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Skin in HIV

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Pruritic Papular Diseases in HIV

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Pruritic eruptions in HIV infected patients refer to a number of conditions which include pruritic papular eruptions (PPE), eosinophilic folliculitis, scabies, Demodex folliculorum, insect bite allergy and other hypersensitivity phenomena.

PRURITIC PAPULAR ERUPTIONS OF HIV

Pruritic papular eruptions of HIV disease are characterized by chronic, sterile pruritic papules and pustules on the extensor surfaces of the arms, dorsum of the hands, trunk and face with sparing of palms and soles and mucous membrane. The condition tends to wax and wane [1]. In majority of cases, the eruption appears in the advanced immunosuppressive stage of the disease [2], but eruptions may appear as an initial cutaneous manifestation of HIV, with high CD4 lymphocyte count [3]. There is no clear consensus on the etiology of PPE, the exact spectrum of this condition, the pathological findings, or the treatment.

The PPE remains the most common cutaneous manifestation in HIV disease, with prevalence varying between 11% and 46% according to the geographic area, and it is more prevalent in less developed countries of the world.

Etiology

The exact etiology and pathophysiology is unknown, but many factors interplay in its causation (Table 4.1). Though PPE is specifically seen in HIV patients, it may occur in non-HIV patients who have a syndrome of idiopathic CD4+ lymphocytopenia.

Table 4.1: Etiological factors implicated in PPE

1)	Insect bite – mosquito, arthropod
2)	Hypersensitivity to insect bites
3)	Generalized hyper sensitivity reaction to insect saliva
4)	Abnormal host cellular immune response to an infective process – scabies, demodex folliculorum, or staphylococcus aureus.
5)	Drugs
6)	Autoimmune skin reaction
7)	HIV per se leading to immune dysregulation.

Clinical Findings

PPE is characterized by multiple discrete skin colored papules that often are excoriated. These papules typically are symmetrical and are found on the extremities, face (Figure 4.1,4.2) and trunk with sparing of the mucous membranes, palms, soles, and digital web spaces [4]. Colebunders and colleagues found that in 95% of patients, lesions are found on the arms and legs [5]. On the arms, lesions are specifically located on the extensor surface and on the dorsum of the hands. Less commonly, lesions may be erythematous or acneiform with pustules. They do not form confluent plaques and may or may not be follicular. Initially, lesions often resemble papular urticaria; generally the only symptom patient experiences is pruritus. Because of this pruritus, most patients scratch to the point of extensive excoriations, with subsequent postinflammatory hyperpigmentation and with time, formation of prurigo like nodules and scarring. The course tends to be chronic and waxes and wanes, but new lesions often appear daily.

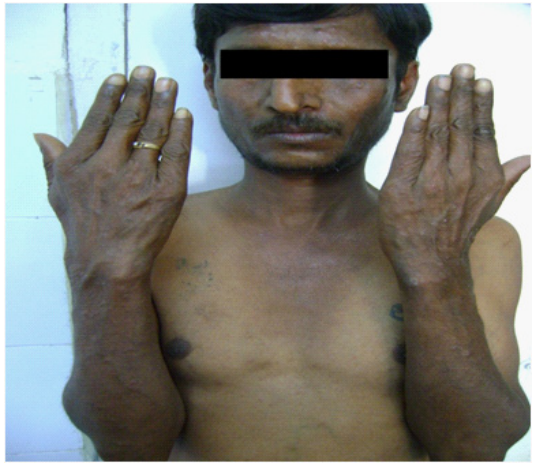

Figure 4.1: Multiple skin colored papules over extremities of PPE.

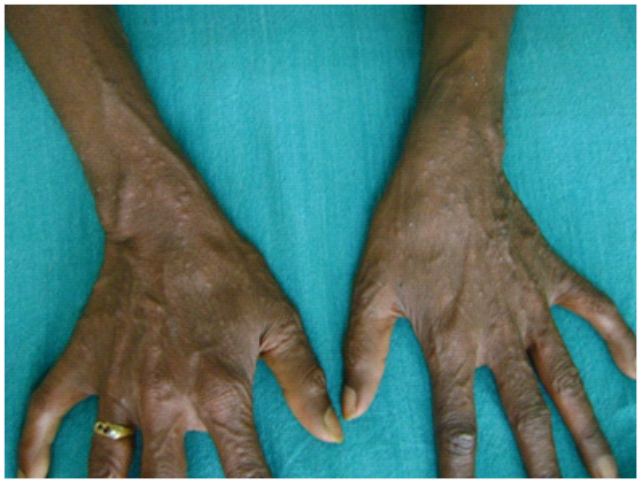

Figure 4.2: Close of view of skin colored papules of PPE

Pathology

Numerous authors have reported the pathologic findings in PPE with much inconsistency. Resneck and colleagues noted that in early PPE, findings resembled arthropod bites, showing dense superficial and deep perivascular and interstitial infiltrate of lymphocytes and eosinophils often extending into the subcutis and associated with epidermal hyperplasia and in some cases a punctum.

