

# Establishing the Diagnosis Histopathology Findings of Papular Pruritic Eruption in HIV-infected Patients: Preliminary Study

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**Abstract:** Papular Pruritic Eruption (PPE) is a common clinical manifestation in patients infected with Human Immunodeficiency Virus (HIV). The hallmark of PPE is a chronic pruritus with a symmetrically scattered papular eruption on the body and extremities. The pathophysiology of PPE is still unknown. Clinically, PPE is difficult to distinguish between prurigo nodularis, insect bite, or other dermatitis, thus requiring histopathologic examination to exclude other diagnosis. Nevertheless, the consensus on the histopathology picture of PPE is still limited. So the of this study was to found the histopathology spectrum of PPE in HIV-infected patients. This is a descriptive analytical study to characterize the histopathology pattern in some PPE cases.

## 1 INTRODUCTION

The distinctive mark of Human Immunodeficiency Virus (HIV) infection is progressive immunosuppression leading to a diverse spectrum of clinical manifestations such as opportunistic infections and tumors, wasting syndrome, and failure of various central nervous systems (Sued et al., 2016) Skin disorders that are often associated with HIV infection include seborrheic dermatitis, molluscum contagiosum, tinea corporis, and Kaposi sarcoma, as well as pruritus and dermatitis with unclear causes, such as papular pruritic eruptions (PPE) (Chua et al., 2014). The prevalence of PPE varies in different parts of the world, ranging from 11% to 46%. (Chua et al., 2014; Kaushik et al., 2014) A study in Surabaya showed a 15.4% prevalence of PPE from all patients with HIV (Arista et al., 2015).

Clinical features of PPE are very similar to eosinophilic folliculitis in HIV patients, usually occurs in HIV patients with low CD4 counts, and may also be part of the Immune Reconstitution Inflammatory Syndrome (IRIS) (Mostwaledi et al., 2014). Also, the possibility of drug reaction should be considered in any case of inflammatory dermatosis in HIV infection. Therefore, skin biopsy has an

important diagnostic role when some form of this distinct skin disorder arises as a similar clinical manifestation, but the normative histopathology criteria of PPE does not exist yet. This objective of this study was to characterize the PPE histopathological findings.

## 2 METHODS

This research is a descriptive analytical study that conducted in the sexually transmitted disease clinic, Department of Dermatology and Venereology in Sardjito General Hospital, Yogyakarta, during October to December 2017. The study subjects were HIV-infected adult patients, who had pruritic, symmetrically scattered multiple papule lesions with a duration of at least 1 month. Skin biopsy was performed on the latest skin lesion with a punch technique, 5mm in size. The tissue is then delivered and processed in Anatomical Pathology laboratory of Sardjito General Hospital. The tissue preparation is cut and stained with standard hematoxylin and eosin. Interpretation is focused on the pattern of skin reaction, exocytosis in the epidermis, and dermis infiltrate, such as type, density, and location of the

infiltrate. Inflammatory cell counts were performed using a direct observation under microscopy in high power field in 5 field of view, with a single observer of anatomical pathologist.

### 3 RESULT

There were 8 patients included, consisting of 2 female and 6 male (Table 1). The mean age of patient is 38.87 years old. Four patients received a combination of drugs in the form of Tenovofir, Hiviral, and Efavirenz

(THE), while the rest received Duviral and Neviral. Duration of the patient's complaint varies from 3 months to 2 years. Two patients complained of itching after dropping out of the first drug regimen, while the rest complained of itching before starting ARV. The mean CD4 count in peripheral blood are 138,25 cells/mm (Arista et al., 2015).

As shown in table 2, orthokeratosis basket weave type is the most common feature of epidermis, with normal stratum granulosum and stratum spinosum, however one specimen showed mild spongiosis and one specimen showed severe spongiosis with intraepidermal cleft.

Table 1. Overview of the patients

Case no.	Sex	Age	Blood CD4 count
1	Male	30 y.o	79 cells/mm <sup>3</sup>
2	Female	48 y.o	300 cells/mm <sup>3</sup>
3	Male	21 y.o	144 cells/mm <sup>3</sup>
4	Male	30 y.o	245 cells/mm <sup>3</sup>
5	Male	48 y.o	23 cells/mm <sup>3</sup>
6	Male	50 y.o	247 cells/mm <sup>3</sup>
7	Female	44 y.o	17 cells/mm <sup>3</sup>
8	Male	32 y.o	51 cells/mm <sup>3</sup>

