

Case Report

Progressive multifocal leucoencephalopathy as a manifestation of immune reconstitution inflammatory syndrome in a patient with HIV infection: a case report

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ABSTRACT

Immune reconstitution inflammatory syndrome (IRIS) is defined as paradoxical worsening of a known condition or the appearance of a new condition after initiating antiretroviral therapy (ART) in HIV-infected patients. IRIS results from restored immunity to specific infectious or non-infectious antigens. Immune reconstitution following initiation of ART may lead to activation of an inflammatory response to detectable or latent JC virus (JCV) infection, an etiological agent of progressive multifocal leucoencephalopathy (PML). We present an interesting case of IRIS manifesting as PML in a newly diagnosed HIV-infected patient started on ART.

Keywords: Antiretroviral therapy, Immune reconstitution inflammatory syndrome, John-Cunningham virus, Progressive multifocal leucoencephalopathy

INTRODUCTION

Immune reconstitution inflammatory syndrome (IRIS) is a constellation of symptoms resulting from restoration of immunity in HIV patients after the initiation of antiretroviral therapy (ART).

It results from a decrease in HIV RNA level and an increase in CD4 count from the baseline. The clinical symptoms are consistent with the inflammatory process but the clinical course is not consistent with expected course of previously or newly diagnosed opportunistic infection and drug toxicity.

A few examples IRIS include disseminated tuberculosis, toxoplasmosis, hepatitis B and C, pneumocystis jiroveci pneumonia, sarcoidosis, Guillan-Barre syndrome, etc. Treatment for this disorder includes continuation of primary therapy against the offending pathogen in order

to decrease the antigenic load, continuation of effective ART, and judicious use of anti-inflammatory agents.¹ PML-IRIS is a rare occurrence and can be challenging to manage.

CASE REPORT

A thirty-one-year-old female, recently diagnosed with HIV-1 infection presented with diminution of vision in both the eyes and tremors of right hand of one-month duration. The diminution of vision started in left eye, insidious onset, painless, involved the other eye over a period of ten days. The tremors started simultaneously with the diminution of vision and were present at rest. The patient had been diagnosed with abdominal tuberculosis four months back which led to the diagnosis of HIV on routine testing. The patient was started on Category-1 anti-tubercular treatment (ATT) and on ART (tenofovir, lamivudine, efavirenz) two weeks later. There were no associated co-morbid conditions. The baseline

plasma CD4 count was 23 cells/mm³. The patient was also on co-trimoxazole and azithromycin prophylaxis. Baseline plasma viral load was 1852 copies/ml. On neurological examination, tone was increased in all the muscle groups of upper and lower limbs. Deep tendon reflexes were 3+ bilaterally and bilateral plantars were extensors. A coarse resting tremor was observed in right hand which had no aggravating factor but disappeared with sleep. A complete ophthalmological examination was done to find out the cause of blindness. PL/PR was negative in both the eyes. Both the pupils were 3mm size, well reacting to light and extraocular movements were also normal. Fundus examination was normal. Cerebrospinal fluid (CSF) examination showed total proteins of 30mg%, sugars 50mg% and no nucleated cells. MRI brain was done which showed non-enhancing, asymmetrical areas of altered signal intensity in subcortical white matter of bilateral parieto-occipital lobes, with predominant involvement of subcortical U-fibres which were hyperintense on T2 and hypointense on T1 images (Figure 1). The plasma CD4 count was repeated which was 306 cells/mm³ and plasma and CSF viral loads were 632 and 4672 copies/ml respectively.

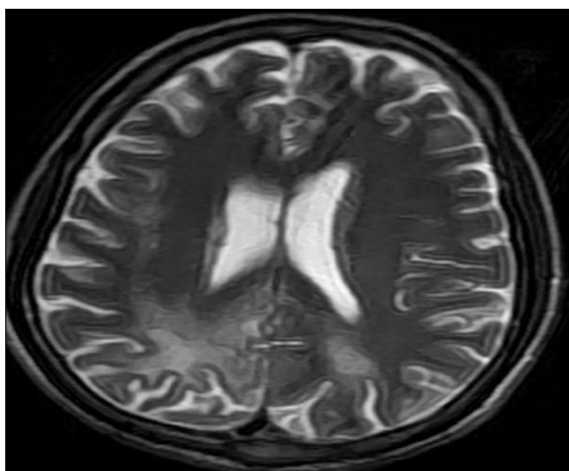


Figure 1: Bilateral patchy ill-defined hyperintensities confined to white matter and subcortical white matter of parieto-occipital lobes.

