

Histopathological study of pruritic papular eruptions in HIV-infected patients in relationship with CD4, CD8 counts

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ABSTRACT

Background: Pruritic papular eruptions (PPE) are common cutaneous manifestations in HIV-infected patients. Their frequencies, patterns and associated factors vary from region to region. There is no clear consensus on the etiology of PPE, the exact spectrum of the condition, the pathologic findings, or treatment. The present study is aimed at documenting the histopathological patterns of PPE, and their relation with CD4, CD8 counts in HIV-infected patients. **Materials and Methods:** The present study lasted for 12 months (September 2005 to August 2006). After informed consent, data on skin disorders, HIV status, CD4 and CD8 counts were obtained by physical examination and laboratory methods. **Results:** Of the 36 HIV-infected patients with clinical diagnosis of PPE, the most common histopathological patterns were prurigo simplex and eosinophilic folliculitis. The mean CD4 count of PPE was 186.49 cells/mm³ with mean CD8 count of 619.60 cells/mm³, and the CD4:CD8 ratio was 0.32. Patients with prurigo simplex had significantly lower mean CD4 counts (50.36 ± 30.67 cells/cmm³, $P < 0.001$) while in eosinophilic folliculitis, the mean CD8 counts were higher (1239.77 ± 402.30 cells/cmm³). **Conclusion:** We conclude that histopathology helps in specifying the pattern of PPE and also indicates underlying immunosuppression and can be a marker of advanced HIV infection. Thus, correlation between the histopathology and immunology findings helps to know the disease process.

KEY WORDS: CD4, CD8 counts, HIV, histopathology, pruritic papular eruptions.

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INTRODUCTION

Pruritic papular eruptions (PPE) are characterized by chronic pruritus and symmetric papular eruptions on the trunk and extremities with the absence of other definable causes of itching in an HIV-infected patient.^[1] Nevertheless, it remains the most common cutaneous manifestation in HIV-infected patients, with a prevalence that varies between 11 and 46% according to the geographic area.^[2-6] Retrospective analysis has shown that it was impossible to differentiate clinically between prurigo and eosinophilic folliculitis, and recommended biopsy confirmation of these lesions.^[7] However, comprehensive histopathological studies in HIV-infected patients with PPE and their relation with CD4, CD8 counts have not been reported. Hence, the present study was undertaken.

MATERIALS AND METHODS

The present prospective cross-sectional study was carried out for a period of 12 months (September 2005 to August 2006) in the Department of Pathology at a tertiary referral center. The skin biopsies from HIV-positive patients with clinical diagnosis of PPE were received from the Department of Dermatology.

After informed consent, information was obtained through structured questionnaire from patients on their socio-demographic status and antiretroviral therapy. Patients on antiretroviral therapy were excluded from the study. Antibodies to HIV were demonstrated by three different methods (Tridot, Capillus and Combaids tests). Physical examination was done to identify the PPE. Skin biopsies were performed in these patients for identification of specific histological pattern of PPE. Paraffin-embedded 3 to 5- μ m thick tissue sections were assessed using hematoxylin and eosin stain. Multiple serial histological sections were examined in all these cases to rule out any folliculocentric pathological process. The measurement of peripheral blood CD4, CD8 counts was performed by Tricolor Flow Cytometry.

The Student's *t*-value was used to determine the strength of association between PPE with CD4 count and CD8 count. *P* value was considered significant when it was less than or equal to 0.05.

RESULTS



Figure 1: Early prurigo simplex: Itchy erythematous papules distributed over the upper back



Figure 1a: Early prurigo simplex: mild acanthosis and mild spongiosis of the epidermis with perivascular lymphocytic infiltrate in the superficial dermis (H and E, x400)



Figure 2: Late prurigo simplex: excoriated papules and few papules are covered with crust, distributed over the right upper limb

