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Case report

Cerebellitis associated with cryptococcal-immune reconstitution inflammatory syndrome

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ABSTRACT

Cerebellitis associated with cryptococcal immune reconstitution inflammatory syndrome (IRIS) has not been previously reported. We describe a unique case of IRIS associated cerebellitis in an AIDS patient with cryptococcosis.

Background

Cryptococcal IRIS can present as "unmasking" IRIS, in which cryptococcal symptoms first appear after the start of highly active antiretroviral therapy (HAART) or as "paradoxical" IRIS during the treatment of cryptococcosis and after initiation of HAART, the form of IRIS thought to be caused by the recovery of cryptococcus-specific immune responses and can occur from one to six months after initiation HAART [1].

Recognized risk factors for cryptococcal associated IRIS include lack of CSF sterilization at week 2 of treatment for cryptococcal meningitis, starting HAART during early part of induction therapy, and rapid initial decline in viral load in response to HAART [2].

Clinical features associated with IRIS include fever, acute headache, seizures, hemiplegia, paraplegia, dysarthria,acute dyspnea and, enlarged lymphadenopathy. Imaging may show pulmonary nodules and infiltrates, diffuse cerebral microabscesses, oedema and abnormal enhancements [2].

Cerebellitis as part of Cryptococcal associated IRIS has not been previously described.

Case report

A 33-year-old woman with AIDS presented with a five-day history of headache, nausea, blurry vision, and ataxia while on maintenance fluconazole for cryptococcal meningitis diagnosed six months prior to admission. She received one-month liposomal amphotericin B and 5-flucytocine at initial diagnosis. The patient was maintained on bictegravir, tenofovir alafenamide and emtricitabine which was started one month prior to admission.

Physical exam revealed dysarthria, gait ataxia, horizontal nystagmus, lower limb dysmetria and, dysdiadochokinesia. Brain MRI showed extensive leptomeningeal enhancement within the cerebellar hemispheres, abnormal T2/FLAIR hyperintense signal associated with cerebellar swelling, mass effect resulting in effacement of basal cisterns and fourth ventricle (Image 1A and B).

Serum cryptococcal antigen titer was 1:2048, HIV-1 viral load 190 copies/ mL (previously 38000), CD4 + T cells 55 cells/μL (previously 4.3). CSF meningitis encephalitis PCR assay was negative for viruses, bacteria, and fungi. CSF protein 16.5 mg/dL, glucose 70 mg/dL and, white blood cells 1 cell/μL. India ink stain and CSF cryptococcal antigen were negative. The patient was thought to have developed IRIS associated cerebellitis.

Intravenous dexamethasone, liposomal amphotericin B, and 5-flucytosin were started and antiretrovirals were held. Repeat MRI three weeks later showed interval worsening (Image 1C and D).

Follow-up MRI at two months revealed near complete resolution of leptomeningeal enhancement within the bilateral cerebellar hemispheres and the abnormal T2/FLAIR hyperintense signal (Image 1E and F), and the patient was clinically asymptomatic. CD4 + T cells count was 49 cells/μL. HIV viral load was 25 copies/ mL. Serum cryptococcal antigen titer was 1:512.

At this point she had completed three weeks of re-induction therapy with liposomal amphotericin B, and 5-flucytosin and was placed on consolidation treatment with oral fluconazole 800 mg daily. The decision was made to re-initiate HAART and she was followed up in the outpatient HIV clinic with no new symptoms.

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Discussion

The lung and the central nervous system are the two most common sites of infection with Cryptococcus species [3]. Following inhalation, hematogenous dissemination can occur with predilection for the CNS [4]. The infection can occur in patients without HIV, or in patients with immunosuppression such as lymphoma or patients with organ transplantation [5-7].

Non-HIV patients with CNS cryptococcosis present with subacute headache, fever, cranial nerve palsies, lethargy, coma, or memory loss or acutely with severe headaches or altered mental status. Infection in HIV infected patients present similarly. Major differences include higher fungal burden, higher incidence of increased intracranial pressure, likelihood of co- infection with other opportunistic infections and, risk of IRIS [8–10].

