Intracranial lymphoma in human immunodeficiency virus-infected patients: A diagnostic dilemma?

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Abstract

Primary central nervous system (CNS) lymphoma is an aggressive malignancy which constitutes one of the acquired immunodeficiency syndrome -defining illnesses. Early diagnosis and timely management can increase the chances of cure. Although many times the diagnosis is straightforward, we present a case of primary CNS lymphoma in a human immunodeficiency virus--positive individual which posed as a major diagnostic dilemma with initially normal imaging findings. A 42-year-old male presented with unremitting fever and a perianal ulcer for 3 months. A battery of diagnostic tests were negative, including a positron emission tomography-computed tomography scan and a magnetic resonance imaging brain. With unresolving symptoms and a high index of suspicion as he developed dizziness and loss of balance, the same were repeated which confirmed a space-occupying lesion in the cerebellum. Although treatment was instituted, the patient did not recover and died in the 4th month of treatment.

Key words: Antiretroviral, human immunodeficiency virus and malignancy, human immunodeficiency virus diagnostic dilemma, non-Hodgkins lymphoma, primary central nervous system lymphomas

Introduction

The risk of Non-Hodgkin's lymphoma (NHL) and Hodgkin's Lymphoma often increases with human immunodeficiency virus (HIV) infection as compared to uninfected individuals.[1] Primary central nervous system lymphoma (PCNSL) associated with HIV infection is often difficult to treat. PCNSL is an aggressive subtype of B-cell NHL.[1] It often occurs among severely immunocompromised patients and is almost always linked with coincident Epstein–Barr virus (EBV) infection.[2] The occurrence of the disease is more frequent in individuals with CD4 counts lower than 100/μl and high HIV viremia levels.[3] In the USA, PCNSL has a prevalence of 12.3% among acquired immunodeficiency syndrome (AIDS) population.[2] However, with the widespread introduction of highly active antiretroviral therapy, the incidence of HIV-related PCNSL has decreased. Often, the diagnosis is straightforward. Here, we present a unique and challenging case study of an AIDS patient with multiple admissions to the nursing home with chronic low-grade fever eventually being diagnosed with PCNSL, through the process of elimination with extensive clinical workup in consultation with multi-specialty doctors.

Case Report

In April 2015, a 42-year-old married male visited the outpatient clinic suffering from high-grade fever and a large painful ulcer around the anus for the past 3 weeks.

Medical history revealed that he was seropositive and diagnosed with HIV in 1997. His history also confirmed high-risk behavior involving anal sexual intercourse with another man. Treatment was deferred repeatedly for antiretroviral treatment (ART) in 1997 and 2005 as his absolute CD4 counts were >400 cells/mm^3. For the past 3 months, (2015), he was experiencing low-grade fever with rising temperature in the evening often associated with chills. He suffered from loss of appetite and had lost 15 kg weight in the past 4 months. He has no history of headache, vomiting, cough, breathlessness, and diarrhea.

Clinical Examination revealed oral candidiasis, a large ulcer measuring 8" X 2" around the anus that was painful and bled on touch as shown in Figure 1. There was no lymphadenopathy. Systemic examination was normal. As the ulcer was painful and bled on touch, a skin biopsy and Tzanck Smear test were recommended.

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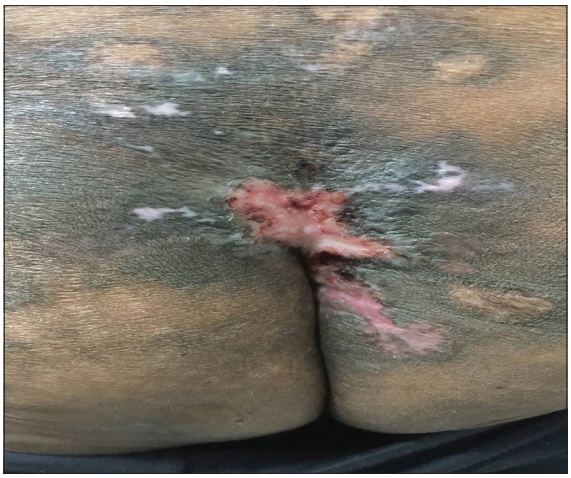

Figure 1: Perianal ulcer

Four days later, on his 2nd visit, as per NACO, his HIV-1 status was confirmed by HIV-enzyme-linked immunosorbent assay. His CD4 count (Absolute count and Percentage) was 10 cells/mm^3, CD4-<4%, and plasma viral load was 43,803 copies/ml. Genotypic drug resistance (DR) testing for HIV-1 was done to rule out (r/o) transmitted DR (TDR) or primary DR.

Hemogram, blood sugar level, renal and liver function tests, urine tests were otherwise normal except thrombocytosis. For investigating fever, the following tests were done which were all negative: Malaria antigen test for *Plasmodium vivax* and *Plasmodium falciparum,* Dengue NS1, IgM, IgG, HBsAg, hepatitis C virus, venereal diseases research laboratory/Treponema Pallidum Hemagglutination, and Herpes IgM, IgG. Blood culture for aerobic and anaerobic organisms showed no growth. All the tests related to fever were insignificant. Koch's infection was also ruled out. He tested IgG positive for toxoplasmosis. He received chemoprophylaxis for opportunistic infections, (Co-trimoxazole, INH, and Azithromycin) and ART regimen of Tenofovir disoproxil fumarate (TDF) + Emtricitabine (FTC) + Efavirenz (EFA) (TDF + FTC + EFV) fixed-dose combination while awaiting the results of DR, and skin biopsy.

