CASE REPORT

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HIV-Associated Cutaneous Kaposi's Sarcoma induced by IRIS following Antiretroviral Therapy

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Introduction

Immune reconstitution inflammatory syndrome (IRIS) is a set of conditions that result from an exuberant response to residual opportunistic pathogens by a newly reconstituted immune system after initiating immune modifying therapeutic treatment or discontinuing the immunosuppressive therapy. It involves a wide range of pathogens, tumours, and some autoimmune diseases. Kaposi sarcoma (KS) is an angio-proliferative tumour capable of affecting the skin, lymph nodes, and viscera. It is a well-known acquired immunodeficiency syndrome (AIDS) defining illness presenting in patients with low CD4 counts and high viral loads, but can also be reactivated in an IRIS-related process[1]. KS remains the most common tumour in individuals infected with human immunodeficiency virus (HIV) and a significant cause of morbidity and mortality.

Case report

A 30-year-old male, diagnosed with HIV two months back, presented to the outpatient department with complaints of multiple reddish patches over his chest, back and shoulders for the last 20 days. He was on highly active antiretroviral therapy (HAART), i.e., Tenofovir 300 mg, Lamivudine 300 mg, and Efavirenz 600 mg for the past 2 months. All routine laboratory investigations were done, as listed in Table I. HIV RNA viral load and CD-T4 lymphocyte levels were also tested again after baseline at the time of diagnosis, as listed in Table II. On examination, the patches were hyperpigmented red-coloured raised plaques (Fig. 1), that were painless in nature and not associated with any itching or burning sensation. A large rounded growth was also noticed behind the left ear (Fig. 2A). Gum hypertrophy was observed with no oral thrush on examination of the mouth (Fig. 2B).

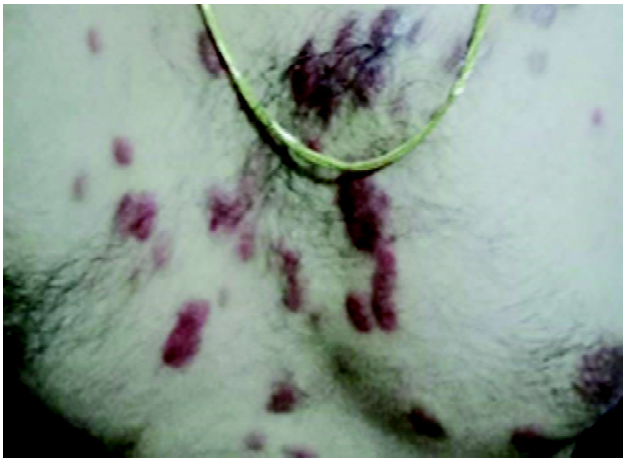

Fig. 1: *Showing multiple hyper-pigmented nodular raised lesions, similar lesions were also found on the back and the shoulder.*

Table I: Routine laboratory investigations.

Tests	Results	Normal range
Haemoglobin	10.5 g/dl	14 - 17 g/dl
TLC	5,000 cells/mm^3	4.5 - 11.0 $\times$ 10^3/mm^3
Platelet count	1,00,000/ul	150,000 - 450,000/ul
ESR	25 mm/1st hr	< 15 mm/1st hr
ALT	36 U/L	7 - 55 U/L
AST	34 U/L	8 - 48 U/L
Serum creatinine	0.9 mg/dl	0.74 - 1.35 mg/dl
Serum sodium	141 mEq/l	135 - 145 mEq/l
Serum potassium	3.7 mEq/l	3.5 - 5.5 mEq/l
S. TSH	3.6 mIU/l	0.5 - 5.0 mIU/l
Abdominal sonography	Normal study	
Urine R/E	Clear	
ECG	Normal sinus rhythm	
Chest X-ray	Normal Skiagram	

Table II: Special laboratory investigations.

HIV specific tests	Baseline values	New values
Viral load	> 100,000 copies/ml	11,238 copies/ml
Absolute CD4 count	208 cells/ml	302 cells/ml

All routine investigations were within normal limits. The HIV RNA levels showed a reduction, whereas CD-T4 lymphocyte counts had increased. Hence, an IRIS-related

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pathology was suspected. For further work-up, a skin biopsy was done to rule-out KS as it could be one possibility of IRIS. Histopathological examination revealed extensive vascular proliferation and spindle cells. Immuno-histochemistry for human herpesvirus 8 (HHV 8) was positive. A diagnosis of IRIS associated with cutaneous Kaposi sarcoma was made. CT chest and abdomen were done to rule-out dissemination, both were within normal limits. Hence, HAART was continued as there was no evidence of dissemination on further imaging.