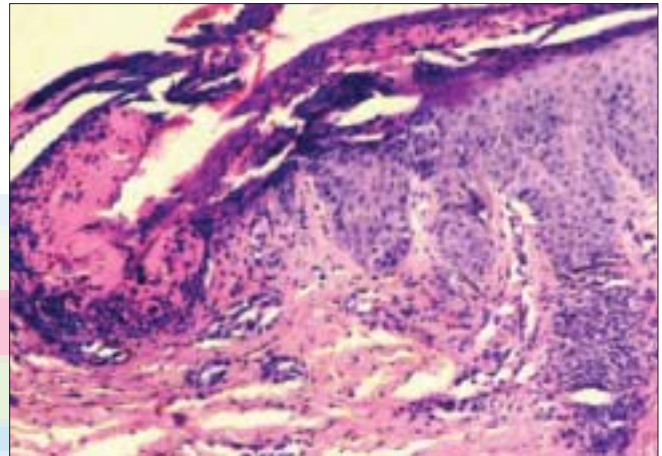


Figure 2a: Late prurigo simplex: excoriated papules show partial absence of the epidermis, and they are covered with a crust containing degenerated nuclei of inflammatory cells. The superficial dermis shows perivascular lymphocytic infiltration (H and E, x400)



Figure 3: Eosinophilic folliculitis: itchy follicular papules distributed over the left upper limb

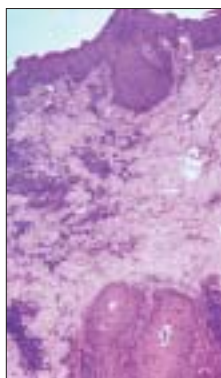


Figure 3a: Eosinophilic folliculitis: In the dermis, there are perivascular, perifollicular and interstitial infiltrates of lymphocytes and numerous eosinophils (H and E, x50)

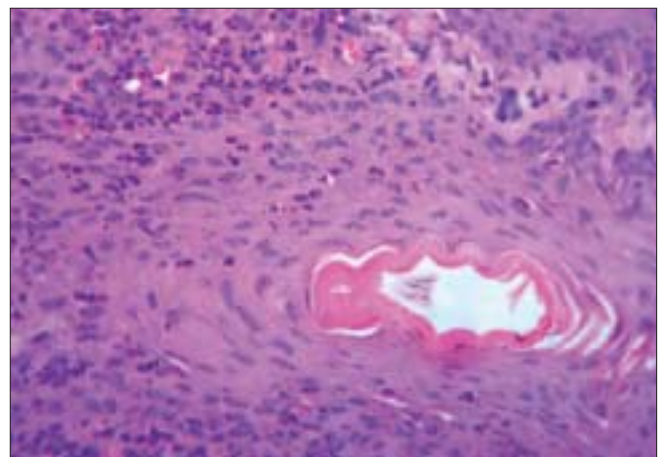


Figure 3b: Eosinophilic folliculitis: perifollicular and intrafollicular eosinophils and lymphocytes are concentrated about the follicular isthmus (H and E, x400)

A total of 36 HIV-infected patients with clinically PPE accepted to take part in the study. The risk factors in men and women included heterosexual contact with multiple sexual partners, while in the pediatric group was vertical transmission. The age ranged from six to 60 years with male:female ratio being 2.6:1. Specific histopathological findings in these PPE were seen in 97.22% (35/36) cases while one case showed nonspecific changes which did not contribute to one or another disease. The most common type of PPE on histopathology were prurigo simplex, followed by eosinophilic folliculitis, prurigo nodularis and lymphocytic vasculitis.

The mean CD4 count of PPE was 186.49 cells/mm³ with mean CD8 count of 619.60 cells/mm³ and the CD4:CD8 ratio being 0.32; 67.74% had CD4 counts of less than 200 cells/mm³. The strength of association of PPE with CD4 count and CD8 count was done by Student's *t*-value (6.91) and the *P*-value <0.001. The relationship of mean CD4, CD8 counts and CD4:CD8 ratio with various histopathological patterns of PPE is enlisted [Table 1].

DISCUSSION

Of the spectrum of cutaneous lesions in HIV-infected patients, PPE are a unique dermatosis associated with advanced HIV infection. Previous studies have shown that PPE were one of the most frequent clinical diagnoses.^[8,9] These eruptions can occur as non-follicular or follicular lesions.^[10] In our study, the non-follicular lesions included prurigo simplex and lymphocytic vasculitis while the follicular lesion constituted only eosinophilic folliculitis (EF). A few studies^[9,11] have observed that the mean CD4 count was <200 cells/mm³ in these pruritic lesions which was consistent with the present study (mean CD4 count 186.49 cells/mm³, Student's *t*-value (6.91) and *P*-value <0.001).