Table 2. Histopathological findings in 8 cases of PPE

<b>Epidermis</b>	Orthokeratosis basket weave type	87,5%
	Normal epidermis	12,5%
	Acanthosis	12,5%
	Eugranulosis	100%
	Mild spongiosis	12,5%
	Severe spongiosis with intraepidermal cleft	12,5%
	Vacuolar degeneration of basal cell	62,5%
	Hyperpigmentation	25%
	Exocytosis	12,5%
<b>Dermal-epidermal interface</b>	Clear	100%
<b>Dermis</b>		
Type of infiltrate	Lymphocyte	100%
	Eosinophil	75%
Density	Sparse	37,5%
	Moderate	62,5%
Distribution	Perivascular	100%
	Periadnexal	50%
	Wedge-shape	0%
Eosinophils count/ 5 HPF	0	12,5%
	1-20	50%
	21-50	25%
	>50	12,5%

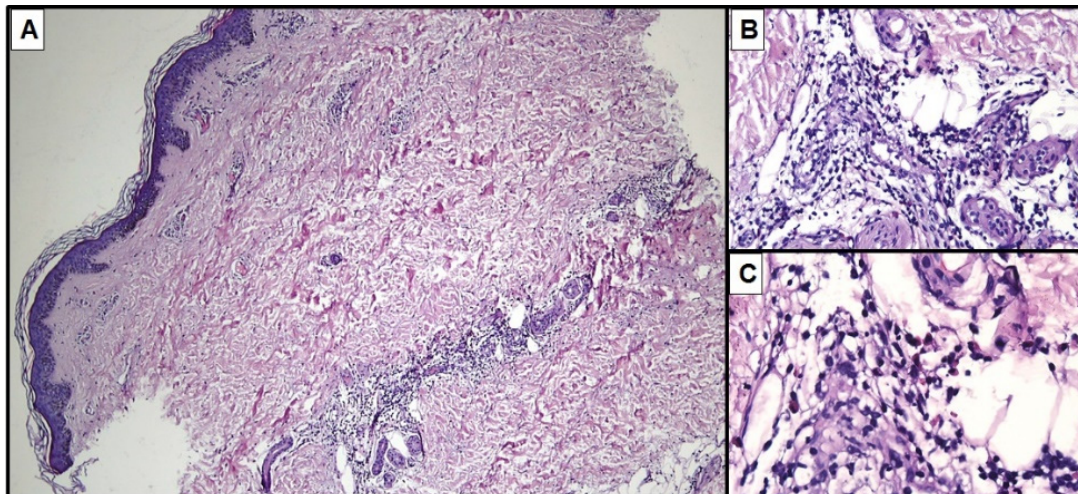


Figure 1. A. Epidermis showing orthokeratosis basket weave and normal layer of granulosum and spinosum. There is perivascular and periadnexal distribution of inflammatory infiltrate in the dermis. B. Lymphocytes predominance of infiltrate in periadnexal. C. Eosinophils are moderately scattered.

There is lymphocytic and eosinophilic infiltrate inside this cleft, showing a feature of spongiotic pustule. This specimen also have an exocytosis of eosinophil. There was only one specimen showing acanthosis of epidermis. All specimens showed clear dermal-epidermal interface.

In the dermis, all specimens show lymphocyte infiltrate predominance. They are scattered in the dermis, and four of them showed sparse infiltrate in perivascular distribution only, while the rest of them have both periadnexal and perivascular infiltration with moderate density. Other infiltrate found is eosinophils in six cases (75%). In contrast to previous studies, no single specimen with wedge shaped infiltrate was found in this study.(7)

Eosinophils are inflammatory cells thought to play an important role in the mechanism of PPE before, so we calculated the amount of eosinophils in high power field magnification (HPF) (400x) in 5 fields of view. Based on the number of eosinophils, the samples are classified into three categories: 0 or no eosinophil, 1-20, 21-50, and >50, to illustrate the number of eosinophil scattered. Most of the specimen have eosinophil count 1-20 cells in 5 HPF or moderately dense. The largest number of eosinophils count is 133 cells/5 HPF.

#### 4 DISCUSSION

Skin is the most frequent organ affected in HIV infection and the lesion of skin disorders have a higher clinical severity than the general population.

Some noninfectious dermatoses are important to note because of their high prevalence, uncommon manifestation, extensive or resistant clinical lesions. In addition, atypical histopathologic features often make it misdiagnose. This study was conducted to observe the histopathologic characteristics of one of the most common non-infectious dermatoses, papular pruritic eruption (PPE) that is defined as a very itchy, chronic, and symmetrically scattered papule, especially on the extremities (Chua et al., 2014). Because of its very itchy complaints, the papules will become excoriated and susceptible to secondary infections, or are characterized by prurigo-like features (Mostwaledi et al., 2014)

The most commonly observed of histopathologic finding from previous studies were insect bite feature. A various cutaneous lesions (maculae, urticae, papules, vesicle, and nodules) are associated with cutaneous lesion of insect bite, will showed variation in histological finding. Spongiosis was the predominant feature characterizing the epidermal change. Sometimes there are erosion or ulceration, or scale crust with neutrophils or eosinophils above the keratin layer. The keratin layer will show a orthokeratosis with some case showed mild acanthosis. Dermis showed an edema in the papillary dermis and wedge-shaped infiltrate with moderately dense distribution in perivascular and periadnexal, consisted mostly by lymphocytes, eosinophil, and neutrophils, sometimes macrophages, with no plasma cells. Most infiltration could involve the adnexal structures such as sweat glands, hair follicle, and sebaceous glands (Miteva et al., 2009).

