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Coronavirus Pandemic

Neurosyphilis with concomitant cryptococcal meningitis in a patient with AIDS after COVID-19: a case report

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Abstract

Background: The common infection agents causing meningitis in patients with human immunodeficiency virus (HIV) include *Cryptococcus neoformans* and *Treponema pallidum*. Furthermore, there is an elevated risk of meningitis in patients with HIV concomitantly infected with SARS-CoV-2.

Case presentation: A 38-year-old male presented with headache and dizziness. After hospitalization, polymerase chain reaction test for SARS-CoV-2 with a nasopharyngeal swab was positive, and lumbar puncture revealed neurosyphilis with concomitant cryptococcal meningitis. He underwent nirmatrelvir-ritonavir, penicillin, antifungal and antiretroviral treatment. The patient had no other neurological symptoms and was stable during the 6-month follow-up period.

Conclusions: During the COVID-19 pandemic patients with HIV, particularly those who did not undergo antiretroviral therapy are at higher risk for severe infections, including central nervous system complications, due to their compromised immune systems.

Key words: COVID-19; human immunodeficiency virus; central nervous system infection; cryptococcal meningitis; neurosyphilis.

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Introduction

Infections of the central nervous system, often the terminal events in patients with HIV, are fatal. *Cryptococcus neoformans* is a leading cause of meningitis in patients living with HIV. Syphilis is common in patients with HIV, given shared routes of transmission, and has a more rapid progression to neurosyphilis. Co-infection of the central nervous system caused by these pathogens is rare [1,2].

In a person with HIV, particularly those not receiving antiretroviral therapy, SARS-CoV-2 infection may elevate the prevalence of opportunistic infections [3]. Associations between COVID-19 and the onset of cryptococcosis, pneumocystis pneumonia, tuberculosis, and syphilis have been reported [4-6]. Furthermore, the intracranial cytokine storm/infiltration caused by SARS-CoV-2 could attack the endothelial cells leading to blood-brain barrier (BBB) damage which facilitates the pathogen into in brain [7].

In this context, we report a case of meningitis caused by *Cryptococcus neoformans* and *Treponema pallidum* subsequent to a SARS-CoV-2 infection.

Case presentation

A 38-year-old male was admitted to The Huzhou Central Hospital because of headache and dizziness. Two weeks before this admission, headache and dizziness developed. The symptoms did not abate after the patient took flunarizine. One day before this admission, the patient had nausea. On admission, the temperature was 36.5°C, the blood pressure 126/71 mmHg, the heart rate 72 beats per minute, and the respiratory rate 19 breaths per minute. Auscultation of the lungs revealed normal breath sounds. The result of the neck resistance test was negative. The patient had a history of AIDS without antiretroviral therapy for five years. Three months before the current admission, an antigen testing of a nasopharyngeal swab for SARS-Cov-2 was positive.

The patient was admitted to our infectious medicine department. On admission day, his white blood cells were 5.4 × 10^9/L (reference range, 3.5-9.5 × 10^9/L), with neutrophils at 3.9 × 10^9/L (reference range, 1.8-6.3 × 10^9/L). The C-reactive protein was 6.9 mg/L (reference range, < 10.0 mg/L). The results of liver and

kidney function tests were normal. SARS-CoV-2 nucleic acid tests (ORF1ab and N genes) of the nasopharyngeal swab samples were positive by qualitative real-time reverse-transcriptase-polymerase-chain-reaction (qRT-PCR) (Shanghai ZJ Bio-Tech Co, Ltd, Shanghai, China). Serologic test for the *T. pallidum* passive particle agglutination (TPPA) (Serodia, Tokyo, Japan) and rapid plasma regain (RPR) (InTec Inc, Xiamen, China) was positive, and the titer of RPR was 1:8. Cryptococcal antigen test for blood samples using the CrAg Lateral Flow Assay (LFA) (Dynamiker Biotechnology Co., Ltd., China) was positive. The patient's CD4 count was critically low at 36 cells/uL. Two days after admission, an examination of the head MRI revealed normal findings. Following this assessment, a lumbar puncture was performed and revealed an elevated cerebrospinal fluid (CSF) opening pressure (> 30 cm H2O). CSF analysis revealed high cell count (6 cells/uL), high protein (0.905 g/L), and low glucose (1.72 mmol/L). Positive results of *Cryptococcus* India ink staining and culture of *Cryptococcus* were obtained from the CSF sample. The *Cryptococcus* culture was grown on Sabouraud dextrose agar. Antifungal susceptibility test of the culture of CSF was performed using the broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI), and results were interpreted based on the breakpoints established by CLSI. Minimum inhibitory concentrations of antifungal agents and detailed results of the susceptibility testing are shown in Table 1. In addition, The CSF-TPPA (Serodia, Tokyo, Japan) test was positive as was the CSF-RPR (InTec Inc, Xiamen, China) test with a titer of 1:1.