In summary, a HIV reactive patient with abdominal tuberculosis on ART and ATT presenting with cortical blindness, tremors and bilateral upper motor neuron signs with rapid increase in CD4 counts along with decrease in plasma viral load from baseline value, plasma-CSF viral load discrimination and typical MRI findings suggestive of PML suggested IRIS manifesting as PML. The patient was treated with 1g/d of IV methylprednisolone for 5 days, prednisolone 1.5mg/kg/d thereafter for 2 weeks followed by 1mg/kg/d for 2 weeks and then 0.5 mg/kg/d for another 2 weeks and temporary cessation of ART. Prednisolone was discontinued after 6 weeks of treatment. ATT was continued and the patient was monitored for any dissemination of the disease. Co-trimoxazole and azithromycin prophylaxis was stopped. The patient showed improvement in muscle tone and

tremors but no improvement was noticed in the vision. But no improvement was noticed in the vision. The ART (tenofovir, lamivudine, efavirenz) was then reintroduced and the patient was asked to keep close follow up.

DISCUSSION

PML is a demyelinating disease of central nervous system caused by reactivation of JCV, a polyomavirus, which infects oligodendrocytes and astrocytes in the CNS, inducing lytic reaction leading to demyelination, necrosis, and cell death. Up to 5% of patients with AIDS develop PML and it is currently one of the AIDS-defining illnesses in HIV-infected patients.² Incidence of PML in HIV-infected patients has declined in the cART era but the cases of PML-IRIS are being more and more recognised. PML may develop or worsen with antiretroviral therapy, despite a recovery of the immune system.³ PML can be a manifestation of IRIS that occurs as a result of “unmasking” of clinically silent infection and is characterized by inflammatory reaction in brain lesions and/or an accelerated clinical presentation suggesting a restoration of antigen-specific immunity.⁴ Factors predictive of development of IRIS include antiretroviral naivety, active or subclinical opportunistic infection at initiation of cART, low CD4 count (<50 cells/cumm) and rapid immune recovery indicated by a prompt decrease in HIV plasma viral load.⁵ Among the risk factors identified, our patient had younger age, antiretroviral naivety, lower baseline CD4 count and decrease in plasma HIV viral load. Potential mechanisms of PML-IRIS development include an unravelling of a latent subclinical infection triggered by immune recovery or JCV-induced reactivation mediated by cytokines.⁴ The clinical presentation of PML-IRIS do not differ from that of PML seen in HIV patients without IRIS except that the onset may occur weeks to months after initiation of cART. Patients typically experience insidious onset of focal symptoms that include behavioural, speech, cognitive and visual impairment.⁶ The visual symptoms in PML result from visual pathway involvement rather than from optic neuritis as seen with other demyelinating diseases. Patients may also demonstrate motor symptoms like head or hand tremors. There can be numerous causes of tremors in HIV patient including opportunistic infections and drugs like co-trimoxazole.^{7,8} In our patient, it was difficult to establish the cause of hand tremor as PML related or cotrimoxazole related. On MRI, PML lesions are hypointense on T1-weighted images and thus can be differentiated from other white matter lesions like HIV encephalitis. T2-weighted and FLAIR sequences characteristically show hyperintense lesions. PML due to immune reconstitution may sometimes demonstrate atypical features like contrast enhancement and mass effect.⁹ No drug is effective against JCV and therapeutic management of PML-IRIS relies on steroids. Steroid treatment in PML-IRIS is anecdotal and the trials are lacking. The use of steroids in IRIS may be advocated if there is major neurologic, clinical or radiologic

worsening.⁴ The optimum time of institution, dose and duration of steroid therapy is not well established but some may benefit from 6-8 weeks of treatment and some may not need any other therapy than Cart.^{10,11} However, the role of long-term use of steroid therapy can only be understood by formal studies in PML-IRIS and its treatment.

CONCLUSION

Initiation of ART in HIV patients with very low CD4 cell count and high plasma viral load should be carefully monitored for the appearance of any symptoms consistent with inflammatory process so that the appropriate diagnostic intervention can be carried out at earliest to find out the treatable etiology.

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