Immune Reconstitution Inflammatory Syndrome (IRIS) Associated Multifocal Leukoencephalopathy (PML) in Patients with Human Immunodeficiency Virus (HIV) Infection: A Case Report

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Abstract—*Progressive Multifocal Leukoencephalopathy (PML) is seen mostly in advanced human immunodeficiency virus (HIV) infection. In some individuals, especially those with very low $CD4^+$ counts, worsening of PML or new-onset PML can be observed after the initiation of highly active antiretroviral therapy (HAART). A case of IRIS associated PML is reported here which is much more rare as compared to PML in HIV patients unrelated to HAART. This is thought to be secondary to immune reconstitution inflammatory syndrome (IRIS). IRIS is defined as a paradoxical deterioration of a previously existing infection which is related to the immune system recovery. It is suggested to occur due to an imbalance of $CD8^+/CD4^+$ T cells. So in HIV cases with low CD4 counts and if one is on HAART then should be further investigated for IRIS and PML.*

Keywords: PML, HIV, HAART, IRIS

I. INTRODUCTION

Subclinical hypothyroidism (SCH) can be best defined as a high serum thyroid stimulating hormone (TSH) and normal serum total/free thyroxine (T4), triiodothyronine (T3) concentrations associated with few or no symptoms/signs of hypothyroidism. It is referred to as a state of mild thyroid failure and is essentially a laboratory diagnosis.[1,2] Subclinical hypothyroidism is much more common than overt hypothyroidism[3,4] with a world-wide prevalence of about 7.5% to 8.5% in women and 2.8% to 4.4% in men. [5]

In the era of combined antiretroviral therapy, despite a dramatic fall in the incidence of most opportunistic infections, progressive multifocal leukoencephalopathy (PML) continues to occur at a similar frequency in HIV infected patients. PML occurs in up to 5% of patients with Acquired Immunodeficiency Syndrome (AIDS). [1]

PML-IRIS may account for up to 18% of HIV-infected patients with PML. Rest 82% PML in HIV is unrelated to HAART treatment. Reactivation of JC virus (JCV), a polyoma virus, leads to PML. JCV infects oligodendrocytes and astrocytes in the CNS and induces a non-inflammatory lytic reaction which leads to demyelination, necrosis, and cell death. In some individuals, especially those with very low $CD4^+$ counts, after the initiation of highly active antiretroviral therapy (HAART) worsening of PML or new-onset PML can be observed. This is thought to be secondary to immune reconstitution

inflammatory syndrome (IRIS). Immune reconstitution inflammatory syndrome (IRIS) is a paradoxical deterioration of a previously existing infection following the initiation of HAART in patients with HIV infection. [2,3]

II. METHODOLOGY

A typical case of HIV with IRIS and PML attended in Medicine OPD of SMS Hospital, Jaipur. So case study was done thoroughly and case report was prepared to publish this rare case.

III. CASE REPORT

A 52-year-old north Indian male with a past medical history of hypertension and diabetes mellitus was presented with noncompliance with medication, who also presented with insidious onset, gradually progressive weakness of left side of the body and progressive dysarthria over a 20-day period that had worsened in the previous 3-4 days along with vertigo, vomiting, imbalance of gait, swaying of left side of the body, ataxia and weakness of left side with cerebellar hypotonia. The patient denied any other neurological symptoms.

On neurological examination, the patient was found to have difficulties with speech, nystagmus, left sided cerebellar signs and hypotonia. The rest of the neurological examination was normal.

During the hospital stay, an MRI of the brain was performed for the suspicion of stroke or demyelination etiology. A contrast enhanced MRI brain showed scalloped, high signal lesion in the left fronto-parietal white matter and left cerebellar hemisphere in the axial T2- weighted fast spin-echo (FSE) image (Figure 1). The lesion is better seen on axial FLAIR-FSE image (Figure 3). There is no mass effect. No enhancement is seen in the contrast enhanced T1-weighted SE (spin echo), which was not typical for ischemic infarction or demyelination (Figure 1 to 5). This subsequently broadened the differential to include sarcoidosis, PML, CMV (Cytomegalo virus) encephalitis. The PCR for JC virus in the CSF was positive; on that basis diagnosis of PML was made.

Figure: 1
MRI Brain- diffuse increased T2 weighted signal throughout the left cerebellar hemisphere

