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ORIGINAL RESEARCH

CLINICOPATHOLOGICAL STUDY OF PAPULONODULAR LESIONS OF SKIN IN HIV

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ABSTRACT

Background: With the progression of the HIV epidemic there is a need to classify the papulonodular eruptions of the HIV infection based on its likely aetiology for proper management of HIV. This study was aimed to study the clinical and pathological aspects of papulonodular lesions of skin in HIV infected individuals.

Methods: The study was conducted among all Human Immunodeficiency Virus (HIV) infected patients who presented with papular and nodular skin lesions at the outpatient's department as well as those admitted in a tertiary care government hospital. Each patient underwent a detailed history taking which included chief complaints, treatment history, and personal history. Dermatological examination included morphology of lesion, site, number, size, shape, colour, margin and surface of skin lesions. Skin biopsy was performed on all the cases and specimen sent to Department of Pathology for histopathology report to correlate the clinical and histopathological diagnoses.

Results: A total of 55 cases were studied. 48 (87.27%) cases were males and 7 (12.73%) cases were females. The age ranged from 25-48years (mean age-34.90 years) for males and 26-46 years (mean age- 36 years) in females. Of the total 55 cases, 18 (32.73%) cases had infective dermatoses and the remaining 37 (67.27%) had non-infective dermatoses. Pruritic papular eruption formed the majority of the cases 20 (54.05%), 15 of them had a low CD4 count <200/µL (Mean CD4 count was (126/µL). All patients showed good response to HAART. Eosinophilic folliculitis was found in 4 cases with 3 cases having CD4 count <200/µL (mean 72/µL).

Conclusion: Patients with infective and non-infective cutaneous manifestations are significantly immuno-suppressed than HIV-positive asymptomatic controls. The absolute CD4 count is inversely related to the number of HIV positive patients with papulonodular eruptions of skin. Hence, there is a need for histopathology examination to separate these closely related entities for precise diagnosis and proper management in HIV patients.

Keywords: Papulonodular lesion, dermatosis, HIV, AIDS, HAART

INTRODUCTION

Diseases of the skin and mucous membranes were among the first recognized clinical manifestations of acquired immunodeficiency syndrome (AIDS) in the early 1980s. Since then, numerous disorders occurring on the skin and mucosa have been reported in Human Immunodeficiency Virus (HIV) disease [1,2,3]. There is no skin condition reported so far that is specific for HIV infection. However, the comprehension and practice of dermatology has profoundly changed by the HIV epidemic. During the course of HIV infection, skin diseases tend to be more chronic, more severe, and more resistant to conventional treatments; and often display unusual clinical presentations, compared to those seen in the non-HIV infected population [4]. Further, the HIV epidemic has brought to attention previously

rare and poorly understood skin diseases, such as bacillary angiomatosis, Kaposi's sarcoma and eosinophilic folliculitis, which manifest as papulonodular eruptions [5,6,7].

It is estimated that more than 90% of HIV-infected patients develop skin or mucous membrane disorders at some time during the course of their infection. The knowledge of dermatological manifestations in HIV infection, thus, is fundamental to medical workers, particularly those practising in developing countries. Papulonodular eruptions comprise a large group of these dermatoses. Identification of papulonodular eruptions of skin seen in conditions like bacillary angiomatosis, underlying systemic infections like tuberculosis and syphilis, folliculitis of Staphylococcal infections, deep cutaneous mycoses e.g. Penicillium marneffei, cryptococcosis, coccidioidomycoses; viral infections like herpes zoster and simplex, molluscum contagiosum ; HIV associated neoplasms like Kaposi's sarcoma; adverse drug reactions may provide a clue for diagnosing previously undiagnosed HIV positive status thereby help in early management [8,9,10]. On the other hand, diagnosing skin disorders such as refractory candidiasis, disseminated molluscum contagiosum, ulcerating herpes simplex, eosinophilic folliculitis or pruritic papular eruptions etc can be a sensitive and useful measure by which the progression of HIV infection can be monitored [11].

There is a paucity of studies which have been conducted to ascertain the exact causes for the papulonodular eruptions in an HIV patient. Some attribute it to increased hypersensitivity reaction in their aetiopathogenesis [12]. A papular eruption like eosinophilic folliculitis, which is taken to be pathognomonic of HIV infection, is also poorly understood. Epidermal langerhans cells may be infected by HIV and decreased langerhans cell's function could account for some of the cutaneous manifestations of HIV disease [13].

With the progression of the HIV epidemic there is a need to classify the papulonodular eruptions of the HIV infection based on its likely aetiology for proper management of HIV. This study was aimed to study the clinical and pathological aspects of papulonodular lesions of skin in HIV infected individuals.

