may increase IFI susceptibility in comorbid patients. We described the case of a 64-year-old man with respiratory failure due to SARS-CoV-2 infection complicated with disseminated cryptococcosis. We analyzed the role played by the SARS-CoV-2-associated lymphopenia and the cumulative risk factors that lead to secondary infection by *Cryptococcus neoformans*, and its part in the dysregulation of the immunity response.

Keywords: cryptococcus; SARS-CoV-2; lymphopenia

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1. Introduction

Opportunistic invasive fungal infection in the setting of severe viral respiratory disease is a well-known condition described in the context of influenza, RSV, and now, COVID-19 [1]. The cytokine storm and immune dysregulation, leading to T-cell exhaustion, observed in COVID-19, may play a role increasing susceptibility to fungal infection development [1]. Specifically, *Cryptococcus* spp. is a saprophytic yeast typically found in soil, on decaying wood, in tree hollows, or in bird droppings [2]. *Cryptococcus* is a constituent of the human microbiota, remaining dormant until the loss of host immunity [2]. Two species complexes, *Cryptococcus neoformans* and *Cryptococcus gattii*, are mainly responsible for human disease [2]. Cryptococcosis in the HIV-negative population is still a limited field of study, and limited data are available in this population [2]. Solid organ transplantation, autoimmune diseases (i.e., sarcoidosis, systemic lupus erythematosus), onco-haematological diseases, prolonged steroid therapy, and cirrhosis are conditions of functional immunosuppression known to increase the risk of *Cryptococcus* spp. infection [2–4].

2. Case Presentation

In April 2021, a 64-year-old Romanian man with a history of obesity (BMI = 35 kg/m^2), heavy drinking, esotoxic cirrhosis, insulin-dependent decompensated diabetes mellitus, previous acute myocardial infarction, atrial fibrillation, and chronic kidney disease (stage 3B), was admitted for acute respiratory distress with confirmed SARS-CoV-2 infection. The patient required non-invasive ventilation and was admitted in our infectious diseases ward. Dexamethasone (6 mg q24h, i.v.) and amoxicillin/clavulanate (2.2 g q8h, i.v.) were started on the same day. Tocilizumab or remdesivir were not administered for major contraindications. After the improvement of his clinical condition, his kidney and hepatic impairment worsened (Table 1) with anasarca and hepatic encephalopathy. In addition, the respiratory exchange ratio had deteriorated with increased respiratory support. Antimicrobial therapy was switched to intravenous piperacillin/tazobactam (2.5 g q6h, i.v.)

and tigecycline (50 mg q12h, i.v.) for a suspected hospital-acquired pneumonia and/or spontaneous bacterial peritonitis with no benefit, and the steroid was given at 8 mg/day. Radiological tests showed interstitial pneumonia, stable from admission, without signs of a possible foci of superinfections.

Table 1. Blood cells count and main laboratory values between admission (Day 0) to discharge from Intensive Care Unit (Day 33).

	Day 0	Day 3	Day 7	Day 14	Day 21	Day 28	Day 33
Total WBC count ($\times 10^9$/L)	7.6	10.8	16.8	9.4	16.8	13.1	9.0
Lymphocytes (absolute count)	510	580	360	420	280	220	130
Monocytes (absolute count)	440	740	780	300	330	320	80
Neutrophils (absolute count)	6670	9480	15, 690	15, 430	16, 210	12, 540	8570
Platelets ($\times 10^9$/L)	218	218	146	76	47	47	49
D-dimer (mcg/mL)	2.99	1.29	1.24	1.13	1.22	1.43	2.91
LDH (U/L)	806	736	802	816	966	823	599
GPT/GOT (U/L)	121/131	76/144	70/129	83/111	85/111	93/110	113/101
Serum creatinine (mg/dL)	1.96	1.63	1.96	2.47	2.99	3.33	1.21
BUN(mg/dL)	89	NA	NA	207	NA	304	82
CRP (mg/L)	132	28	16	25	97	123	116
PCT (ng/mL)	0.63	0.95	0.82	1.27	1.86	1.67	1.95
IL-6 (pg/mL)	6.1	8.5	6.5	NA	NA	166	174
Ferritin (ng/mL)	401	311	NA	232	NA	NA	NA

Abbreviations: WBC, white blood cell; LDH, lactate dehydrogenases; GOT, glutamyl oxaloacetic transaminase GPT, glutamyl pyruvic transaminase; BUN, blood urea nitrogen CRP, C-reactive protein; PCT, procalcitonin; IL-6, interleuchin-6, NA, Not Available.