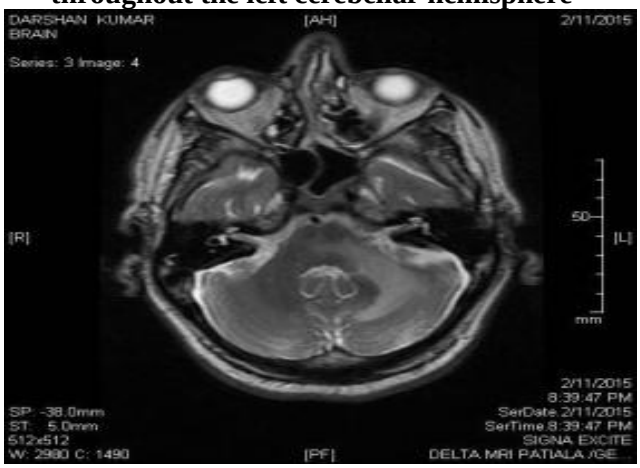


Figure: 2
MRI Brain- increased T2 weighted signal in left frontal lobe

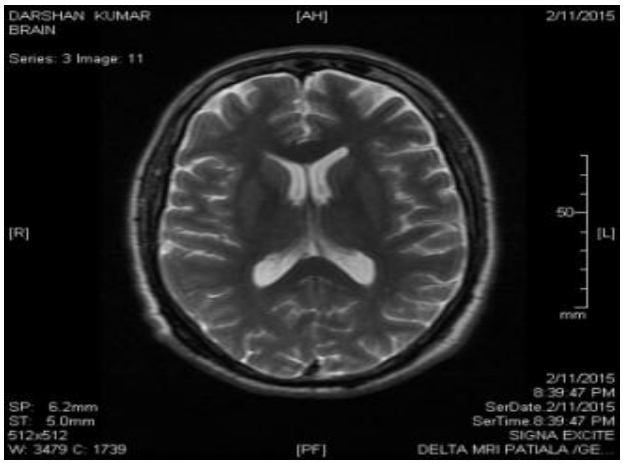


Figure: 3

MRI Brain- increased axial FLAIR signal in pons

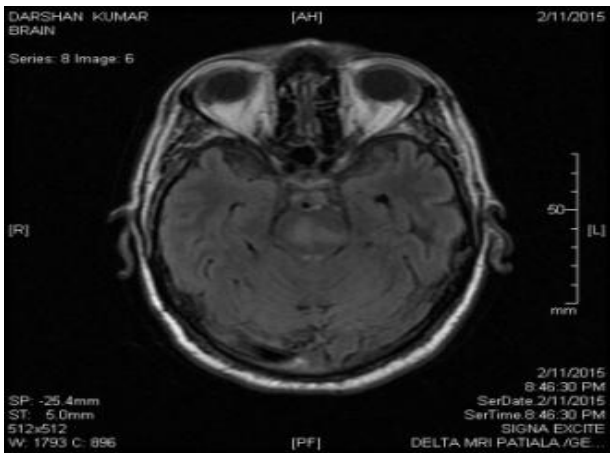


Figure: 4

MRI Brain- increased coronal FLAIR signal in left frontal lobe

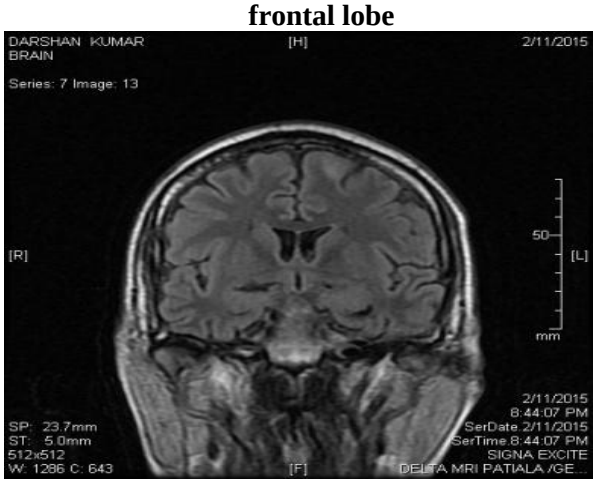
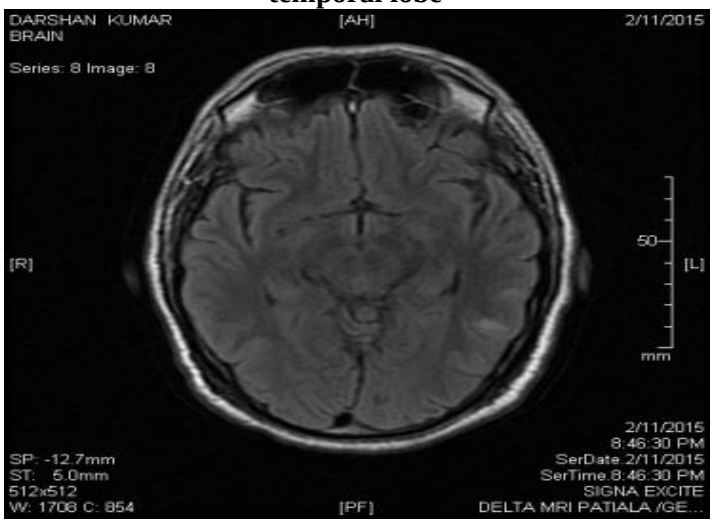


Figure: 5

MRI Brain- increased axial FLAIR signal in left temporal lobe



The patient was HIV positive with CD4 count of 26. The CD4 count had increased diminutively from 26 to 77 during last 2 months after starting HAART. The patient was assessed to have possible immune reconstitution inflammatory syndrome (IRIS) given the new-onset weakness and dysarthria.

