

## **Life Saving Role of Steroid Therapy in Progressive Multifocal Leukoencephalopathy Induced Immune Reconstitution Inflammatory Syndrome (PML-IRIS)**

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### **Abstract**

As a rule of thumb corticosteroids are avoided in immunosuppressed patients with AIDS in the fear of predisposing the patient to an array of opportunistic infections. However, in a life-threatening condition called Immune reconstitution inflammatory syndrome brought about by the abrupt reinstatement of HAART in a severely immunocompromised patient, corticosteroids do play a crucial and lifesaving role in preventing further deterioration. This case report seeks to establish the importance of timely identification of such a condition and the administration of corticosteroids which forms the crux of the management in Immune reconstitution inflammatory syndrome.

**Keywords:** Steroid Therapy; Progressive Multifocal Leukoencephalopathy Induced Immune Reconstitution Inflammatory Syndrome (PML-IRIS)

### **Background**

Progressive multifocal leukoencephalopathy (PML) is a rare complication of poorly controlled Autoimmune Deficiency Syndrome (AIDS). It is a grave opportunistic infection caused by the JC virus with predominant involvement of the central nervous system. Although its presentation varies, it may manifest by inducing a condition known as immune reconstitution inflammatory syndrome (IRIS). In such a case of AIDS-associated PML-IRIS, highly active antiretroviral therapy (HAART) is considered to be the standard therapy as it has been shown to significantly improve the survival rates of these patients [1]. Furthermore, the use of corticosteroids, long known for their anti-inflammatory and immunosuppressive effects, are often deferred due to the risk of placing the patient at risk for opportunistic infections. However, AIDS-associated PML induced IRIS is an exception to this practice which merits steroid therapy even in the presence of AIDS. The following case highlights the importance of diagnosing such a condition where steroid therapy has the potential to be lifesaving in an immunocompromised patient with retroviral disease and can lead to a better prognosis.

### **Case Presentation**

A 55-year-old male with AIDS presented to the medicine out-patient department (OPD) with difficulty walking for 3 months. It was insidious in onset and progressive in nature. He is a known case of retroviral disease for 14 years on HAART. Two weeks before his presentation, he started to experience slurring of speech and a sensation of swaying. Further history elicitation revealed that the patient

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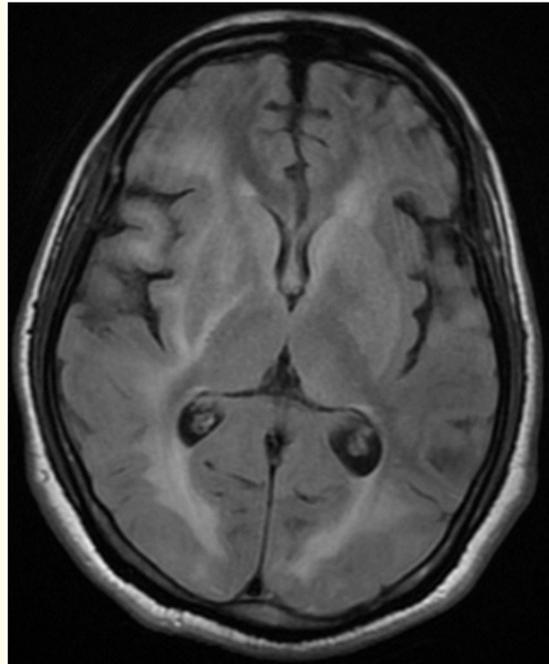
had been non-compliant with his medications. The patient’s neurological examination revealed signs of a cerebellar pathology such as an ataxic gait, dysmetria, scanning speech, dyssynergia, dysdiadochokinesia, and action tremors.

On day 1 of presentation, the patient was started on second line HAART in view of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance; tenofovir (300 mg), lamivudine (150 mg), atazanavir (400 mg), and ritonavir (100 mg), all once a day. On day 10, patient returned to the OPD for follow up visit. He stated mild improvement of symptoms. On day 14, patient was brought to the hospital due to sudden worsening of symptoms. He could no longer walk without support. In addition to initial symptoms, he now reported a slowness of movements, decreased speech, involuntary movements. Further examination revealed shuffling gait, intention tremors, mask-like facies, and a positive glabellar tap, indicative of basal ganglia lesions. In view of these symptoms, the patient was admitted to the hospital. This characteristic worsening of symptoms observed after the commencement of HAART is attributed to PML-IRIS, which is a rare presentation.