The patient received a five-day course of nirmatrelvir-ritonavir for COVID-19 and a two-week high-dose Penicillin G (18-24 million units per day) treatment for neurosyphilis, followed by thrice-weekly 2.4 million units benzathine penicillin. Concurrently, he was treated for cryptococcal meningitis with intravenous amphotericin B deoxycholate (0.5 mg/kg/day) and 600 mg/day of fluconazole for two weeks, followed by an eight-week consolidation phase with oral fluconazole (600 mg/day) then maintenance therapy (fluconazole 200 mg/day). Antiretroviral therapy for HIV with bictegravir-emtricitabine-tenofovir alafenamide was commenced two weeks after starting the antifungal treatment. The patient was discharged after a stay of 24 days in the hospital. At a 6-month follow-up, the patient's condition had stabilized.

Table 1. Antimicrobial susceptibility analysis of the strain of *Cryptococcus neoformans* isolated from CSF sample.

Antibiotics agent	MIC (mg/L)	Susceptibility category
Voriconazole	≤ 0.006	S
Fluconazole	≤ 1	S
Amphotericin B	≤ 1	S
Itraconazole	≤ 1	S
5-Fluorocytosine	≤ 1	S

MIC: minimum inhibitory concentrations; S: susceptible.

Discussion

Opportunistic infections of the central nervous system are a significant complication of HIV-infected individuals, with common causative agents including *Cryptococcus species, Mycobacterium tuberculosis, Toxoplasma gondii,* and *Treponema pallidum*. Cryptococcal meningitis predominantly occurs in HIV-infected patients with a CD4+ T lymphocyte count below 100/uL [8]. The risk of neurosyphilis is higher in patients with low CD4+ T lymphocyte count or in those who are not receiving antiretroviral therapy. Concurrent meningitis attributed to *Cryptococcus* and Syphilis is exceedingly rare, with literature documenting only three co-infection cases, all in HIV-infected patients [9-11]. Both HIV and SARS-CoV-2 can activate the nucleotide-binding domain, leucine-rich repeat-containing protein 3 (NLRP3) inflammasome, precipitating immune imbalances through inflammasome activation [12]. Research has indicated that the novel coronavirus may instigate a cytokine storm, targeting endothelial cells and compromising the blood-brain barrier, consequently elevating the risk of central nervous system infections [13].

Following SARS-CoV-2 infection, patients are susceptible to opportunistic fungal infections. The inflammation and pulmonary parenchymal injury caused by SARS-CoV-2 facilitate fungal invasion of lung tissues. Cryptococcal spores, with potential for several years of latency in human hosts, might be activated under circumstances such as corticosteroid use, immunosuppression, diabetes, or malignancies, leading to invasive cryptococcosis [14]. Corticosteroids, frequently used in COVID-19 treatment, are among the factors contributing to Cryptococcal meningitis. It inhibits lymphocyte proliferation, T-cell activation, and cytokine release, thereby compromising the immune response. Furthermore, SARS-CoV-2 can affect the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, inducing the infected cells resistant to type-I interferons, which increases the risk of opportunistic infections like cryptococcosis [15]. Finally, the lymphopenia attributed to SARS-CoV-2 is

due to its induction of T-cell exhaustion, subsequently resulting in a decreased CD4 cell count, which is intrinsically linked to the elevated risk of cryptococcosis.

The precise impact of SARS-CoV-2 on syphilis has yet to be elucidated. Nevertheless, the period coinciding with the pandemic has witnessed a pronounced increase in syphilis cases. During the early stages of the COVID-19 pandemic, there was a significant reduction in testing for sexually transmitted infections (STIs), including syphilis, due to the reallocation of medical resources to combat SARS-CoV-2. This decrease in testing likely contributed to the underdiagnosis and underreporting of asymptomatic cases. However, as pandemic control measures eased and healthcare resources were reallocated back to STI testing services, there was a return to near-baseline testing levels. This led to the identification of previously undiagnosed cases, contributing to an apparent rise in syphilis incidence, as observed by Josip Begovac *et al.* in Croatia [16], where they reported a 91% increase in the incidence rate of syphilis during the COVID-19 era. Delays in diagnosis and treatment of syphilis can potentially lead to severe complications such as neurosyphilis. During the syphilis eradication process, the count of CD4 T cells in the cerebrospinal fluid, along with the γ-interferon they produce, plays a pivotal role [17]. However, SARS-CoV-2 infection may elevate pro-inflammatory markers such as IL-1, IL-6, and TNF-α, suppress the expression of γ-interferon, and diminish the quantities of both CD4 and CD8 cells, all of which might augment the risk of contracting syphilis [18].

In our case, the classic signs of meningeal irritation are absent on physical examination. Characteristic signs of meningeal inflammation were observed in only 37% of HIV patients with CNS cryptococcosis [19]. The lack of meningeal irritation correlated with the CSF profile. Impaired immune responses, such as lower CSF cell counts, may explain why there were fewer typical presentations.

Conclusions

Although SARS-CoV-2 predominantly compromises the respiratory system, it also affects the immune response. HIV specifically attacks the immune system, especially the CD4 cells. During the COVID-19 pandemic, it is imperative to prioritize individuals with HIV, particularly those who are not receiving antiretroviral therapy, due to their elevated susceptibility to severe central nervous system infections, including potential co-infections.

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Authors' contributions

Yunfei Pan conceived the manuscript and revised the manuscript for publication; Qi Wang drafted the manuscript and revised all versions. All authors read and approved the Manuscript.

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Conflict of interests

No conflict of interests is declared.

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