Prurigo simplex was diagnosed after we had ruled out systemic causes for the symptoms and other infectious and/or inflammatory processes. Prurigo simplex can lead to prurigo nodularis.^[12] The distribution of cutaneous papular lesions was all over the body except genitalia. Clinically, in early prurigo simplex, the cutaneous lesions are erythematous papules [Figure 1] while the late lesions have papules with central crust [Figure 2]. In patients with prurigo simplex, the histological feature of early papule was mild acanthosis and mild spongiosis of the epidermis while lymphocytic infiltrate in a largely perivascular arrangement was observed in the superficial dermis [Figure 1a]. There was partial absence of the epidermis in the late lesions as they are covered with a crust containing degenerated nuclei of inflammatory cells [Figure 2a]. Intense, intractable pruritus

among HIV-infected patients is thought to be due to immune dysregulation; previous studies have found higher levels of IgE and increased concentrations of certain helper T-cell type cytokines (interleukins 4 and 5) in HIV patients with idiopathic pruritis, as compared with HIV patients without pruritis.^[13] The levels of IgE are known to increase with advancing disease (decreasing CD4 cell count). Therefore, it was not surprising that we found CD4 counts less than 100cells/mm³ (*P* <0.001) in prurigo simplex. All these HIV-infected patients with prurigo simplex were treated with highly active antiretroviral therapy. It was observed that the reduction in lesions of prurigo simplex following the use of highly active antiretroviral therapy could be secondary to immune reconstitution and "re-regulation" of immune system.

The distribution and morphological features of cutaneous lesions in HIV-EF were itchy erythematous papules distributed over the face, upper limbs [Figure 3] and trunk. In 11/36 (30.55%) patients with EF, we found the histology to be characterized by perifollicular and intrafollicular infiltrate of lymphocytes and eosinophils [Figure 3a], focused at the level of the follicular isthmus [Figure 3b]. In the early lesions of EF, lymphocytes predominate over the eosinophils and were distributed perifollicularly, and also interstitially while in the late developed lesions of EF, the eosinophils predominate over the lymphocytes and were confined to the perifollicular and follicular region. Previous studies on immunophenotypic analysis showed the lymphocytes to be T cells with a marked CD8 predominance (CD8/CD4 ratio of 10:1),^[7,14] which was observed in the present study (CD8/CD4 ratio of 4.1:1). The CD4 count in HIV-EF was <250 cells/mm³ in other studies,^[10] but in our study the mean CD4 count was 302.36cells/mm³. The exact etiology of HIV-EF remains unknown. Any explanation must take into account the prominence of eosinophils in the cellular infiltrate, the folliculo-centric nature of the disease and the typical distribution of the eruption in the context of profound immunodysregulation.^[15] Several theories postulated center around the possibility that opportunistic organisms are involved.^[7] In 2/11 patients with HIV-associated EF, we found mite fragments suggestive of *Demodex folliculorum* within the infundibulum of the involved follicle.

There was also one case each of lymphocytic vasculitis and nonspecific dermatitis.

CONCLUSIONS

PPE has a major impact on the quality of life of the affected patient, both from a medical and a cosmetic point of view,

Table 1: Relationship of mean CD4, CD8 counts and CD4/CD8 ratio with PPE

Skin diagnosis	No. (%)	CD4count (cells/mm ³)	CD8count (cells/mm ³)	Ratio
Prurigo simplex	23 (63.89%)	50.36±30.67	438.76±101.82	0.13
Eosinophilic folliculitis	11 (30.55%)	302.36±64.64	1239.77±402.30	0.32
Lymphocytic vasculitis	1(2.77%)	16.58±0	237.69±0	0.07
Non-specific dermatitis	1(2.77%)	330.09±0	1187.42±0	0.28

subjecting patients to HIV-related stigma in their communities. The correlation between the histopathological findings and immunological features helps to know the underlying disease process. PPE in HIV-infected patients indicates underlying immunosuppression and can be a marker of advanced HIV infection. Thus recognizing PPE helps in allowing better treatment of this recalcitrant and distressing condition.

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