The patient was continued on HAART and started intravenous dexamethasone, antiepileptic medications and Pneumocystis carinii prophylaxis.

On follow up in next visit, patient showed improvement in his neurological deficit along with radiological improvement.

IV. DISCUSSION

PML-IRIS develops between 1 week and 26 months after initiation of antiretroviral therapy. There is sparse literature on HIV/AIDS with PML from developing countries including India. Progressive multifocal leukoencephalopathy (PML) is a CNS (central nervous system) demyelinating disease. It is caused by JC polyoma virus (JCV). Acquired immunodeficiency syndrome (AIDS), after the advent of

the HIV epidemic, became the most common predisposing factor for the occurrence of PML.[4] The incidence of PML has fallen less dramatically when compared to other CNS diseases after the advent of HAART.[5] The use of combined antiretroviral therapy markedly improves immune function and prognosis in HIV-infected patients; however, PML may develop or worsen with antiretroviral therapy, despite an immunological recovery. Immune reconstitution inflammatory syndrome (IRIS) is responsible for this manifestation.[6]

IRIS, by definition, comprises of an inflammatory component which occurs in the setting of reconstitution of the immune system that cannot be elaborated or justified by toxicity of the drug, a new opportunistic infection (OI), or the expected course of a previously diagnosed OI. The clinical features of IRIS are the result of dysregulated and enhanced cellular immune responses and are linked to the site and type of pre-existing infections. Wide range of pre-existing infections which include Pneumocystis carinii, mycobacterial and cryptococcal infections, Kaposi's sarcoma, cytomegalovirus, non-Hodgkin lymphoma and PML.[7]

In this case, PML-IRIS was defined by the following clinical criteria: 1) Patient with HIV infection; 2) The diagnosis of PML was established by detection of JCV DNA in the CSF 3) By the presence of characteristic clinical and neuro-radiological features with exclusion of other opportunistic infections (tuberculosis, toxoplasmosis, cryptococcosis, other viral infections) and CNS lymphoma; 4) Symptoms could not be explained by a newly acquired infection, the expected course of a newly diagnosed opportunistic infection, or drug toxicity.

Risk factors for the development of IRIS in HIV-infected individuals include antiretroviral naive, using a boosted protease inhibitor, low CD4 lymphocyte counts (<100 cells/mm^3), higher level of viraemia at baseline, rapid decrease in HIV load, rapid immune recovery following the initiation of HAART, and the presence of active or subclinical opportunistic infections at the time of initiation of HAART.[8]

This patient is antiretroviral naive, CD4 count <50, and no active opportunistic infection at the time of initiation of HAART. Risk factors for the development of IRIS in this patient is antiretroviral naive, and CD4 count 22 with no history suggestive of opportunistic infection.

For the prevention or treatment of PML-IRIS, till date, there are no evidence-based guidelines. Some cases of IRIS are mild and resolve with continuation of combined antiretroviral therapy. Others result in significant morbidity and sometimes death. Anti-inflammatory agents such as steroids have been used and may be effective in the treatment of IRIS following other AIDS-related CNS infections.[9]

There are no effective drugs that inhibit or cure the virus infection without toxicity. Therefore treatment aims at reversing the immune deficiency to slow or stop the disease progression. In patients on immunosuppressant which means stopping the drugs or using plasma exchange to accelerate the removal of the biologic agents like rituximab and natalizumab may put the person at risk for PML.[10] In HIV infected people, starting highly active antiretroviral therapy (HAART) may lead to PML. AIDS patients starting HAART after being diagnosed with PML tend to have a slightly longer survival time than patients who were already on HAART and then develop PML. [11]

In patients with PML-IRIS, the standard treatment is continuation of HAART therapy in addition to high-dose glucocorticoid therapy (e.g., dexamethasone). However, the efficacy and safety of using steroids in PML-IRIS remain largely unknown due to limited data. A combination of neurologic deterioration and radiologic evidence of brain swelling is a relative indication for steroid usage.[12,13]

In three separate case reports, HAART was discontinued for 2-3 weeks following diagnosis of PML-IRIS, and the patients did well on the followup. However, the practice of discontinuing HAART is not currently advocated.[14]

Following the diagnosis of PML-IRIS in our patient, HAART was continued, and dexamethasone was added in an attempt to counteract the cerebral edema. This corresponds to the standard treatment of PML-IRIS. In this case, we examine the effects of steroid use in HIV-infected patients with PML-IRIS.

Cidofovir, Cytarabine (also known as ARA-C), a chemotherapy drug and antimalarial drug Mefloquine with activity against the JC virus were studied as possible treatment for PML[15,16,17] and has been used on a case by case basis, working in some but not others.

V. CONCLUSION

It can be concluded from this study that subjects with HIV, following the initiation of HAART, reconstitution of immune system may lead to activation of an inflammatory response which may leads to detectable or latent JC virus infection. Early and prolonged treatment with steroids may be useful in patients with PML-IRIS but requires further investigation.

CONFLICT OF INTEREST

None declared till now.

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