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Case Report

Management of Progressive Multifocal Leukoencephalopathy - Immune Reconstitution Inflammatory Syndrome (PML-IRIS) In a HIV Positive Male with Steroidal Support and Antiretroviral Therapy with Greater CNS Penetration-Effectiveness Score (CPE): A Case Report

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Abstract

Introduction: We present a case of Progressive Multifocal Leukoencephalopathy (PML) associated with Immune Reconstitution Inflammatory Syndrome (IRIS) in a male aged 47 year diagnosed with AIDS and a CD4 count of 44/μL who was treated with steroidal support and antiretroviral therapy with greater CNS penetration-effectiveness score (CPE).

Case Presentation: A 47-year-old male diagnosed with HIV-1 with AIDS who was started on antiretroviral therapy (ART) presented with confusion, disorientation and inability to walk 10 days after ART initiation with Tenofovir, Emtricitabine, and Efavirenz. History revealed progressive fatigue and weakness. On examination, he was hypotonic with slurring of speech. PML was diagnosed based on MRI and positive JC virus PCR in CSF. This posed a clinical dilemma as to whether this was PML alone or PML-IRIS.

Management and outcome: Based on clinical judgment, PML-IRIS was diagnosed. Prednisolone was added to help reduce inflammation. On account of better CNS penetration, Tenofovir, Emtritabine, and Efavirenz was switched to Zidovudine. Lamivudine and Efavirenz. Over a period of three months he made rapid progress and completely regained consciousness, orientation with coherent speech. He was able to walk without support and is now preparing to return to work as a civil engineer.

1.1. Discussion: Distinguishing between PML and PML-IRIS can be challenging. It is important nonetheless since management differs. This case report is among the first from India to highlight this entity and its clinical management. We strongly believe that in our patient early initiation of corticosteroids resulted in dramatic improvement. Once initiated steroids probably need to be continued for 6-8 weeks.

Keywords: Acquired Immunodeficiency Syndrome (Source: MeSH-NLM); Immune Reconstitution Inflammatory Syndrome; Leukoencephalopathy, Progressive Multifocal; JC Virus; HIV

Introduction

Progressive Multifocal Leukoencephalopathy (PML) is a demyelinating disease of the central nervous system, characterised by multifocal areas of demyelination of varying sizes, distributed throughout the brain [1]. The causative agent is JC Virus (John Cunningham virus) which causes an opportunistic infection [2-4]. PML is an AIDS defining condition that occurs when the CD4 count<100/μL [5].

PML-IRIS is a paradoxical worsening or unmasking of PML which occurs following the initiation of Antiretroviral Therapy (ART). Immune Reconstitution Inflammatory Syndrome (IRIS) is caused by the rapid recovery of the immune system in the presence of the pathogen [5,6]. There are very few studies which have looked into the outcome of PML-IRIS in HIV infected patients across the globe [5,7]. Data on AIDS-associated PML-IRIS from India is largely unavailable [5]. In this paper, we describe the clinical findings and progress of the disease in an Indian patient with HIV having a CD4 count of 44/μL.

Case Report

A 47-year-old male presented to us in April 2017. He was confused, disoriented and unable to walk. There was a history of weight loss since 2 years, excessive tiredness since 20 days, difficulty in walking since 15 days, and slurring of speech since 10 days. The patient was apparently normal 20 days prior to presenting to us when he noticed excessive fatigue and weakness which was progressive. Five days after onset of initial symptoms, he started having increasing difficulty in walking. Around this time, he also developed difficulty in swallowing. On further questioning his wife gave a history of progressive weight loss since 2 years of 20Kgs. There was no history of tuberculosis, diabetes mellitus, hypertension, and blood transfusions. No previous surgeries or allergies were reported. The patient had been married for 12 years. His wife provided the history that he was a homosexual and their only child was conceived by artificial insemination.

Ten days before coming to our centre he was seen at a private clinic and diagnosed with HIV-1 with AIDS. His CD4 count was 44/μL. There, he was started on an Antiretroviral Treatment (ART) regimen containing Tenofovir, Emtricitabine and Efavirenz and also started empirically on anti-tubercular therapy. Subsequently the patient was discharged. However, he deteriorated at home and was then brought to our centre. When brought to our center, the patient was on a stretcher. While conscious he was neither oriented nor responsive to questioning. He was poorly nourished. He was febrile (100°F). CNS examination showed slurring of speech. There were no focal neurological deficits. Limbs were hypotonic. Deep tendon reflexes were present. No signs of meningitis were present.