Hevia and colleagues found a superficial and mid dermal mixed perivascular and perifollicular infiltrate of lymphocytes and eosinophils with variable degrees of follicular damage [6]. Rosatelli and colleagues noted an increase in CD8+ T lymphocytes, mast cell, macrophages and eosinophils in lesional skin when compared with healthy skin suggested that PPE better justifies eosinophilic folliculitis [7].

Differential Diagnosis

There is an extensive clinical differential diagnosis of PPE as listed below. Table 4.2 highlights the difference between PPE, EF and insect bite reaction .

1. Eosinophilic folliculitis
2. Demodex folliculorum
3. Scabies
4. Papular urticaria
5. Nodular prurigo
6. Bacterial folliculitis
7. Pityrosporal folliculitis

8. Acne and rosacea
9. Papular atopic dermatitis
10. Drug eruptions
11. Papular syphilis
12. Psoriasis
13. Seborrheic dermatitis

Table 4.2: Difference between PPE, EF and insect bite reaction

	PPE	EF	IBR
Predominant lesion	Skin-colored papules often excoriated	Edematous papules & rarely pustules	Excoriated papules
Common sites	Mainly extremities	Face & Upper trunk	Exposed parts
Histopathology	Dermal perivasuclar and interstitial lymphocytes, eosinophils	Follicular spongiosis, Folliculocentric infiltrate rich in eosinophils	Deep dermal mixed cell infiltration.

Treatment

S. Jhansi Lakshmi et al tried 100 mg Dapsone daily, 400 mg b.i.d pentoxyphilline, and antihistamines and topical steroids for 8 weeks, and followed up for 6 months. Patients treated with pentoxyphilline showed little improvement. Patients treated with Dapsone and antihistamine with topical steroids did not show any improvement [8].

Barbara Castelnuovo et al reported that PPE seems to disappear in most patients with HIV infection during an effective HAART [9]. Occasionally, PPE may temporally increase shortly after starting HAART. Whether this is an IRIS phenomenon needs further investigation.

EOSINOPHILIC FOLLICULITIS

Syn: Eosinophilic pustular folliculitis, Sterile eosinophilic pustulosis, Ofuji disease.

Eosinophilic folliculitis (EF) is a chronic, intensely pruritic condition of unknown pathogenesis characterized by papulopustular follicular eruption of the upper trunk, face, neck and proximal extremities. In 1965, Ise and Ofuji described this condition in a Japanese woman [10].

Types of EF

There are 3 types of EF (Table 4.3). Classic EF, also known as Ofuji's disease (OD) is limited to Japan. HIV associated type is more common which is discussed in this section.

Table 4.3: Types of EF [11].

Classic	30-50 yrs M>F Common in Japan. Polycyclic plaques with a healing center and spreading periphery studded with erythematous papules and pustules
HIV associated	Associated with HIV with low CD4 counts. Severe pruritus Recurrent erythematous or urticarial follicular papules located on the upper body
Infantile	3-10 months old babies. Presents as erythematous Papulopustules Scalp - common site.
EF associated with miscellaneous causes	Associated with drug therapy (e.g. allopurinol, timepidium, and cancer chemotherapy), hematologic malignancies (e.g. chronic lymphocytic leukemia and non-Hodgkin lymphoma) and silicone injections.

Etiopathogenesis

The exact etiology of eosinophilic folliculitis of HIV is not known. One theory is that it is an exaggerated reaction to pityrosporum yeast or other organisms normally present within the follicular infundibulam in HIV infected patients and is a reflection of abnormal immune responses [12]. Immune dysfunction involving altered chemotaxis, epidermal antibodies, and immunoglobulin levels are associated with EF [13]. It is thought that eotaxin-1 and TH2 cytokines play a crucial role in the eosinophil recruitment, inflammation, and tissue damage [14]. Also, neuronal nitric oxide synthase concentration is more in eosinophils of EF patients [15].

Originally thought to be an early sign of HIV infection, it occurs at CD4 cell count of 250-300cells/mm^3 and therefore identifies patients at immediate risk of developing OIs.

Clinical Features

Persistent pruritic rash is the characteristic feature. Pruritus is often severe and persistent. Multiple tiny discrete erythematous urticarial follicular papules (Figure 4.3, Figure 4.4) most frequently affecting the shoulders, trunk, upper arms, neck and forehead is the common presentation. Less frequently it is seen in the lower half of the body. Lesions are follicular and are often markedly excoriated.