About 10–30% of people with HIV who have cryptococcal meningitis

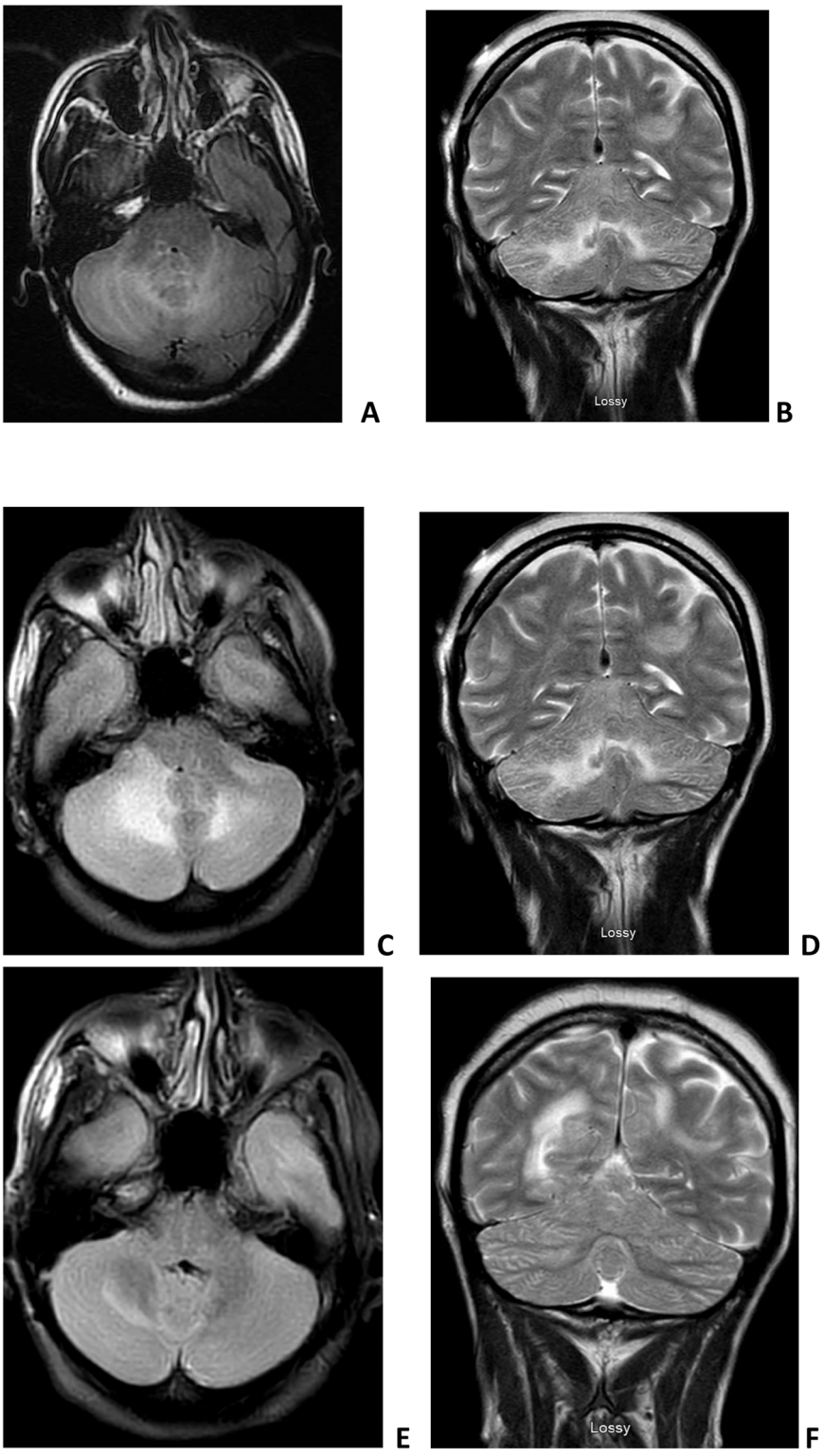

Image 1. MRI showing extensive leptomeningeal enhancement within the cerebellar hemispheres, abnormal T2/FLAIR hyperintense signal associated with cerebellar swelling, mass effect resulting in effacement of basal cisterns and fourth ventricle. Repeat MRI three weeks later showing interval worsening of abnormal T2/FLAIR hyperintense signal associated with cerebellar swelling. Follow-up MRI at two months revealing near complete resolution of leptomeningeal enhancement within the bilateral cerebellar hemispheres and the abnormal T2/FLAIR hyperintense signal.

experience IRIS after initiation or re-initiation of HAART [11,12]. Risk factors for development of IRIS include significant drop in HIV load and modest recovery CD4 cells [13]. During treatment for cryptococcal meningitis, IRIS may present with increasing headaches, new seizures, hemiplegia, paraplegia, dysarthria, appearance of more inflammatory cells in the CSF, and possibly increased intracranial pressure [14]. Distinguishing immune reconstitution from progressive infection can be difficult, but CSF cultures are generally negative in IRIS, even though cryptococci may be present on a smear and cryptococcal antigen titers may be decreasing.