MATERIALS and METHODS

The study was conducted among all Human Immunodeficiency Virus (HIV) infected patients who presented with papular and nodular skin lesions at the outpatient's department as well as those admitted in a tertiary care government hospital from July 2020 to June 2021.

Each patient underwent a detailed history taking which included chief complaints, treatment history, and personal history including history of high-risk behaviour, IV drug abuse, tattooing of skin, having received blood transfusion, occupation, alcoholism, smoking, bowel and bladder habits was also elicited in a pretested proforma. General physical and systemic examination of cardiovascular, respiratory, abdominal and central nervous system were done.

Dermatological examination included morphology of lesion, site, number, size, shape, colour, margin and surface of skin lesions. Configuration and distribution including symmetry of the lesion were noted. Examination of palms and soles, nail, hair, oral, genital and perianal mucosa was also done.

Skin biopsy was performed on all the cases and specimen sent to Department of Pathology for histopathology report to correlate the clinical and histopathological diagnoses. The patient was explained about the procedure and written consent obtained. The site was shaved half an hour before procedure. The skin was cleaned with savlon followed by normal saline. Povidone iodine lotion painted followed by methylated sprit. The skin was infiltrated with 2ml of 1% lignocaine with adrenaline solution. Wedge shaped incision was made parallel to relaxed skin tension line, measuring about 1 cm x 0.5 cm upto subcutaneous fat, one of the edges of ellipse was lifted with fine dissecting forceps and the biopsied tissue excised. The specimen was placed on blotting paper and then transferred to a vial containing 10% formalin solution. Undermining of the edges done with mosquito artery forceps skin hooks applied in both the edge of the wound and the wound closed with simple interrupted 4-0 silk sutures. Mupirocin ointment applied over the wound and covered with sterile guaze and adhesive tape. Sutures were removed on 8th post operative day.

Tissue processing was done so as to allow paraffin wax impregnation, which in turn made the tissue firm enough to enable thin sections to be cut and yet remain soft enough so as not to damage the knife or tissue. Tissue processing was followed by embedding (block making) followed by microtomy (section cutting) where the processed blocked tissue was cut into thin section using microtome measuring 05 microns and transferred to the albuminised slides. Then the slide was transferred to an

oven at 56°C for 02 hours and thereafter to an incubator at 37°C overnight. The final step included staining with standard haematoxylin and eosin stain (Figure 1).