The patient was transferred to the Intensive Care Unit due to the worsening of his general condition. On day 21 after admission, blood culture became positive for *Cryptococcus neoformans* (Figure 1), for which he was started on liposomial amphotericin B (3 mg/kg, 300 mg q24h, i.v.) plus isavuconazole. The diagnosis of disseminated cryptococcosis in the COVID-19, HIV-negative, high-comorbidity patient was made, with no signs of neurological involvement. The diagnosis was confirmed with positive qualitative serum antigen on the latex agglutination system (CALAS ®—Meridian Bioscience, Cincinnati, OH, USA), and a biochemical characterization of cryptococcal subspecies was performed with VITEK® 2 (bioMérieux). No lumbar tap or bronchoalveolar lavage to rule out the central nervous system and pulmonary involvement had been performed, due to the patient's critical condition and rapid evolution. Unfortunately, the outcome was poor, and the patient died five days after blood isolation of *C. neoformans*.

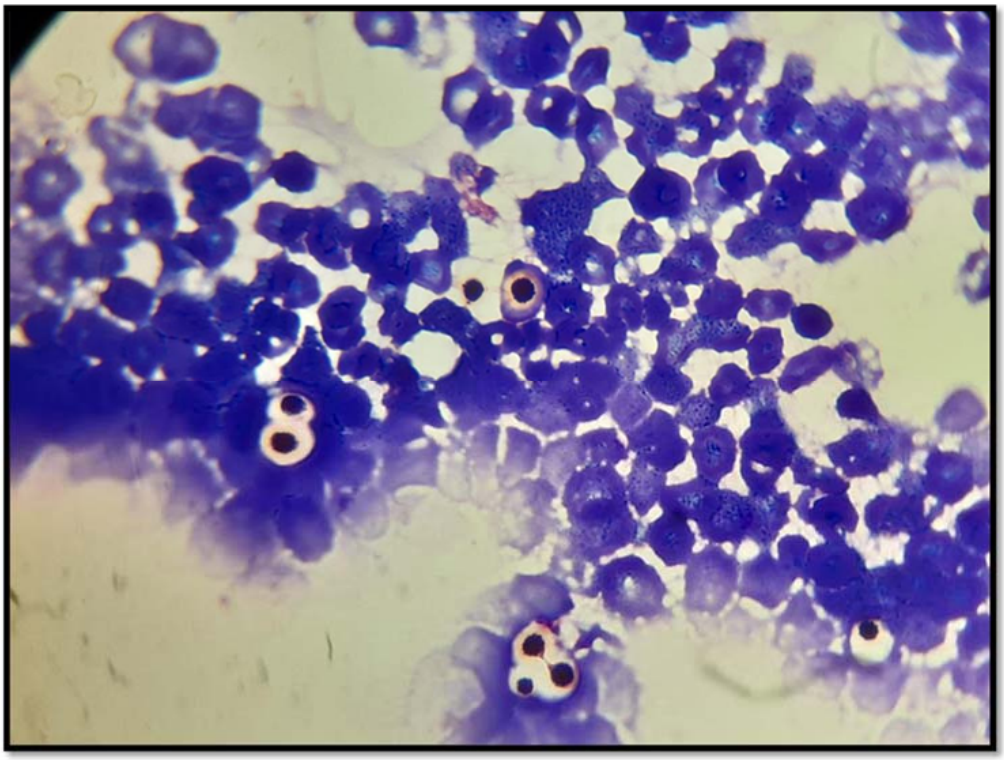

Figure 1. *C. neoformans* from blood culture (periodic acid Schiff positive stain).

3. Discussion

In our patient, decompensated esotoxic cirrhosis, diabetes mellitus, critical illness and prolonged steroid therapy could be involved in disseminated cryptococcosis.

COVID-19 patients are at risk of bacterial and fungal superinfections, although cryptococcosis is still a rare infective complication [5]. In the last months of the pandemic, we have learned the role of lymphopenia as a diagnostic and prognostic factor in the COVID-19-suffering population [5].