Prurigo simplex and eosinophilic folliculitis sometimes shows similar lesion clinically. Histopathological findings of prurigo simplex include compact orthokeratosis, irregular acanthosis, hypergranulosis, and sometimes focal parakeratosis in the epidermis. Dermis will showed fibrosis in papillary to reticular dermis, with main infiltrate are lymphocytes and macrophages, sometimes eosinophils (Miteva et al., 2009). Histological feature of eosinophilic folliculitis include eosinophilic spongiotic pustulosis involving infundibular region of the hair follicle, and the infiltrate extends to attached sebaceous glands. Sometimes there is disruption or destruction of the follicular wall by inflammatory infiltrate, including follicular necrosis and folliculocentric necrotizing eosinophilic vasculitis. Inflammatory infiltrate are moderately dense, with perivascular and perifollicular distribution composed of lymphocytes, mast cell, neutrophils, and prominent eosinophils (Fujiyama et al., 2013).

In this study, the pattern of epidermal reactions and the characteristics of the infiltrate found in the dermis were not too match to the findings of the insect bite. Although there was 87,5% specimens showed orthokeratosis of epidermis, only two specimens showing spongiosis. Specimens with severe spongiosis with moderate density of lymphocyte and eosinophils might be resemble of vesicular stage of insect bites. But we have no perfectly wedge-shaped infiltrate found in all specimens. None of specimens in this study also showed an adnexal structure disruption, although there were infiltration around adnexal structure. Our results are inconsistent with previous research that stated the histopathologic features of PPE are resemble the insect bite, instead it showed variable feature of perivascular infiltrate of lymphocyte and eosinophils. (Resneck et al., 2004; Weedon, 2010) Although clinically the papules of PPE closely similar, the histopathological feature of prurigo simplex and eosinophilic folliculitis were not found in this study.

Etiologic factors that suspected play a role in PPE pathogenesis are: arthropod bites, hypersensitivity to insect bites, generalized hypersensitivity to insect saliva, host immune response to abnormal infection (e.g scabies, demodectidosis, bacterial infection), drugs, or direct effect of the virus through skin immune dysregulation. One of the study found that there was an increase in local antibodies against mosquito saliva antigens. It is thought that pruritus is a form of chronic delayed type hypersensitivity reaction that generalized to antigen based on non-specific B cell activation, common reaction that

involving a humoral reaction with Th2 predominant. This phenomenon is also thought to be related to other conditions in similar complaints that appear in malignant diseases (Tokura et al., 2001). The variable feature seen in this study that not so spesific does made a estimation that PPE is only a part of HIV immunosuppression progression. Therefore, it may further explain why PPE can improve with ARV administration only.

As the HIV infection progression, there will be a reduction of CD4 lymphocytes and increase of CD8 lymphocytes count. (Weedon, 2010; Rosatelli et al., 2000) It is shown in this study by low mean CD4 count that are below 200 cells/mm<sup>3</sup>. (Samanta et al., 2009). An increase in CD8 cells may exert functions similar to the Th0/Th2 response, these cells could be responsible for the production of cytokines, explaining the increase of eosinophils in the infiltrate. (Rosatelli et al., 2000) This normal response also include an increase number of macrophage and mast cells, that thought to be responsible to intense itching complain of PPE patients. Observation of mast cells count with toluidin blue staining might be useful in future study, along with immunohistochemistry staining such as CD4, CD8, and CD20 to confirm the B cell role in this disease.

## 5 CONCLUSION

The histopathological findings of PPE in this study are variable. The most observe feature are orthokeratosis basket weave type, normal stratum granulosum and spinosum, without dermal-epidermal interface reaction, infiltration of inflammatory cells in perivascular and periadnexa with lymphocyte predominance and moderately dense eosinophils. This findings was not spesifically resemble insect bites feature like previous study stated. However, owing to small number of patients in this study, it is difficult to identify the true variability of PPE histopathological feature. Therefore, studies with larger numbers of patients and more immunohistochemistry staining are required to determine the complete characterization and compile a histopathologic criteria of PPE.

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