There was no improvement in his symptoms despite treatment for over 3 weeks. Thereafter, he was admitted to the hospital with high-grade fever and large painful perianal ulcer. He received intravenous antibiotics along with ongoing medications.

His perianal biopsy report was suggestive of superficial aphthous ulcer. Tzanck smear test was done suspecting herpetic infection but was negative. 18F-fluoro-2-deoxy-D-glucose positron emission tomography computed tomography (^{18}FDG-PET) scan was done which did not show any abnormal uptake suggestive of malignancy. Thus, tuberculosis and malignancy were ruled out by the TB specialist and oncologist. The dermatologist treated the ulcer as a giant herpetic ulcer with valaciclovir 1 g thrice a day for 2 days, thereafter 500 mg thrice a day while continuing the chemoprophylaxis. While on valaciclovir, the ulcer size reduced in size and developed scarring and pigmentary changes.

While this treatment was ongoing, the ART DR report showed he was resistant to Nucleoside Reverse

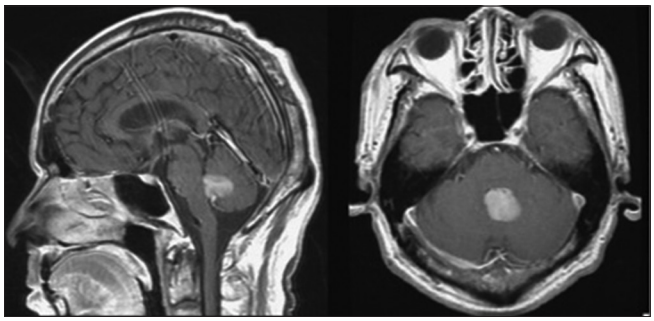

Figure 2: Radiological image

Transcriptase Inhibitors (NRTIs) and Non-NRTIs (NNRTIs) while being susceptible to protease inhibitors and integrase strand transfer inhibitors. Before switching the patients' regimen, CD4 and viral load tests were repeated which showed that his CD4 absolute count was 10 cells/mm^3 and CD4– below 4% and plasma viral load was 52,935 copies/ml. The regimen selected post DR test report and counseling was Lopinavir/ritonavir (LPV/r) + Lamivudine (3TC) + Raltegravir (RAL). The patient was afebrile and asymptomatic. The skin lesion healed and he was discharged within 15 days while maintaining the ART regimen.

Five days later, while on the new ART regimen, the patient complained of giddiness and loss of balance. The patient was managed conservatively with oral betahistine (Vertin) by an Otorhinolaryngologist. Subsequently, within few days, the symptoms worsened with him developing headache, vomiting, and blurring of vision. Neurological evaluation revealed tendency to fall on either side during tandem walking, bilateral finger nose ataxia, and Romberg's sign was present. Magnetic Resonance Imaging brain suggested acute demyelination with a differential diagnosis of lymphoma.

FDG-PET scan was repeated after a gap of 40 days from the previous scan. It showed a single space-occupying lesion in the vermis of cerebellar area with no other abnormality as shown in Figure 2. Stereotactic biopsy suggested lymphoma– Non-Hodgkin's diffuse large B-cell lymphoma. Immunohistochemistry showed positive expression for CD20 and negative expression for CD-10. Cultures of CSF and tissue did not reveal any aerobic or anaerobic infection. Fungal culture, TB-MGIT, and identification of MAC and Gene Xpert for MTB were negative. EBV was present.

The patient was eventually diagnosed with PCNSL through a process of elimination. The patient was started on chemotherapy but did not improve. Despite being on ART for 3 months and taking chemotherapy/radiotherapy, his CD4 counts did not rise although, his viral load was undetectable. The patient ultimately died in the 4th month of his treatment.

Discussion

More than 20 years ago, PCNSL was defined by the Centers for Disease Control in Atlanta, Georgia as an AIDS-defining illness.[4] It is an aggressive malignancy that normally occurs in individuals with a heavily compromised immune status. The prognosis for this condition is poor. The estimated survival rate at 5 years is 22% without treatment. Thus, early diagnosis is essential to assure a chance of survival for the patient; however, it can be challenging given the extensive etiology of focal brain masses and heterogeneity of diseases behaviors typical of the AIDS population.[1]

In this case study, despite 3 months of ART which suppressed the viral loads to undetectable levels immune reconstitution never occurred for the patient. His CD4 level never improved. ART unmasked the malignancy seen in the patient. Despite a dedicated clinical team with a high index of suspicion for malignancy, initially, malignancies were ruled out by a negative PET scan, and a negative initial biopsy from perianal ulcer.

Some of the other management lessons from this patient are that patients with ulcers around the anus or penis often respond to valacyclovir even though biopsy has ruled out herpetic ulcer and HSV2 IGG and IGM are negative. Furthermore, genotypic resistance testing should be considered when treating naïve patients to rule out TDR, especially when NNRTI or NRTI is being used.

A number of series have been published about the management of PCNSL in seropositive individuals, all of them describe the diagnosis to be straightforward. However, in reality, the diagnosis can be masked. The imaging features can be misleading in view of the severe immunodeficient status. This case highlights the diagnostic dilemma a clinician may face as treatment with ART may unmask other conditions including a malignancy.

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Conflicts of interest

There are no conflicts of interest.

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