CASE REPORT

Persistent meningeal signs despite previous treatment for cryptococcal meningitis – a case report

Michela M. Fabricius, BS[1] and Shannon Ejiofor, DO[2]

[1]School of Medicine, University of Missouri-Columbia, Columbia, MO, USA
[2] Department of Medicine, University of Missouri-Columbia, Columbia, MO, USA

Corresponding author: Michela M. Fabricius, School of Medicine, University of Missouri-Columbia, Columbia, MO, USA. Email: mmtcd6@health.missouri.edu

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ABSTRACT

Cryptococcal meningitis continues to be a life-threatening fungal infection in patients with HIV. Treatment involves a year of antifungal therapy, and persistent meningeal signs months after treatment initiation are uncommon. We report a case of a 29-year-old male with HIV who was diagnosed with cryptococcal meningitis ten months earlier and underwent induction, maintenance and consolidation therapy and ART. Subsequently, he continued to have persistent headaches and developed severe meningeal signs with leptomeningeal enhancement on imaging. This case discusses the importance of keeping both immune reconstitution inflammatory syndrome and a cryptococcal meningitis relapse in the differential diagnosis for patients with persistent meningeal signs.

INTRODUCTION

Cryptococcus spp. continue to be the most life-threatening fungal infection in patients with human immunodeficiency virus (HIV). Initial infection occurs via respiratory inhalation and pulmonary infiltration, followed by subclinical antigenemia for at least three weeks before eventual dissemination into the central nervous system.[1] Defects in cell-mediated immunity, CD4+ and CD8+ T-cells, as in progressive HIV infection, allow for dissemination.

The global prevalence of cryptococcal antigenemia in HIV-seropositive persons with CD4+ T-cell count < 100 cells/uL is estimated at 6%, with 223,100 incident cases of cryptococcal meningitis occurring annually and accounting for 15% of AIDS-related mortality.[2] Treatment is trifold: first, induction therapy with amphotericin and flucytosine for two weeks, followed by consolidation therapy with fluconazole 400-800 mg daily for eight weeks and finally maintenance therapy with fluconazole 200 mg daily for greater than one year.[3]

Unlike with other opportunistic infections, antiretroviral therapy (ART) is generally deferred for four to six weeks after antifungals are started for cryptococcal meningitis. Deference is associated with a decrease in six-month mortality due to immune reconstitution inflammatory

syndrome (IRIS).[4] IRIS occurs when restoration of immunity with ART leads to a pathological inflammatory response and a paradoxical worsening of clinical presentation. Patient factors may alter this timing, and in general, ensuring that the patient's cerebrospinal fluid (CSF) cultures are sterile before starting ART also reduces the risk of IRIS.[4,5] With respect to imaging, the restoration of immunity often reveals leptomeningeal enhancement on either a computed tomography (CT) scan or magnetic resonance imaging (MRI) and can be accompanied with a communicating hydrocephalus.[6] This, along with linear perivascular enhancement in the sulci and new meningeal or choroid plexus enhancement, are specific image findings for cryptococcal meningitis related IRIS.[6] Furthermore, the majority of IRIS presentations occur within the first three months, with a median between nine to ten months after initiation of ART.[7-9]

We report a case of persistent meningeal signs and leptomeningeal enhancement in a patient with HIV, ten months after his initial treatment for cryptococcal meningitis and nine months after initiation of ART.

CASE PRESENTATION

First Admission

In January 2021, a 29-year-old male was admitted to our academic hospital due to multiple syncopal episodes in the span of 10 days. He also endorsed emesis, dizziness, migraines of increasing intensity and a 20-pound weight loss in 3 weeks. He had been afebrile. Of note, our patient had been previously diagnosed with HIV in April 2017 (HIV viral load 49,800 copies/mL & CD4+ T-cell 299 cells/mcL) and had been prescribed Stribild (elvitegravir-cobicistat-emtricitabine-tenofovir) as ART which was never filled from pharmacy.

A non-contrast CT head and spine and MRI brain were performed which were negative for acute abnormalities (Figure 1). He was pancytopenic (WBC $2.43x10^9$/L, RBC $3.61x10^{12}$/L, platelets $90x10^9$/L), and CD4+ T-cells on admission were low (19 cells/mcL). A lumbar puncture (LP) was performed, and CSF investigation revealed a low glucose (31 mg/dL) with positive yeast on India ink staining. CSF culture from this LP eventually grew *Cryptococcus neoformans*. Given this, he was started on antifungal induction therapy – amphotericin B liposomal 250 mg qday and flucytosine 2000 mg q6hr on January 29, 2021 for cryptococcal meningitis. He also received azithromycin 1200 mg q weekly and Bactrim single strength qday for *Mycobacterium avium* complex (MAC) and *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis. ART initiation was withheld while our patient received induction therapy for cryptococcal meningitis. Throughout his hospital course, he continued to have periodic headaches where he had three separate therapeutic LPs with resolution of symptoms after each (2/5/2021: Opening pressure (OP) 37 mmHg, 55 mL collected; 2/9/2021: OP > 55 mmHg and 60 mL collected; 2/19/2021: OP < 10 mmHg and 25 mL collected).

