HIV related progressive multifocal leukoencephalopathy Immune reconstitution inflammatory syndrome (PML-IRIS)

Dr Krishna Thazhatheyil, Dr Albert Egwele, Dr Jeyanthy Rajkanna
Peterborough City Hospital, Peterborough, UK.

Introduction

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection affecting immunocompromised patients. It is a rare devastating disease of the CNS caused by the reactivation of JCV in immunocompromised patients. Patients can develop PML during antiretroviral therapy. HIV infection currently accounts for approximately 80% of new PML cases. No drug is effective against JCV. Since the restoration of CD4 and CD8 JCV-specific T cell immune responses, allowing the control of JCV replication, the initiation of combined antiretroviral therapy (cART) in HIV-infected patients remain the only available therapeutic alternative for PML. cART-induced immune recovery improved PML survival in HIV-infected patients. However, immune restoration is not always beneficial. 20% of HIV-infected patients with PML worsen after cART initiation, due to severe neuroinflammation within settings of immune reconstitution inflammatory syndrome (PML-IRIS). The contribution of IRIS toward the clinical worsening of PML is difficult to distinguish from natural evolution of classical AIDS-associated PML. Therapeutic management of PML-IRIS usually relies on steroids. However this may blunt the anti-JCV immune responses that are instrumental in the long-term control of JCV replication. We describe a case with PML in relation to immune reconstitution inflammatory syndrome (PML-IRIS).

History and Clinical Progression

Background

- A 53 year old lady was diagnosed to have HIV 15 years ago. She was previously treated for Syphilis and Pulmonary tuberculosis in 2003.
- Later she disengaged from medical treatment.

October 2018

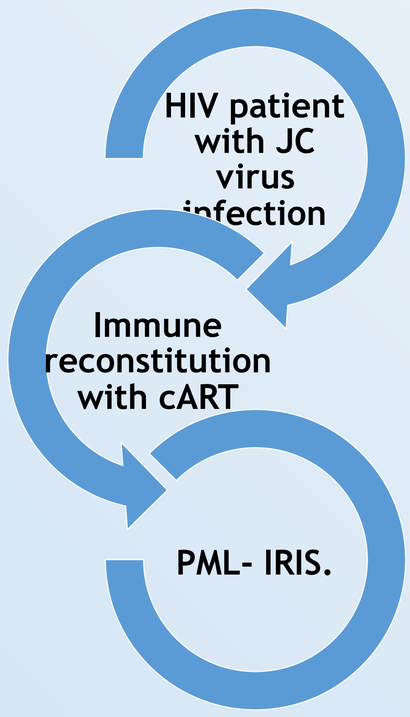
- She presented with non-specific febrile illness and significant weight loss of 5 kg.
- In view of the low CD4 count, high HIV RNA viral load and positive IgG for toxoplasma, she was treated with highly active antiretroviral therapy (HAART) and Atovaquone.

November to December 2018

- Ten days later she developed right hemiplegia and expressive dysphasia. As she was positive for JC virus in CSF: Progressive multifocal leukoencephalopathy was diagnosed. She also developed clinical seizures. There was no clinical evidence of CMV infection.
- MRI Brain revealed multifocal hyper-intense lesions in the T2 and FLAIR sequence in white matter of left cerebral hemisphere. MRI Brain was suggestive of PML-IRIS.

January 2019:

- Gradual deterioration of the symptoms: worsening of right hemiplegia, upper motor neuron weakness of left upper limb, incoordination of movements and aphasia.
- MRI Brain showed new lesions in both cerebral hemispheres, cerebellar hemispheres and pons. The HIV RNA viral load was not detectable with HAART, but CD4 count has decreased to 21.
- The final diagnosis was a severe HIV-related PML-IRIS.
- This is a severe life-threatening condition. Brainstem involvement, no response to steroids and low CD4 count are poor prognostic factors.