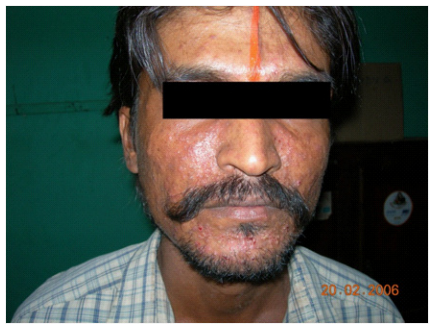

Figure 4.3: Pruritic papules of EF over face.

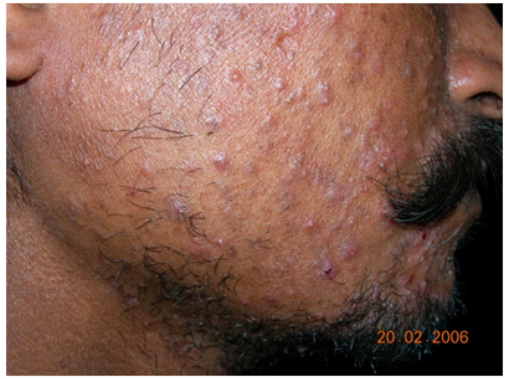

Figure 4.4: Close of view of EF over face.

Histopathology

The biopsy should be taken from the fresh lesion avoiding excoriated lesions and serially sectioned to avoid missing of affected follicle. In a study done by Mc Calmont et al, the following histopathology patterns were noted (table 4.4) [16]. Investigation shows leukocytosis with hypereosinophilia. Serum immunoglobulin E (IgE) levels may also be raised.

Table 4.4: Histopathology of EF

Early phase	Folliculo centric infiltrate with little inflammation elsewhere in the dermis
Mature lesion	Lymphocytes and eosinophils diffusely infiltrate the infundibulum, isthmus, and sebaceous gland of the follicle but lining of wall is intact.
Late phase	Eosinophilic pustule formation that distends the infundibulum, spongiosis of the follicular epithelium.

Treatment

Treatment of EF is difficult and clinical course of EF is one of waxing and waning. Many patients have disease that lasts for years, although eventual recovery is expected in some cases [17,18]. Various drugs have been tried with varied success rates but none with complete clearance (Table 4.5) because the underlying pathogenic mechanism of EF is still obscure. Topical corticosteroids [19] is the first choice of drug considered in managing EF but NSAIDs especially indomethacin [20] is used with good success. Ultraviolet B phototherapy is regarded as the gold standard treatment for EF, especially for the HIV-associated variant [21].

Table 4.5: Management of EF [19-21].

Topical
Corticosteroid
Tacrolimus, Pimecrolimus
Permethrin
Phototherapy
Broadband UVB
PUVA
Systemic
Corticosteroid
Indomethacin (50-75 mg/day) & other NSAID's
Cetirizine (20-40 mg/day)
Metronidazole (250mg TID)
Itraconazole (200 mg/day and increasing to 300-400 mg/day)
Roxithromycin (300mg/day)
Synthetic retinoids (isotretinoin 1 mg/kg/day, acitretin 0.5 mg/kg/day) cyclosporine 5 mg/kg/day
Interferon (IFN)-alpha-2b, IFNgamma.
Minocycline (100mg BD)
Dapsone (50-100mg BD)

INSECT BITE REACTIONS

Exaggerated reaction to insect bites is seen in patients infected with HIV-1. Persistent reactions to insect bites lasting for weeks with individual lesions measuring several centimeters in size may be considered exaggerated. Exaggerated insect bite reaction and other accentuated reactions that are seen in HIV-1 positive patients result from loss of cells that program for unresponsiveness [22]. Also, these are due to delayed hypersensitivity reactions to insect bites (to which they have already been desensitised in early life) which reappear as a result of failing immunity [23]. Qualitatively and quantitatively less effective Langerhans cells in the skin of HIV infected individuals also can be a contributory factor for the altered immunological response to the insect bite. Lesions predominantly seen on the exposed parts of the body and patients give history of insect (mainly mosquitoes and fleas) bite. IBR may be indistinguishable clinically from PPE and can be excluded more easily by a detailed history and clinical examination.