After 14 days of induction therapy and with improvement of his presenting symptoms, ART with Biktarvy (bictegravir-emtricitabine-tenofovir) was initiated. CSF cultures were also drawn at this time. Despite having received induction therapy for 14 days, our patient remained on his induction therapy until these CSF cultures were negative for an additional 7 days. On February 20, 2021, CSF cultures remained negative for 7 days and our patient was discharged on Biktarvy and fluconazole 400 mg as consolidation therapy for 8 weeks.

Follow Up

Over the following 8 months, our patient had consistent follow up with outpatient infectious disease and continued to take his Biktarvy, fluconazole 400 mg qday and acetazolamide 500 mg qday. CD4+ T-cells increased (4/28/2021: 160.7 cells/mcL; 8/31/2021: 163.0 cells/mcL). Viral load became undetectable in June 2021 and remained there during subsequent visits.

He continued to receive therapeutic lumbar punctures for headaches after discharge with some showing low glucose (2/24/2021: OP 42 mmHg, 25 mL collected, glucose 24 mg/dL; 5/3/2021: OP 32 mmHg, glucose 35 mg/dL; 10/7/2021: OP 25 mmHg, 13.5 mL collected, glucose 48 mg/dL; 11/05/2021: OP 24 mmHg, glucose 37 mg/dL, protein 156 mg/d). CSF cultures from each LP remained negative, and headache was relieved post-LP. An MRI was done in May 2021 and was negative for acute findings (Figure 1).

Second Admission

On November 16, 2021, our patient was admitted to our academic hospital due to new symptoms of persistent headache, worsening neck stiffness, inability to flex his neck, worsening balance and persistent vision changes. MRI brain demonstrated leptomeningeal enhancement and parenchymal FLAIR hyperintensity (***Figure 1***). CD4+ T-cells were low (183 cells/mcL) though HIV viral load remained undetectable. Atovaquone was restarted for PJP prophylaxis. An LP demonstrated positive CSF cryptococcal antigen (titer >1:2560) though CSF cultures remained negative. It also showed pleocytosis (47 leukocytes/mcL), elevated protein (258 mg/dL) and low glucose (31 mg/dL).

Again, our patient noted that his headache improved after the LP. An LP was repeated two days later (OP 27 mmHg, 20 mL collected) with negative cryptococcal PCR though positive cryptococcal antigen (titer 1:640). There was mild pleocytosis (26 leukocytes/mcL), elevated protein (168 mg/dL) and low glucose (39 mg/dL). Despite elevated cryptococcal antigen titers, cryptococcal cultures continued to be negative and paradoxical IRIS was considered higher in the differential as compared to cryptococcal disease. The following day, November 20, 2021, he was started on prednisone 1 mg/kg/day = 70 mg qday, and his fluconazole was increased to a consolidation dose of 800 mg.

After steroid initiation, he noted that his headache was relieved and the following day reported no meningeal symptoms. He was considered to be safe for discharge with two weeks of 70 mg qday prednisone with taper, and he was continued on a consolidation dose of fluconazole.

DISCUSSION

We present a case that complicates the diagnosis for an HIV patient with persistent meningeal signs. Our patient's meningeal symptoms during his second admission started nine months after initiation of antifungal therapy for *Cryptococcus neoformans* and ten months after initiation of ART. During our patient's second admission, imaging demonstrated leptomeningeal enhancement though LP cultures never grew Cryptococcus spp. despite pleocytosis, low glucose and positive antigen titers. Two differential diagnoses prevailed: (1) our patient had potentially failed induction therapy and had a cryptococcal relapse or persistence, or (2) our patient was experiencing IRIS. The simultaneous increase of his fluconazole to a consolidation dose with the prescribing of prednisone further clouded the ability to definitively distinguish between the two.[10,11]

With respect to this case, in cryptococcal relapse, CSF cultures become

negative and remain so at four weeks, with the patient becoming reinfected sometime after this. It is usually caused by inadequate primary therapy or failure of compliance with consolidation or maintenance doses of fluconazole [5]. Whereas, in persistent cases, CSF cultures remain positive after four weeks of antifungal therapy, and it generally raises concern for the presence of fluconazole resistance [5]. Our patient could have potentially experienced a relapse ten months after the initiation of antifungal therapy, but given the negative CSF cultures despite his leptomeningeal enhancement, this seems less likely.