A MRI contrast of the brain and spinal cord and Lumbar Puncture (LP) with CSF analysis was done at a referral hospital. The MRI was suggestive of PML. CSF protein, glucose, cell count and cell type were within normal limits. However, a multiplex PCR test for a panel of pathogens associated with meningoencephalitis was positive for JCV. While at the referral hospital, his ART and antitubercular therapy was discontinued. The patient was examined by a neurologist who noted cogwheel rigidity. The patient was started on a combination of levodopa and carbidopa. After a week, he was sent back to our centre. He was unconscious and febrile (100°F). Nystagmus was noted bilaterally and cogwheel rigidity was present in all four limbs.

At our center, we were confronted with the following clinical dilemmas. Firstly, was his condition explainable by a diagnosis of PML alone or was this PML-IRIS? Secondly, should we restart ART or withhold it? Thirdly, was there a role for steroids in his management? and lastly, if we chose to start ART, should we switch to a regimen with better CNS penetration?. After reviewing the literature and discussion internally, we thought this presentation was more likely due to PML-IRIS than PML alone. We felt that the literature supported ART continuation, and hence continued ART. We chose to add steroids though the literature was equivocal on its benefit. Prednisolone of 40 mg once a day was started. Prednisolone was tapered over a period of 5 weeks. We also switched his ART regimen from Tenofovir, Emtricitabine, and Efavirenz to a combination of Zidovudine, Lamivudine and Efavirenz (Zidovudine has better blood brain barrier penetration compared to Tenofovir).

By the eighth day of switching ART and adding prednisolone, the patient started improving. He was able to sit in a chair and his speech was clearer and he became afebrile. After 40 days of initiating treatment, patient was fully oriented and able to walk without support. However, he had difficulty maintaining balance and still had episodes of amnesia. He was discharged from our centre on 17th of June with advice for regular follow up. A review on the 20th of July, 2017 showed further improvement in his condition. He had gained 10 Kg since his presentation at our centre. He walks with a steady gait, and speech is much clearer. He contemplated returning to work as a civil engineer.

Discussion

PML is the only known clinical manifestation of the JC virus [6]. JC virus (John Cunningham virus or JCV) was named after the patient from whom it was first isolated in 1971 [2-4]. A paradoxical worsening of pre-existing, untreated, or partially treated opportunistic infections due to rapid recovery of the immune system following ART initiation is called Immune Reconstitution

Inflammatory Syndrome (IRIS) [6]. The mechanism via which treatment with ART leads to PML-IRIS is not clearly understood but it is postulated that a sudden recovery of T cell activity due to ART with a high pathogen (JCV) load results in a T-cell mediated encephalitis characterized by a massive inflammatory response that damages the brain [2] Occasionally the damage can be so severe that it leads to a massive swelling of the brain with herniation and death [2]. PML-IRIS is usually seen in patients starting therapy with CD4 count is less than 50/μL [6]. It is important to differentiate between the diagnosis of PML and PML-IRIS as they differ in treatment and failure of appropriate treatment will lead to the death of the patient.

PML-IRIS can be differentiated PML by on the following:

a) Clinical profile of worsening symptoms on initiation of treatment. The worsening of PML following the initiation of therapy is believed to be a result of IRIS [8]. The onset of PML-IRIS can vary from 1 week to 26 months [8]. Our patient presented with worsening of symptoms 10 days after initiating ART.

b) MRI T1-weighted images of PML are hypointense and do not show enhancement with gadolinium [2]. However, patients who develop PML-IRIS may show variable degrees of enhancement [2].

There is no recommended specific antiviral therapy against JC virus [2]. The literature suggests that continuing ART is associated with better outcomes in patients with PML. The prognosis of patients without initiation of antiretroviral treatment is poor with an average survival of 2-4 months [2]. Hence, we continued ART but replaced Tenofovir with Zidovudine for better CNS penetration [9].

Although there are no treatment guidelines that clearly recommend the use of steroid in PML IRIS, some studies note a trend for lower mortality in patients with PML-IRIS with early treatment with corticosteroids [5]. We strongly believe that in our patient early initiation of corticosteroids resulted in dramatic improvement. Once initiated steroids probably need to be continued for 6-8 weeks. Our literature search did not reveal any case reports of PML-IRIS successfully diagnosed and treated from India. This case report is among the first from India to highlight this entity and its clinical management. The lack of reports from India exposes the probability of under diagnosis of PML-IRIS [9]. Significant recovery of our patient with the continuation of ART with steroidal support strongly advocate the need for clinicians to have a high index of suspicion for early detection detect and PML-IRIS and initiate steroid therapy with continued ART as suggested above.

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