Bullous disorders as a manifestation of immune reconstitution inflammatory syndrome: A series of three cases

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Abstract

Bullous disorders such as pemphigus vulgaris, bullous pemphigoid after the initiation of highly active antiretroviral therapy in certain human immunodeficiency virus reactive individuals have been described in this case series as a manifestation of an immune reconstitution inflammatory syndrome. This phenomenon should be suspected in individuals who present with bullous lesions within 3-8 weeks after initiation of therapy despite of improved immunological response. Strong clinical suspicion, through clinical examination, appropriate laboratory investigation such as CD4 T-cell count, histopathological examinations with H and E stain, direct immunofluorescence test are required for diagnosis.

Key words: Bullous pemphigoid, immune reconstitution, pemphigus vulgaris

INTRODUCTION

Human immunodeficiency virus (HIV) immune reconstitution inflammatory syndrome (IRIS) is a newly described clinical syndrome, which occurs after initiation of antiretroviral therapy (ART), resulting in exacerbated inflammatory response to a pre-existing antigen or pathogen and a paradoxical deterioration of clinical status. This phenomenon results into exacerbation of infectious and non-infectious diseases. IRIS is thought to be caused by improvement of host immune response to pathogen or antigen, particularly when the CD4 T-cell count was very low at the initiation of ART. Several autoimmune diseases have been reported as a manifestation of IRIS such as systemic lupus erythematosus (SLE), autoimmune thyroiditis etc., Pemphigus vulgaris (PV) and bullous pemphigoid (BP) are an important group of bullous disorder caused by pathogenic autoantibody against intercellular substance (desmoglein) and dermo-epidermal junction respectively. Here, we report three cases of bullous diseases, which occurred in HIV patients during immune reconstitution.

CASE REPORTS

Case 1
A 45-year-old, Hindu, male, truck driver was found to be HIV reactive 4 years back. Since then, he was on regular monitoring of CD4 T-cell count at ART clinic. He had recurrent attacks of loose motion 3 months back. Investigations showed his CD4 T-cell count was 44/µL. Highly active antiretroviral therapy (HAART), comprising zidovudine, lamivudine and nevirapine was started after routine laboratory investigations. After 4 weeks, multiple flaccid bullous lesions appeared on the different parts of the body. Oral and genital mucosa were involved.

Clinical examination showed positive Nikolsky sign. Tzanck smear showed acantholytic cell under light microscope.
Investigation revealed increased CD4 T-cell count (252/µL). Incisional biopsy for histopathological examination (HPE) with haematoxylin and eosin stain showed intra-epidermal bullae [Figure 1] and perilesional punch biopsy for the direct immunofluorescence (DIF) showed intra-epidermal deposition of immunoglobulin G (IgG). Considering all the findings, PV was diagnosed.

**Case 2**
A 38-year-old known HIV positive, Hindu, male, goldsmith had a history of sudden loss of weight for last 3 months. Investigations revealed the CD4 T-cell count was 53/µL. HAART was started. Bullous lesion appeared on the trunk and face, 3 weeks after the initiation of HAART. Clinical examination showed multiple erosions and crusted lesions present almost all over the body. The soft palate and inner side of lips were also involved. Nikolsky sign was positive. The CD-4 T-cell was found to be increased to 274/µL. Nevirapine was stopped immediately, but the lesions were persisting. Tzanck smear showed acantholytic cell under light microscope. Histopathology from a fresh lesion showed intra-epidermal bullae. DIF from perilesional skin showed IgG deposition within the epidermis in lacy pattern. The clinical features and investigations point toward the diagnosis of PV.

**Case 3**
A 42-year-old known HIV positive, Hindu lady showed CD4 T-cell count 50/µL during her 6 monthly routine follow-up. HAART was started with Zidovudine, Lamivudine and Nevirapine. After 8 weeks, she came to dermatology out-patient department with the complaints of multiple reddish, itchy rashes on the different parts of the body. They were transformed into bullous lesions within 2-3 days. Nevirapine was stopped immediately, but the lesions were persisting. Investigation revealed CD4 T-cell count was 260/µL. Clinical examination showed the multiple tense bullous having round margin and appeared on erythematous urticarial base on the skin. Mucosa were not involved. The bullous spread sign was positive, but Nikolsky sign was negative. Tzanck smear showed no acantholytic cell. HPE revealed sub-epidermal bullae [Figure 2] with eosinophilic infiltrate. IgG and C3 deposition was found at the dermo-epidermal junction on DIF. Hence BP was diagnosed.

**DISCUSSION**
IRIS is paradoxical response to HAART in patients with HIV and acquired immunodeficiency syndrome to a pre-existing antigen or pathogen. Generally, HAART in HIV infected patients lead to recovery of CD4 T-cell numbers and restoration of protective immune response, which reduces the frequency of opportunistic infections and prolonged survival. However, in a subset of HIV patient, receiving HAART leads to unbalanced reconstitution of effector and regulatory T-cell and results into exuberant inflammatory response. Most of the IRIS has been reported in 10-32% of patients starting HAART in a developed country.[3]

The risk factors for IRIS are rapid decline of viral load, low base line CD4 T-cell count <50/µL, and rapid increase of CD4 T-cell after initiation of HAART, for opportunistic infection.[4] The most common infectious IRIS is tuberculosis. Other major diseases described with IRIS are Mycobacterium avium complex causing endobronchial disease, herpes virus infection and hepatitis B and C infection,[5] tuberculoid leprosy,[6] cryptococcal

![Figure 1: (a) Flaccid bullae with crust over the arm in pemphigus vulgaris, (b) Intraepidermal bullae with acantholysis (H and E, ×400)](image1)

![Figure 2: (a) Multiple tense bullous in an erythematous base of bullous pemphigoid, (b) Sub-epidermal bulla with numerous inflammatory cells (H and E, ×400)](image2)
meningitis, Kaposis sarcoma, Tegumentary leishmaniasis, etc. The reported cases of non-infectious IRIS are few, those are Sweet’s syndrome, Reiter’s syndrome, SLE, urticaria, autoimmune thyroiditis, type B insulin resistance syndrome, myopathy, radiculopathy, porphyria, non-Hodgkin’s lymphoma, Guillain-Barre syndrome, Sarcoidosis etc.

Bullous diseases such as PV and BP have not yet been reported in the literature as a manifestation of IRIS among HIV patients. Bullous disease occurs after a rise of CD4 T-cell counts in our case series, which were started 3-8 weeks after initiation of HAART. The bullous lesions were persisting even after stoppage of Nevirapine. The CD4 T-cell count was around 50 when the HAART was initiated. The median CD4 T-cell count in our patients, during the presentation of bullous lesion was 262/µL. None of our cases had a past history of bullous disease. In addition, there was no documentary history of other autoimmune diseases. Bullous disease of skin and mucous membrane resulting from immune restoration has had relatively recent recognition and might be viewed as a consequence of organ-specific autoimmunity during the late period of T-cell repopulation, specifically of CD4 positive naïve cells. This phenomenon may occur due to aberrant T-cell signal to B cells, forming immunoglobulin due to the sudden increase of CD4 T-cell count following initiation of HAART.

Limitation
Due to lack of logistic supports, indirect immunofluorescence and electron microscopy, HIV viral load was not performed in any case.

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