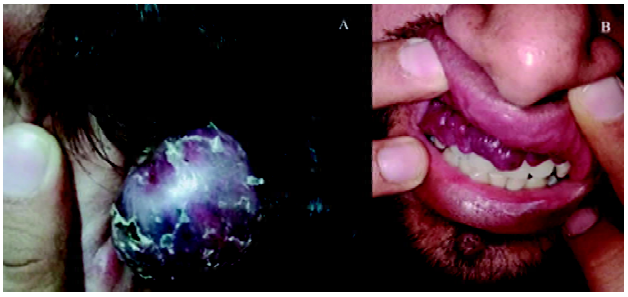

Fig. 2A: *Showing large nodular growth behind the left ear.* ***2B:*** *Showing gum hypertrophy.*

Discussion

The most common presentation of KS is the HIV-related epidemic type. HIV-KS has been considered an AIDS-defining condition due to its presentation in the setting of severe immunodeficiency with low CD4 T-cell counts and high viral loads. Although there have been case reports that suggested that IRIS-KS occurred in patients with high CD4 counts as well[2]. The pathogenesis of HAART-induced IRIS-KS is characterised by dysregulation of the restored host inflammatory response. HAART causes an increase in CD4+ T-cells and a decrease in HIV viral load which promotes the production of inflammatory cytokines in the host that trigger the expression of HHV-8 gene products into antigens[2]. The production of HHV-8 antigens causes a shift from Th2 (CD4+ T-cell dominant) to Th1 (CD8+ T-cell dominant) immune response, that specifically targets HHV-8 antigen[3]. The strengthened Th2 and Th1 arms of the immune system result in aberrant signalling for excessive inflammation, promotion of angiogenesis, and transformation of endothelial cells by the HHV-8 antigen, all of which contribute to the angio-proliferative manifestations of KS disease. Patients with greater immunodeficiency at the initiation of HAART are at increased risk of developing IRIS, with an incidence reported as high as 25% in patients with a baseline CD4 T-cell count of < 50 cells/mm. Diagnostic criteria for IRIS-induced HIV-KS include a patient on HAART with new, worsening, or recurrent KS lesions in the setting of increased CD4 count greater than or equal to 50 cells/ml or a two-fold increase, and a decrease in HIV-1 viral load greater than 0.5 log. The time frame for development of KS following initiation of HAART is not clearly defined, although several cases report cutaneous lesions developing within eight to twelve weeks of initiating therapy[2,4,5]. Prognosis in patients with IRIS-associated HIV-KS is promising, particularly in the setting of immunocompetence[6]. The introduction of antiretroviral therapy has led to a decrease in the overall incidence and prevalence of HIV/AIDS-related KS secondary to the recovery of host immune response and reduction of HIV and HHV-8 viral loads. HAART is mainly preventative and therapeutic for clinical HIV-KS, a subset of HIV-seropositive individuals will have onset of new, worsening, or recurrent KS lesions secondary to a paradoxical phenomenon known as immune reconstitution inflammatory syndrome following initiation of antiretroviral therapy[7]. Optimal control of HIV infection by continuing HAART is an integral part of successful therapy, with recommended additional adjunctive local or systemic therapy depending on the extent of the disease. No preventive treatment for KS-IRIS has yet been confirmed. Glucocorticoids are held in reserve for life-threatening cases only, as they may be risky for use in KS-IRIS treatment[8]. Disseminated KS is a rare entity with worst prognosis, though our patient did not have any evidence of dissemination there have been case reports of disseminated KS in HIV patients in India[9]. There have been other case reports about IRIS-KS which further led to complications like Kaposi sarcoma inflammatory cytokine syndrome that further led to poor prognosis and death of the patient[10]. HIV patients who do not receive ART are at a higher risk for progression of KS with a considerable mortality rate. The delay in diagnosis can lead to more opportunistic infections thereby increasing the risk of developing IRIS. Skin lesions in KS can be effortlessly mistaken as haematomas, purpura, angiomas, or naevi. Therefore, it is important to consider HIV-associated cutaneous KS as a differential for any multiple painless reddish skin lesions[11]. IRIS-KS is often not easily identified and may occur in patients who resume HAART after a long gap[8]. There have been many case reports where KS progressed from presenting as skin lesions to further worsening with pulmonary lesions. Such cases had a poorer prognosis[12].

Conclusion

IRIS-associated HIV-KS is a paradoxical immune-inflammatory reaction brought about by improvement in immune status following antiretroviral therapy. In our current era of HAART-controlled HIV disease, dermatologists must remain suspicious of IRIS-associated HIV-KS, regardless of initial CD4+ T-cell count or HIV viral load. Judicious and appropriate screening is recommended for pre-existing KS lesions as well as for evidence of new eruptions following

recovery of the immune system. This condition is best managed with continued disease control on HAART as well as adjunctive local or systemic therapy depending on clinical severity on a case-by-case basis.

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