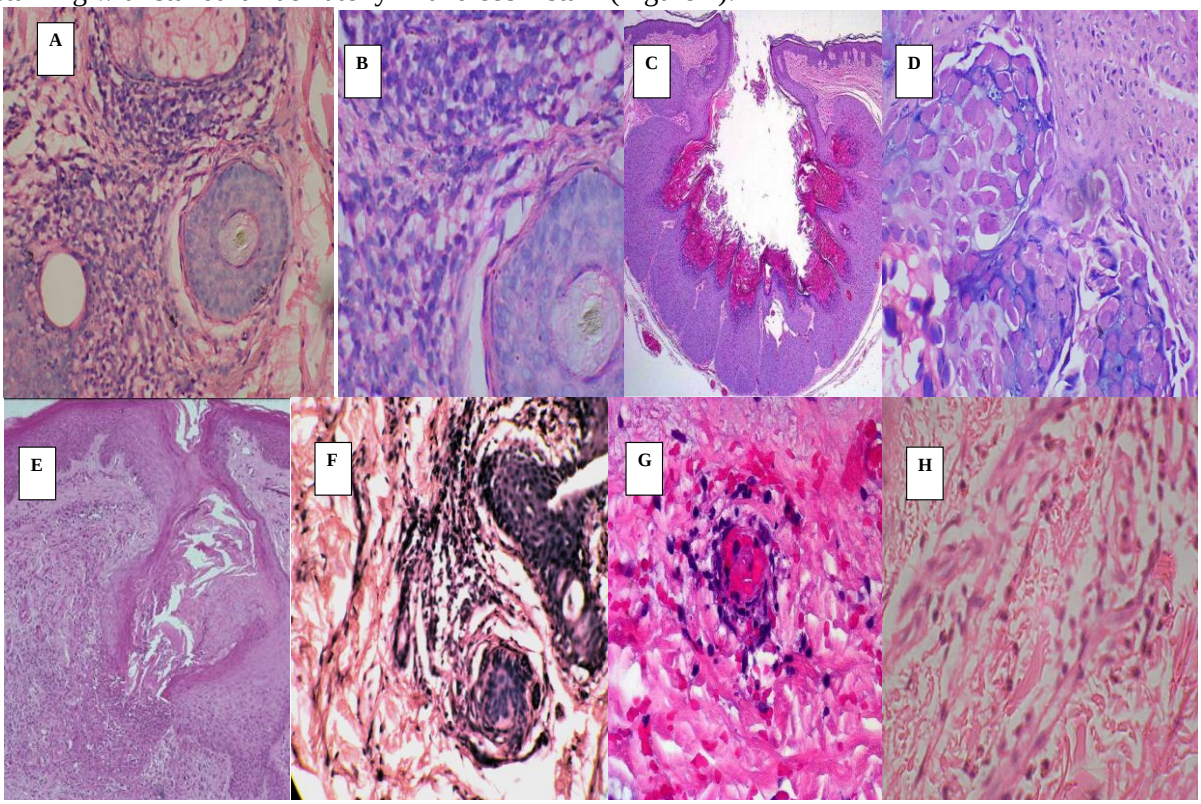

Figure 1. Histopathology of papulonodular lesions among subjects. (A, B). H & E stain (X 400) showing periadnexal inflammatory infiltrate comprising predominantly of lymphocytes and occasional eosinophils. (C, D). H & E stain (X 100 & X 400) showing molluscum bodies (single, minute & ovoid eosinophilic structures) within the keratinocytes. (E, F). H & E stain (X 100 & X 400) showing periadnexal inflammatory infiltrate with acute and chronic inflammatory cells in a case of pruritic papular eruption of HIV. (G, H). H & E stain (X 100 & X 400) showing presence of perivascular neutrophilic infiltrate with fibrinoid degeneration of vessel wall.

Statistical analysis

The dataset of patients at the hospital was evaluated, and descriptive statistics such as mean, standard deviation, and percentage for the study variables were calculated using the measuring scale.

RESULTS

A total of 55 cases were studied. 48 (87.27%) cases were males and 7 (12.73%) cases were females. The age ranged from 25-48years (mean age-34.90 years) for males and 26-46 years (mean age- 36 years) in females. Majority of the patients 22 (40.00%) were in the age group of 31-35 years. Majority of our patients 43 (78.18%) had transmission through heterosexual contact, followed by 10 (18.18%) patients those whose mode of transmission was not known. IV drug abuse accounted for 2 (3.64%) patients. 35 (63.63%) of our cases were on HAART of which 30 (54.54%) were male patients and 5 (9.1%) were female patients. 3 (8.57%) patients were both on HAART and anti-tubercular therapy (Table 1).

Table 1. Baseline characteristics of enrolled subjects (N=55).

Variables	Number	%
Gender		
Male	48	87.27
Female	7	12.73
Age group		
25-30 years	10	18.18

31-35 years	22	40.00
36-40 years	11	20.00
41-45 years	6	10.91
46-50 years	6	10.91
Mode of transmission		
Heterosexual	43	78.18
IV Drug abuse	2	3.64
Blood transfusion	0	0.00
Needle Stick injuries	0	0.00
Denied History	10	18.18
On HAART therapy		
Yes	35	63.63
No	20	36.37
Indication for HAART therapy (n=35)		
Disseminated TB	3	8.57
Low CD4 count	32	91.43

Of the total 55 cases, 18 (32.73%) cases had infective dermatoses and the remaining 37 (67.27%) had non-infective dermatoses. Amongst the infective dermatoses, 9 (50.00%) patients had molluscum contagiosum, 7 (38.89%) patients had verruca vulgaris, and 2 (11.11%) patients had scabies. 37 cases had non-infective dermatoses. Pruritic papular eruption was seen in 20 cases, eosinophilic folliculitis in 4 cases, leukocytoclastic vasculitis in 3 cases, seborrheic dermatitis in 3 cases, prurigo nodularis in 2 cases, interphase dermatitis, urticarial vasculitis, dermatitis herpetiformis, lichen planus and acute exanthema of HIV seen in one case each (Table 2) (Figure 2).

Table 2. Description of dermatoses among enrolled subjects (N=55).

Dermatoses	**Number**	**%**
Infective dermatoses (n=18)		
Viral	16	88.89
Bacterial	0	0.00
Fungal	0	0.00
Parasitic	2	11.11
Non-Infective dermatoses (n=37)		
Papular eruption of HIV	20	54.05
Leukocytoclastic vasculitis	3	8.11
Acute exanthemata of HIV	1	2.70
Eosinophilic folliculitis	4	10.82
Inter-phase dermatitis	1	2.70
Prurigo nodularis	2	5.41
Seborrhoeic dermatitis	3	8.11
Urticarial vasculitis	1	2.70
Dermatitis herpetiformis	1	2.70
Lichen planus	1	2.70

