Brief Report

Immune reconstitution inflammatory syndrome

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ABSTRACT

Background: Immune reconstitution inflammatory syndrome (IRIS) is a paradoxical deterioration in clinical status in a patient on antiretroviral treatment (ART) despite satisfactory control of viral replication and improvement of CD4 count. **Aim:** To study development of IRIS as a part of ART. **Methods:** Hundred patients on antiretroviral treatment were studied prospectively in the Department of Skin and VD over a period of 2 years. Patients were asked to come if they developed any symptoms or on a monthly basis. They were screened clinically and investigated suitably for evidence of opportunistic infections. **Results:** Out of 100 patients, 10 patients did not come for follow-up. Twenty (22.2%) out of the 90 patients developed IRIS. Herpes zoster (HZ), herpes simplex virus (HSV), and tuberculosis (TB) were the cases of IRIS seen in the present study. **Conclusions:** IRIS in terms of HSV/TB is known to accelerate HIV disease progression. Hence early detection and prompt treatment, along with continuation of highly active ART, are of utmost importance.

Key Words: Immune reconstitution inflammatory syndrome, Antiretroviral therapy

INTRODUCTION

The immune reconstitution inflammatory syndrome (IRIS) is a spectrum of clinical signs and symptoms resulting from the restored ability to mount an inflammatory response associated with immune recovery.[1] It can present with the signs and symptoms of a previously subclinical and unrecognized opportunistic infection, as a paradoxical worsening of treatment response several weeks into therapy, or as an autoimmune disease such as Grave's disease (hyperthyroidism) in the context of immune recovery on antiretroviral therapy (ART). There are no specific laboratory markers to differentiate HIV IRIS from opportunistic infections that develop owing to inadequate restoration of immunity after an insufficient ART. However, the appearance of opportunistic infections within a rather loosely defined period with a median time of 8 to 12 weeks should be identified as IRIS.[2] There are also reports stating that IRIS may occur even years later.[3]

The incidence of IRIS is estimated to be 10% among all patients initiating ART and up to 25% among patients initiating ART with a CD4 cell count below 50 cells/mm^3.[4,5]

Risk factors predicting the likelihood of IRIS include initiating ART close to the time of diagnosis of an opportunistic infection, being antiretroviral-naive at the time of diagnosis of an opportunistic infection, initiating ART when the CD4 count is below 50 cells/mm^3 and having a more rapid initial decrease in the HIV-1 RNA level in response to ART compared to patients with higher CD4 counts.[6]

METHODS

This study was carried out in our HIV referral clinic, during the period from September 2004 to October 2006. One hundred HIV infected patients on antiretroviral treatment (ART) were enrolled.

A detailed history of every patient was taken, including past history of ART. All patients were clinically evaluated and treated for opportunistic infections. Baseline laboratory investigations such as hemoglobin, total count, differential count, Erythrocyte sedimentation rate, urine (albumin, sugar, and microscopic examination), Venereal disease research laboratory (VDRL) test, Hepatitis B surface antigen test (HBsAg), Mantoux test (MT) and Fine needle

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aspiration cytology (FNAC) of lymph nodes were carried out in each patient. X-ray chest (PA view) and ultrasonography of abdomen were done in all cases to find out focus of tuberculosis. Lymphocyte enumeration was carried out before starting anti-tuberculous therapy (ATT), and viral load was not advised routinely.

All the patients were given 3 drug regimens according to affordability of the patient. All patients on ART were subjected to clinical and laboratory monitoring periodically. Patients were screened for OIs and drug toxicity on each visit. CD4 count was done every 6 months or more frequently if clinically indicated. Plasma viral load was not done routinely. It was carried out in patients with treatment failure. Adherence to medication given during this study was assessed based on patients' self-report. They were asked to bring empty bottles and strips.

A diagnosis of IRIS was considered in patients presenting with infections in the initial few weeks of ART or in patients who were otherwise improving clinically or immunologically. CD4 count could not be carried out in all patients at the time of development of IRIS because of resource restriction.

RESULTS

Hundred patients were enrolled in the study. Ten patients were lost to follow-up after the first visit, and only ninety patients were available for evaluation. The most common presentation was herpes zoster and herpes simplex, followed by tuberculosis [Table 1]. TB IRIS was observed in 4 cases [Figure 1]. Two of them had abdominal TB detected on ultrasonography. Two patients had tuberculous lymphadenitis, which was confirmed by FNAC. Two of these 4 patients had past history of pulmonary TB, for which they had completed treatment. In all 4 cases, AKT was started on diagnosis of TB IRIS, along with a shift to efavirenz-based ART. All cases with IRIS were investigated thoroughly; ART was continued and they were managed conservatively.