We therefore speculate that prolonged lymphopenia due to severe SARS-CoV-2 infection may be another important precipitating factor.

Mechanisms of CD4+ T cell depletion in SARS-CoV-2 infections are not completely understood. T cell depletion in the peripheral blood in COVID-19 patients may resemble the lymphopenia seen in advanced HIV-1 infections [6]. The CD4+ T cell count is significantly lower in severe COVID-19 cases than in mild and moderate cases, indicating that CD4+ T cell reduction is associated with disease severity [6].

Moreover, Cryptococcosis may also be involved in the downregulation of white blood cell response to infection.

The *C. neoformans* capsule plays an important role in virulence and pathogenicity in cryptococcal infections. The capsule is composed of glucuronoxylomannan (GXM), galactoxylomannan (GalXM) and mannoprotein (MP), which are important virulence factors [7]. GXM can either be bound to the fungal cell wall or shed as soluble exopolysaccharide, and can persist in monocytes/macrophages and downregulate T cell responses, by interfering with the antigen-presentation process [7,8]. Moreover, GalXM has recently been found to suppress T cell proliferation and function, and induce T cell apoptosis [7,8].

On day 28, we noted a peak of IL-6 at the cryptococcemia diagnosis. IL-6 may have been lower the previous day because of the high dosage of steroids employed in respiratory failure in SARS-CoV-2 infections [9].

Delfino et al. and Retini et al. noted that cryptococcal microbial products, such as GXM and GalXM, can induce IL-6 [10,11]. Furthermore, an analysis by Delfino et al. showed that monocytes are predominantly responsible for IL-6 release in response to *C. neoformans*

components, followed, to a lesser extent, by neutrophils [10,11]. These two populations were well represented in our patient at the disseminated cryptococcosis diagnosis.

Cryptococcosis is a rare complication in COVID-19, but in our hypothesis, SARS-CoV-2-related lymphopenia, added to immunosuppressant therapies, may play an important role in the development of cyptococcal-disseminated infection, due to a dysregulated immune system in those patients already at risk of bacterial and fungal superinfections. Increased IL-6 at the time of diagnosis of *Cryptococcus* spp. superinfection seems to confirm the preliminary data of immune response against this saprophytic yeast.

Of note, twelve previous cases of cryptococcosis in COVID-19 have been reported in the literature [12–24]: in seven of them [12,14,15,17,19–21], as in our patient, blood stream infections were described; all but two (71%) had a poor outcome. In three of them, *C. neoformans* was isolated in CSF and in the other 2, on BAL culture. The overall mortality was 58%.

Of those reports, 67% (8/12) had previous immunosuppressive clinical conditions; specifically, 5 out of 12 had diabetes mellitus, 2 were receiving chronic immunosuppressive therapies, and one had a new HIV infection diagnosis. In four cases, no traditional risk factors for cryptococcosis were identified. During the hospitalization, 92% of them (11/12) received high doses of corticosteroid [12–24].

Moreover, Messina et al. described five cases of cryptococcosis in advanced HIV-positive COVID-19 patients, with median CD4+ counts of 13 cell/uL: in those patients, the role of SARS-CoV-2 infection in the pathogenesis was not completely clear, and severe immunodepression is a major confounding factor [25].

Cryptococcosis in immunocompetent patients has been widely described in the recent literature [26–33], with several cases of disseminated *Cryptococcus* spp. infections [28], or localized in the central nervous system [29,30], lungs [31,32] and skin [33]. Recent discoveries support the idea that both *C. neoformans* and *C. gattii* use specialized mechanisms to adapt to the host environment, and manage to escape the immune system reaction [26,27].

There is still limited knowledge of the pathogenesis cryptococcosis in SARS-CoV-2 infection, due to spare data and case descriptions. The differing burden of immune dysregulation and the cumulative risk factors leading to secondary infections by opportunistic agents, like *Cryptococcus* spp., are yet to be understood.

4. Conclusions

In our case report, we present a possible correlation between COVID-19-induced lymphopenia and cryptococcal-disseminated infection in a comorbid patient. More studies are required to better understand the role played by the virus, the characteristics of the host with the burden, and the type of immunosuppression in invasive fungal infections.

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Data Availability Statement: Data are available upon request to the author.

Conflicts of Interest: The authors declare no conflict of interest.

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