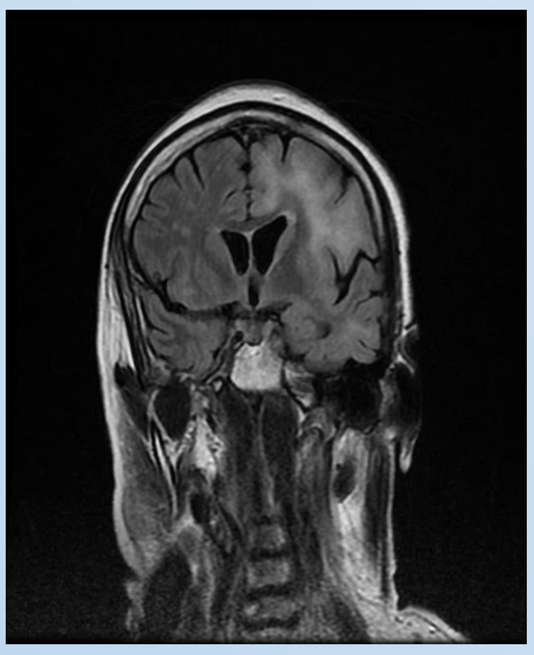


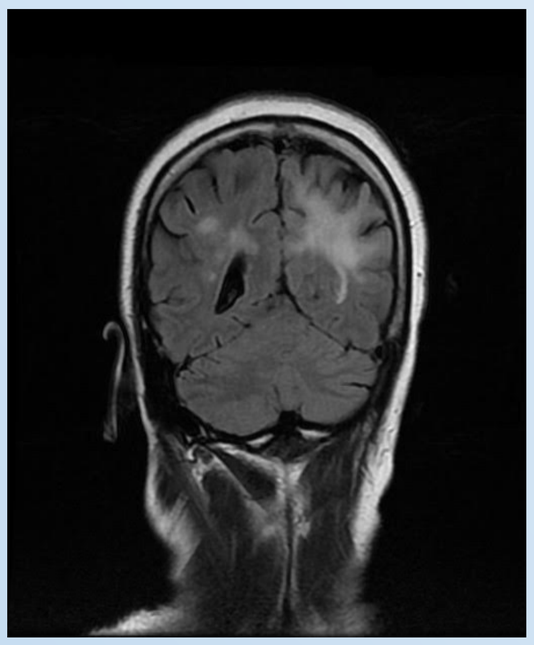
Investigation

- **HIV 1 and 2:** Positive.
- **HIV viral load**→ 5300 → 4131
- **CD4 count:** 65→80.
- **Toxoplasma** IgG-positive, IgM negative.
- **CSF PCR:** JC virus detected.
- Broncho-alveolar lavage isolated Moraxella.
- Urine culture grew E Coli.
- Investigations for all other opportunistic infections associated with HIV were negative.
- USS abdomen and liver: Normal

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- **CD4 count:** 21
- **HIV viral load:** Undetectable
- **MRI Brain:** Significant progression of the focal and diffuse hyper-intensities in T2-weighted and FLAIR images in the both cerebral hemispheres





Treatment and Follow up

- HIV was treated with highly active anti-retroviral therapy (HAART). A combination of Abacavir/dolutegravir/lamivudine (Triumeq) was used. Maraviroc was later added.
- PML-IRIS was treated with dexamethasone.
- Seizures were treated with Lamotrigine.
- Toxoplasmosis was treated initially with Atovaquone. It was later changed to Sulfadiazine plus pyrimethamine.
- She was also on Co-trimoxazole and Azithromycin.
- She was cared by multi-disciplinary team including neurology, neuro-rehabilitation, infectious diseases and HIV team.

Key Points

Diagnosis of AIDS-related PML-IRIS required three major criteria

- **HIV-infected patient**
- **Criteria for definite PML:**
  - Subacute onset of neurological deficits
  - MRI features
  - Presence of JCV DNA in cerebrospinal fluid (CSF)
- **Criteria for definite PML-IRIS in adult HIV-infected patients:**
  - Administration of effective cART within the previous 2 years
  - Subacute onset of neurological deficits that either appeared or was exacerbated after initiation of cART.
  - Decrease in plasmatic HIV RNA viral with or without an increase in CD4 T cell count.
  - Evidence of an inflammatory reaction in the brain demonstrated by MRI and/or CNS histopathology if available.