Stronger in diagnosis is paradoxical cryptococcal meningitis IRIS, though this remains a diagnosis of exclusion. The principal consideration for this is the exclusion of culture-positive relapse. It is important to note that India ink and qualitative cryptococcal antigen are not useful for distinguishing IRIS from relapse.[12] Culture is the hallmark, and given our patient's negative cultures for his second admission, IRIS seems more likely. While cryptococcal antigen titers have high sensitivity and specificity in the initial diagnosis of cryptococcal meningitis, there is less utility with respect to relapse.[12]

CONCLUSION

In summary, our case demonstrates the difficulty in distinctly classifying between cryptococcal relapse and IRIS. This differentiation is vital as the management and outcome of the conditions are different and can be contradictory.

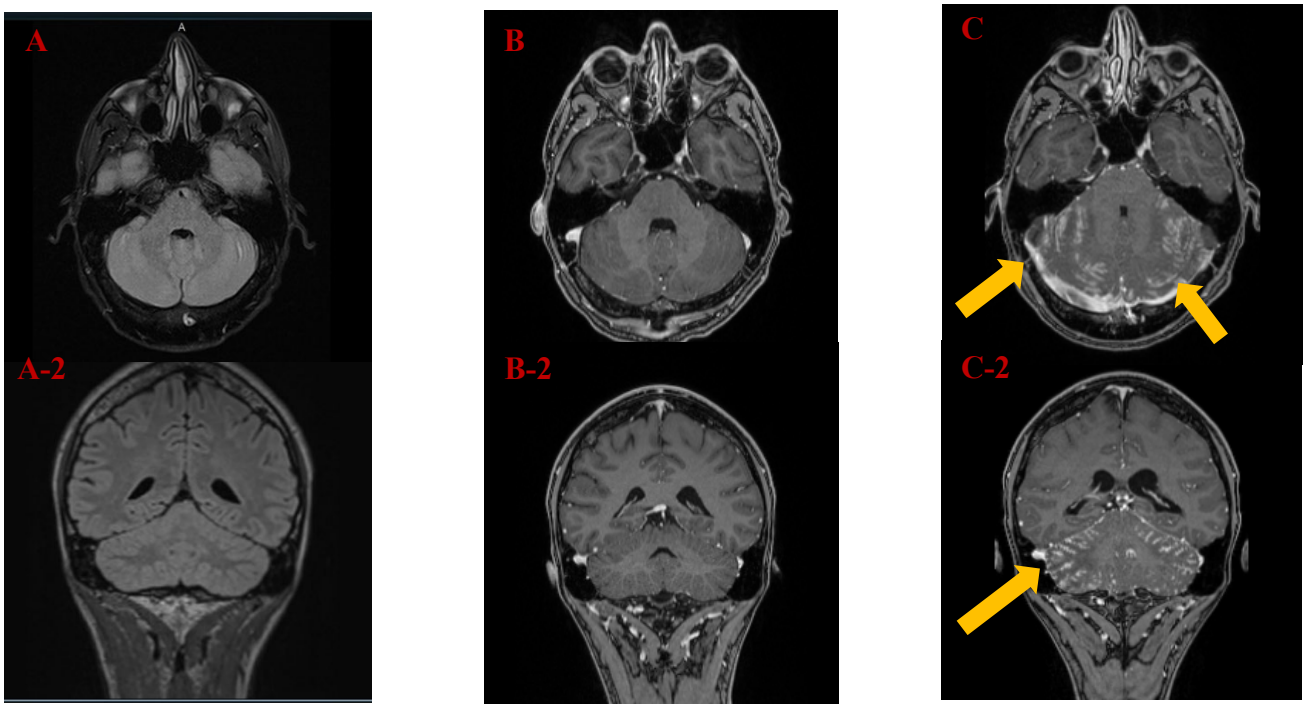

Figure 1: MRI FLAIR Imaging. (A & A2) Initial admission (1/27/2021) with no evidence of acute or significant intracranial abnormality. No abnormal enhancement is noted in the brain. (B & B2) Continued normal MRI during follow up period (5/03/2021). (C & C-2) Second admission (11/16/2021) with increased FLAIR hyperintensity predominantly involving cerebellar hemispheres as well as leptomeningeal enhancement. Examples of radiological findings are indicated with yellow arrows.

Notes
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