Clinical challenges of managing advanced AIDS in the tropics: Histoplasmosis, COVID-19, and shigellosis coinfections

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Keywords: COVID-19, HIV, Shigella, Histoplasma, Histoplasmosis
Original Submission: 6 July 2022; **Revised Submission:** 11 July 2022; **Accepted:** 10 August 2022
Article published online: 18 August 2022

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Dear Editor,

Coinfections in HIV-positive patients are common [1]. These coinfections can translate into fatal outcomes, especially for COVID-19 and invasive fungal infections [2,3]. Herein, we report a case of advanced HIV/AIDS complicated by disseminated histoplasmosis and *Shigella flexneri* bacteremia with an incidental COVID-19 infection.

A 33-year-old man from northwest Colombia, with a history of HIV infection since 2001 and poor adherence to ART with zidovudine/lamivudine plus efavirenz, arrived at the emergency department in February 2022 with chills, cough, fevers, night sweats, abdominal pain, and diarrhea of 1-month duration and acute onset dyspnea. Physical examination revealed cachexia (40 kg), hypoxemia (pulse oximetry on room air was 93%), tachycardia (heart rate of 108 bpm), as well as generalized abdominal tenderness, and hepatomegaly. A chest examination revealed bilateral crepitations and wheezes of lower predominance.

Laboratory tests showed moderate anemia (hemoglobin 8.3 g/dL), leukopenia (WBC 3.5 × 103/μL) severe lymphopenia (0.1 × 103/μL), normal platelet count, and elevated inflammation-related biomarkers (LDH 4233 U/L, ferritin 2506 ng/mL, C-reactive protein 185 mg/dL), severe D-dimer elevation (5030 mg/dL), severe hypoalbuminemia (1.86 g/dL) and mild transaminitis. Kidney function was normal. VDRL was nonreactive. IgM anti-hepatitis A virus was negative, also screening for Hepatitis B and C viruses. T-CD4 cell count was 4 cells/mm^3 (0.67%) and the viral load greater than 10, 000, 000 copies/mL ($\log_{10}$ >7). *Pneumocystis jirovecii* direct immunofluorescent antigen was not performed due to a lack of resources.

Chest CT scan demonstrated diffuse tree-in-bud branching opacities, thick septa interstitial lesions, lower lobe upper segment consolidation patches, multiple bronchiectases in the middle and lower left lobes, and centrilobular nodules from mucus plug bronchiectasis (Fig. 1). A nasopharyngeal swab test (RT-PCR) confirmed the presence of SARS-CoV-2. Initially, he was provided supplemental oxygen via nasal cannula and treated with piperacillin/tazobactam and clarithromycin. Due to concerns about potential opportunistic infection and drug-drug interactions, we decided to withhold immunomodulatory treatments for SARS-CoV-2.

Initial blood cultures via BBACTEC™ Plus Aerobic/F were positive for *Shigella flexneri*, sensitive to ceftriaxone with minimum inhibitory concentration (MIC) of $\leq$ 1, and ciprofloxacin (MIC $\leq$0,125), though resistant to trimethoprim/sulfamethoxazole (MIC > 2/38). Giemsa staining in sputum evidenced the presence of *Histoplasma capsulatum*-like intracellular yeasts. Later, sputum culture was positive for *Histoplasma capsulatum*. Molecular identification and antifungal susceptibility testing were not performed due to limited capabilities in the local microbiology laboratory. GeneXpert MTB/RIF was negative. Serum cryptococcal antigen was also negative. Treatment with intravenous liposomal amphotericin B at 3 mg/kg/day was administered. Later, stool culture was also positive for *Shigella flexneri,* consequently processed by the Colombian National Health Institute for serotyping through Multiplex real-time PCR and identified as *Shigella flexneri* serotype 6. Also, fungal blood cultures via BACTEC™ Myco/F Lytic evidenced *Histoplasma caspsulatum.*

The patient remained hemodynamically stable, there was a resolution of fever and diarrhea, and his oxygen requirements decreased during hospitalization. Also, there was an improvement in the paraclinical abnormalities. Blood, sputum, and stool follow-up cultures were negative after one week of hospitalization. The antifungal therapy was switched to itraconazole (200 mg PO TID for 3 days, then 200 mg PO BID) after 14 days of intravenous treatment with liposomal amphotericin B and piperacillin/tazobactam. ART was switched to tenofovir