References

1. Eisman S. Pruritic papular eruption in HIV. Dermatol Clin. 2006; 24: 449-457.
2. Boonchai W, Laohasrisakul R, Manonukul J, Kulthanan K. Pruritic papular eruption in HIV seropositive patients: a cutaneous marker for immunosuppression. Int J Dermatol. 1999; 38: 348-350.
3. Raju PV, Rao GR, Ramani TV, Vandana S. Skin disease: clinical indicator of immune status in human immunodeficiency virus (HIV) infection. Int J Dermatol. 2005; 44: 646-649.
4. Bason MM, Berger TG, Nesbitt LT Jr. Pruritic papular eruption of HIV-disease. Int J Dermatol. 1993; 32: 784-789.
5. Colebunders R, Mann JM, Francis H, Bila K, Izaley L. Generalized papular pruritic eruption in African patients with human immunodeficiency virus infection. AIDS. 1987; 1: 117-121.
6. Hevia O, Jimenez-Acosta F, Ceballos PI, Gould EW, Penneys NS. Pruritic papular eruption of the acquired immunodeficiency syndrome: a clinicopathologic study. J Am Acad Dermatol. 1991; 24: 231-235.
7. Rosatelli JB, Soares FA, Roselino AM. Pruritic papular eruption of the acquired immunodeficiency syndrome: predominance of CD8+ cells. Int J Dermatol. 2000; 39: 873-874.
8. S Jhansi Lakshmi, G Raghurama Rao, Ramalakshmi , Satyasree , K Ananda Rao, et al. Pruritic papular eruptions of HIV: A clinicopathologic and therapeutic study. Indian J Dermatol Venereol Leprol. 2008; 74: 501-503.

9. Castelnuovo B, Byakwaga H, Menten J, Schaefer P, Kamya M. Can response of a pruritic papular eruption to antiretroviral therapy be used as a clinical parameter to monitor virological outcome? AIDS. 2008; 22: 269-273.

10. Ise S, Ofuji S. Subcorneal pustular dermatosis. A follicular variant? Arch Dermatol. 1965; 92: 169–171.

11. Scavo S, Magro G, Caltabiano R. Erythematous and edematous eruption of the face. Eosinophilic pustular folliculitis. Int J Dermatol. 2010; 49: 975-977.

12. Chen TM, Cockerll CJ. Cutaneous manifestations of HIV infection and HIV-related disorders. In: Bolongia JL, Jorizzo JL, Rapini RP, editors. Dermatology. London: Mosby. 2003; 1199-215.

13. Nunzi E, Parodi A, Rebora A. Ofuji's disease: high circulating titers of IgG and IgM directed to basal cell cytoplasm. J Am Acad Dermatol. 1985; 12: 268-273.

14. Amerio P, Frezzolini A, Feliciani C, Verdolini R, Teofoli P. Eotaxins and CCR3 receptor in inflammatory and allergic skin diseases: therapeutical implications. Curr Drug Targets Inflamm Allergy. 2003; 2: 81-94.

15. Maruo K, Kayashima KI, Ono T. Expression of neuronal nitric oxide synthase in dermal infiltrated eosinophils in eosinophilic pustular folliculitis. Br J Dermatol. 1999; 140: 417-420.

16. McCalmont TH, Altemus D, Maurer T, Berger TG. Eosinophilic folliculitis. The histologic spectrum. Am J Dermatopathol. 1995; 17: 439-446.

17. Nervi SJ, Schwartz RA, Dmochowski M. Eosinophilic pustular folliculitis: a 40 year retrospect. J Am Acad Dermatol. 2006; 55: 285-289.

18. Mc Kee PH, Calonje E, Granter SR. Neutrophilic and eosinophilic dermatoses. In: Mc Kee PH, Calonje E, Granter SR, editors. Pathology of the Skin: With clinical correlations. 2nd ed. Philadelphia: Elsevier Mosby; 2005: 673–708.

19. Ellis E, Scheinfeld N. Eosinophilic pustular folliculitis: a comprehensive review of treatment options. Am J Clin Dermatol. 2004; 5: 189-197.

20. Tang MB, Tan E, Chua SH. Eosinophilic pustular folliculitis (Ofuji's disease) in Singapore: a review of 23 adult cases. Australas J Dermatol. 2003; 44: 44-47.

21. Buchness MR, Lim HW, Hatcher VA, Sanchez M, Soter NA. Eosinophilic pustular folliculitis in the acquired immunodeficiency syndrome. Treatment with ultraviolet B phototherapy. N Engl J Med. 1988; 318: 1183-1186.

22. Smith KJ, Skelton HG 3rd, Vogel P, Yeager J, Baxter D. Exaggerated insect bite reactions in patients positive for HIV. Military Medical Consortium for the Advancement of Retroviral Research. J Am Acad Dermatol. 1993; 29: 269-272.

23. Ajithkumar K, George S, Babu PG. Abnormal insect bite reactions: a manifestation of immunosuppression of HIV infection? Indian J Dermatol Venereol Leprol. 2001; 67: 72-74.