**Investigations**

On initial presentation, an investigative workup was conducted to assess the patient’s health status. The patient’s CD4+ count and viral load was found to be 78 cells and 618 copies/ML, respectively. A lumbar puncture was done and revealed the cerebrospinal fluid (CSF) to have pleocytosis and mildly elevated protein. The CSF was negative for tuberculosis, cryptococcal infection, toxoplasmosis, varicella zoster infection, herpes simplex 1 and 2. MRI of the brain revealed multiple white, hypodense, non-contrast enhancing lesion in the cerebellar region.

After hospital admission on day 14, a repeat MRI of the brain revealed multiple white, hypodense, non-contrast enhancing lesions in the basal ganglia with pre-existing cerebellar lesions (Figure 1).



*Figure 1: MRI of the brain showing multiple white, hypodense, non-contrast enhancing lesions in the basal ganglia with pre-existing cerebellar lesions.*

**Treatment**

Methylprednisolone 1 g/day in 2 doses, 12 hours apart for 5 days was initialed. This was followed with an oral prednisolone taper of 20 mg/day.

**Outcome and follow-up**

Day(s) From Hospital Admission	Progress of Patient
<b>Day 1:</b> patient administered methylprednisolone iv 1 gm; HAART continued. Syndopa and carbidopa give 110 mg in 3 doses in view of basal ganglia lesions.	Patient unable to walk without support. Cerebellar and parkinsonian features present.
<b>Day 6:</b> patient started on oral prednisolone 20 mg 3-0-0. Syndopa and carbidopa continued with HAART.	Patient’s tremors have reduced. He is better able to articulate words and speech output has increased.
<b>Day 15:</b> patient taken off steroids. Syndopa and carbidopa continued.	Patient is able to walk on his own; CD4+ count-319

**Discussion**

We believed this case of PML-IRIS should be reported because of its atypical presentation as well as the potential, lifesaving role of corticosteroids in managing this condition. Preceding the establishment of HIV, PML had remained a rare disorder that was seen in immunosuppressed individuals, recipients of organ transplant, and hematological malignancies. According to a database on medical service claims, the incidence of this disorder has risen to 4.4 cases for every 100,000 individuals [2]. A more recent study analyzed the national inpatient sample and found that PML was present in 82% of individuals with HIV, 8.4% in those with hematological malignancies, and 2.83% with solid organ malignancies [3]. The mortality rates related to PML have risen from 1.5 to 6.1 deaths for every ten million individuals [4]. PML is a demyelinating disorder of the central nervous system (CNS) with progressive inflammation and damage of subcortical white matter in the brain in the setting of severe immunosuppression (< 100 CD4+ count). PML occurs due to the reactivation of the JC virus and is seen in severely immunocompromised patients [5,6]. The primary infection caused by the JC virus is asymptomatic in immunocompetent individuals. It is found in the tonsils and lymph nodes and is dispersed by B lymphocytes to the spleen, kidney, bone marrow, and lung where it remains dormant until an individual’s immunity is compromised, and then reactivates to invade the CNS [7,8]. Diagnosis can be made by means of imaging modalities, specifically MRI. A T1 weighted MRI image will show hypointense lesions whereas a T2 weighted MRI image will show hyperintense lesions [9]. In a typical case of PML, the usual treatment is HAART but a rare complication called PML-IRIS may develop. The underlying process is believed to be due to reconstitution of antigen-specific T cell-mediated immunity. Although CD8+ T lymphocytes make up the majority of the cytotoxic cells, they are few in number in the normal brain [10]. In contrast to an individual with PML-IRIS, a robust cellular response occurs. This response is driven by CD8+ cytotoxic T lymphocytes that are JC virus specific [11]. Since the pathogenesis of the entity is an inflammatory one, therapy with systemic corticosteroids can alleviate symptoms and anecdotally improve outcomes by decreasing mortality. Moreover, the use of corticosteroids have been recommended by a few experts in PML-IRIS in the presence of suspected brain herniation [12]. This case has clinical implications as corticosteroids may be added to current HIV regimens as well as improve the overall mortality and outcome of PML-IRIS.

**Conclusion**

It is highly important to recognize the entity of PML-IRIS, as the mainline treatments may not be sufficient in treating the condition and as such, other medical modalities must be sought. Corticosteroids are avoided due to fear of severe immunosuppression giving way to opportunistic infection. However, steroid therapy may prove to be beneficial and lead to a better prognosis in mortality and outcome.

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