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https://doi.org/10.1016/j.nmni.2022.101015

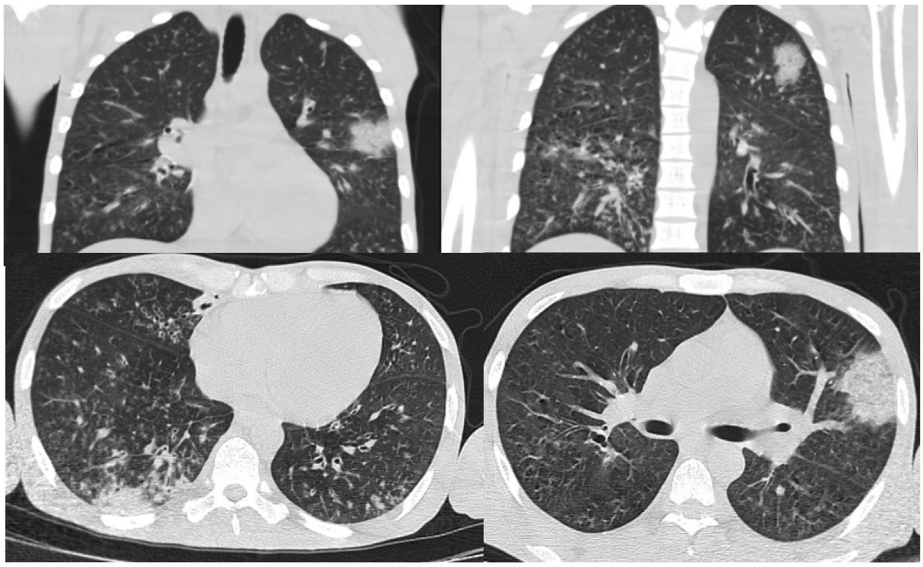


FIG. 1. Chest CT scan with diffuse branching opacities and upper segment of the lower lobe consolidation patches, and multiple bronchiectases in the middle and lower left lobes.

disoproxil fumarate/emtricitabine plus dolutegravir. At the June 2022 follow-up, the patient recovered approximately 20 kg of weight, completing management with itraconazole and on ART with an undetectable viral load.

After a careful review of international databases, no similar cases among HIV patients involving SARS-CoV-2, histoplasmosis, and shigellosis have been found. Histoplasmosis is one of the most common opportunistic diseases in HIV/AIDS patients. It presents many diagnostic challenges, especially in developing countries where *H. capsulatum* antigen testing is not widely available, leading to delayed diagnoses and worse outcomes. The diagnosis of COVID-19 cannot delay the search for other respiratory opportunisms, including invasive fungal infections [4]. Although the patient recovered, testing for PJP should be part of any initial workup on patients with AIDS and dyspnea, especially if they are hypoxic.

In a Canadian study, *Shigella flexneri* (serotype 1) resulted in a substantial burden of illness and health care resource use secondary to hospital admissions in men who have sex with men. In a study in the USA, *Shigella flexneri* bacteremia was associated with age > 18 years, black race, and HIV infection [5]. Additionally, other pathogens may cause disease and be involved, as was the case of *Shigella flexneri* serotype 6. Bacteremia is a potentially lethal complication in immunocompromised patients (our patient had a CD4+ count of just 4 cells/mm^3).[6] Bacterial enteropathogens in immunocompromised patients with diarrhea should be considered for early diagnosis and treatment.

In patients with advanced AIDS and severe immunosuppression, COVID-19 may coexist with other AIDS-related conditions, including respiratory and gastrointestinal opportunistic infections, especially in tropical countries such as Colombia. This could lead to challenges in patient management, where the risks and benefits of immunomodulatory therapy for COVID-19 must be carefully evaluated. There is an absence of specific guidelines in the context of AIDS-related conditions and COVID-19. Timely suspicion of opportunistic infections, including invasive fungal infections is critical. Often, patients with advanced AIDS can present with multiple opportunistic infections. Early recognition results in prompt and appropriate treatment, leading to improved mortality.

Funding

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

Transparency declaration

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

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