Table 1: Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome	Present Study (n=90)	Thevarajan I *et al*. (n=200)[7]
Herpes zoster	11 (12.2%)	04 (2%)
Herpes simplex	05 (5.5%)	24 (12%)
Tuberculosis	04 (4.4%)	03 (1.5%)
Viral warts	00	10 (5%)
Molluscum contagiosum	00	04 (2%)
	20 (22.2%)	45 (22.5%)

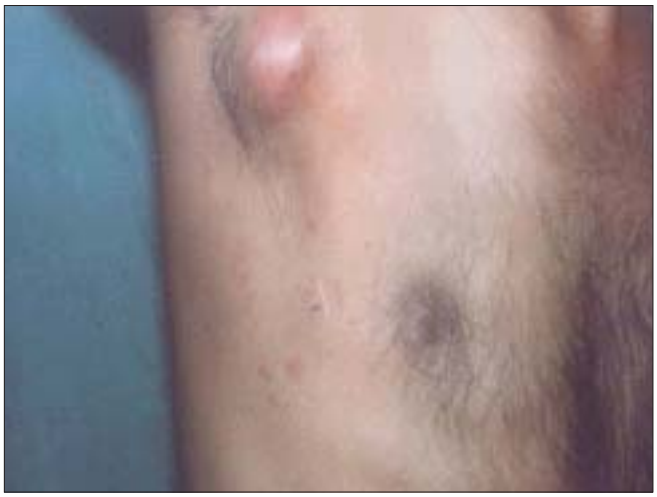

Figure 1: Tuberculous lymphadenitis as an IRIS

DISCUSSION

The most frequently occurring IRIS events are associated with mycobacterial disease (tuberculosis (TB) or mycobacterium avium complex infection) and cryptococcal disease. Together, they account for approximately 60% of all cases of IRIS in developed countries.[7]

Mechanism of IRIS is poorly understood. Its development appears to be linked not only to increase in CD4 levels but also to higher CD8 counts induced by HAART. An elevated CD8 cell count has been suggested as a prime contributing factor in worsening of both herpes zoster (HZ) and hepatitis B or C symptoms after initiation of ART. Guillamune Foulon *et al,* reported that IL-2 and IFN-gamma appeared to speed up the development of sarcoidosis in patients on ART.[8]

Diseases and pathogens associated with IRIS are cytomegalovirus (CMV) retinitis, toxoplasmosis, *Cryptococcus neoformans*, chronic active hepatitis due to hepatitis B and C virus, Reiter's disease, Herpes zoster (HZ), psoriasis, *Mycobacterium avium complex* (MAC), lymphadenitis, *Mycobacterium leprae*, PML (progressive multifocal leukoencephalopathy), human papilloma virus (HPV) – warts, sarcoidosis, Gullian Barre syndrome, appendicitis, and parvovirus B-19.[8]

Treatment of IRIS includes NSAIDs, steroids (when life threatening or in condition of threatened organ dysfunction), discontinuing ART if steroids fail and for tuberculous lymph nodes, surgical drainage of nodes.

Thorough screening for hidden/opportunistic infections (OIs) should be done before starting ART to prevent development

of IRIS. All cases with past history of OIs should be closely watched for development of IRIS. IRIS was observed in 20 (22.2%) of the total number of patients

Christian Hoffman reported that IRIS is more prevalent in patients with CD4 count less than 200 cells/mm^3; in the present study, 10 patients had CD4 count <100 cells/mm^3.[9] Median CD4 count at the time of initiation of ART in patients having IRIS was 94 cells/mm^3 [Table 2]. In a Kings College study, median time and CD4 count for development of IRIS were 12 weeks and 172 cells/mm^3 respectively; while in the present study, they were 11 weeks and 94 cells/mm^3 respectively.[8] IRIS is seen most often in patients who start ART with advanced HIV disease, particularly in those with very low CD4 counts; it usually develops in the initial weeks of therapy. The poorer the immune status and longer is the interval between initiation of ART and occurrence of IRIS, higher is the danger of IRIS. Chest radiography, abdominal ultrasound, and fundoscopy should be included in routine investigations of such patients before treatment and clinical examination should be taken seriously.

IRIS is not a sign of treatment failure. It is not a reason to switch therapy but should be evaluated thoroughly to exclude treatment failure or the presence of other infections. It is usually self limited in duration and will resolve within a few weeks by continuing ART and treatment for existing OIs. Unless IRIS is life threatening, there is usually no reason to stop ART. Furthermore, the occurrence of IRIS does not mean that maintenance treatment for OIs should be changed or that previously completed treatment for OIs (e.g., tuberculosis) should be re-initiated. Similarly, the dosages of chronic suppressive treatment for OIs should not be increased because of presence of OIs caused by IRIS.

There are no clear guidelines for the management of severe IRIS; approaches include temporarily stopping ART until the patient has stabilized and using systemic corticosteroid therapy to reduce inflammation.

Table 2: Profile of cases having IRIS (n = 20)

Immune reconstitution inflammatory syndrome (n=20)	CD4 count/mm^3	Weeks since initiating ART
Herpes zoster (n=11)	26	03
Median CD4 = 90	65	11
Median time = 13.5 wk	175	25
	90	17
	158	18
	224	22
	28	14.5
	179	10.5
	94	04
	29	13.5
	26	5.5
Herpes simplex (n=05)	75	11
Median CD4 = 105	105	0.5
Median time = 4 wk	190	1.5
	146	04
	58	22
Tuberculosis (n=04)	181	65
Median CD4 = 131	158	17
Median time = 12 wk	53	05
	104	07

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