CNS IRIS may either occur early (i.e., within a few days or months after the introduction of HAART. Time of occurrence appears shorter in cases of cerebral IRIS. New fever and cerebral signs and symptoms of meningitis with or without an increase of CSF pressure, can be construed as signs of treatment failure.

Failure to recognize IRIS can result in significant morbidity and death from herniation [15].

Despite the fact that cryptococcal meningitis is one of the most common opportunistic infection that can be complicated by IRIS, there are no case reports of AIDS-associated IRIS cerebellitis. However,

Cryptococcal cerebellitis has been reported in non HIV hosts. Hafsa et al. reported a rare case of cryptococcal cerebellitis in an asplenic patient, seronegative for HIV [16].

Their patient presented with fever, dysdiadokokinesia, dysmetria, ataxia, nystagmus and, intention tremor, similar to our patient.

Unlike our patient, Cryptococcus neoformans was isolated from CSF with positive antigen titer 1: 512. In both cases, contrast enhanced MRI showed leptomeningeal enhancement involving cerebellum indicating acute cerebellitis that responded to liposomal amphotericin B and 5-FC.

Fickweiler et al. described a patient with multiple myeloma who received chemotherapy and autologous stem cell infusion, [17] the patient was diagnosed with cryptococcal cerebellitis, and a low CD4 count was thought to be the risk for the syndrome.

Similar to our patient, the patient presented with nausea and vertigo, and cerebellar signs of downbeat nystagmus, dysmetria and intention tremor.

An MRI showed diffuse infiltrating mass with adjacent edema, and parenchymal and leptomeningeal enhancements as with our patient. The CSF India Ink stain was positive for *Cryptococcus neoformans* and the organism was grown from CSF. Our patient had a sterile CSF, a key finding with IRIS. The patient responded clinically to Amphotericin B, 5-FC with a transition to prolonged Fluconazole.

Cryptococcal cerebellitis has also been described in recipients of sold organ transplant receiving tacrolimus, mycophenolate mofetil and prednisone as well as in chronic hepatitis C associated liver cirrhosis [18].

In our patient, possible risk factors for developing IRIS cerebellitis may include rapid decline in HIV viral load, high serum fungal burden and the modest increase in her CD4 + T cells one month following consistent use of HAART.

The clinical features of acute cerebellitis varies according to the extent and geography of cerebellar involvement [19]. Vertigo, nystagmus, limb dysmetria, ataxia and imbalance are all attributable findings. Our patient presented with headaches, ataxia, nausea and nystagmus with confusion that was likely due to concomitant cerebritis noted on her MRI.

Magnetic resonance imaging plays a pivotal role in defining cerebellar lesions. Swelling, enhancements, effacement of basal cisterns and fourth ventricle along with abnormal T2/FLAIR hyper intense signals were all noted on our patient's MRI brain.

Treatment strategy for IRIS include restarting amphotericin B therapy or increasing the fluconazole dose to 1200 mg per day is recommended as well as concomitant use of higher dose dexamethasone when there is severe CNS inflammation and 2–6-week corticosteroid taper. If present, reducing intracranial pressure is recommended.

At hospital discharge, restarting fluconazole therapy at consolidation therapy doses to be continued for 8 weeks [20].

Conclusion

To our knowledge this case is the first case of IRIS associated cerebellitis in an AIDS patient with cryptococcal meningitis. It is important to consider CNS IRIS if a patient presents with new cerebellar signs and symptoms after initiating HAART while on maintenance treatment for cryptococcal meningitis as prompt recognition and use of steroids could decrease morbidity and mortality.

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Ethical approval

N/A.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Dennis Hogan: writing and editing. Eliahu Bishburg: writing and editing. Madhu Suryadevara: literature review.

Declaration of Competing Interest

I have no conflicts of interest.

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