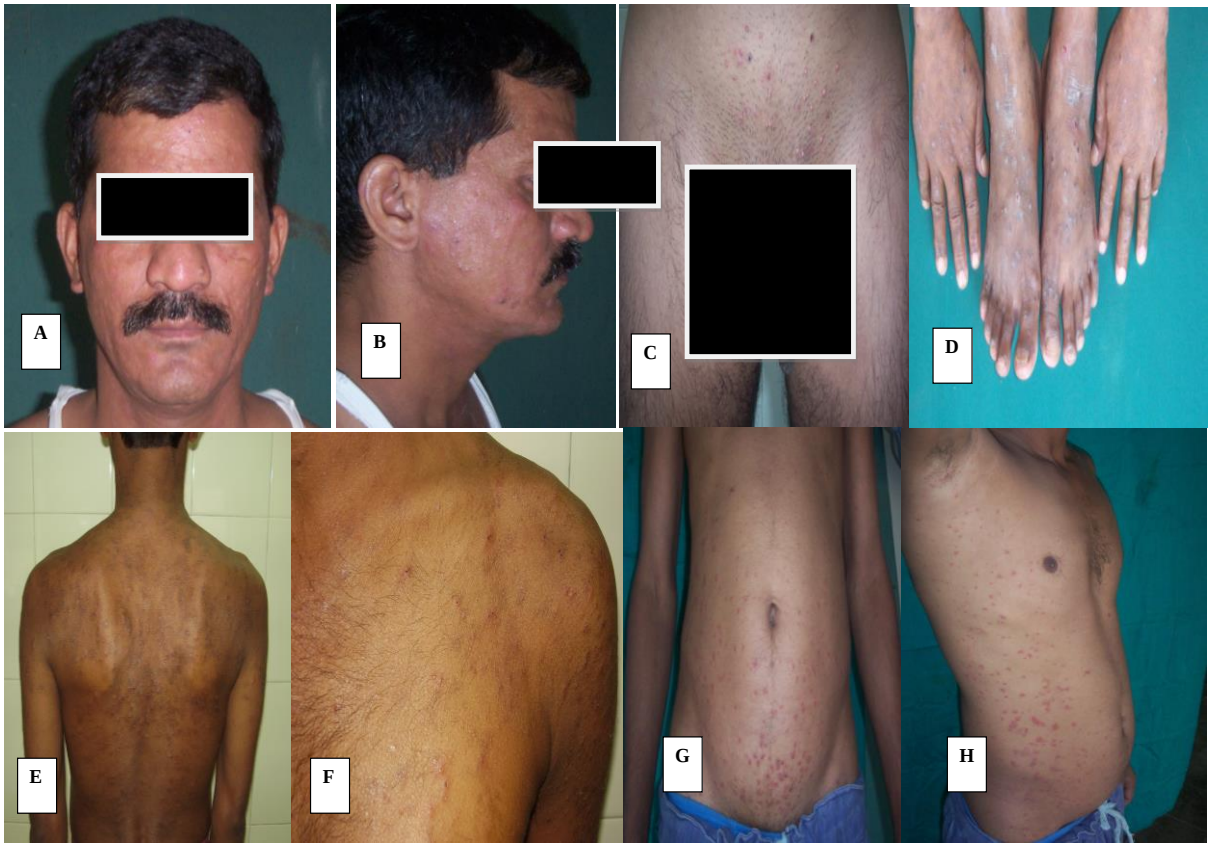

Figure 2. Papulonodular lesion among enrolled subjects. (A, B). A case of HIV infection with eosinophilic folliculitis. (C). A case of HIV infection with Molluscum Contagiosum. (D). A case of HIV infection with scabies. (E, F). A case of pruritic papular eruption in a HIV infected patient. (G, H). A HIV patient not on HAART with Leukocytoclastic vasculitis

Pruritic papular eruption formed the majority of the cases 20 (54.05%), 15 of them had a low CD4 count <200/µL (Mean CD4 count was (126/µL). All patients showed good response to HAART. Eosinophilic folliculitis was found in 4 cases with 3 cases having CD4 count <200/µL (mean 72/µL).

Leukocytoclastic vasculitis was seen in 3 patients, 2 patients had a CD4 count of less than 200/µL (mean 190/µL). Seborrheic dermatitis was found in 3 patients, 2 of them had low CD4 count <200/µL (mean 126/ µL). Majority of the infective dermatoses observed were viral. Molluscum contagiosum was found in 9 cases, 6 of them had a low CD4 count<200/µL (mean 105/µL). Verruca vulgaris was found in 7 cases. 5 of them had a low CD4 count<200/µL (mean 177/µL). Scabies was found in 2 cases. Both the cases had a low CD4 count<200/µL (mean 102/µL) (Table 3).

Table 3. Co-relation of CD4 count with observed dermatoses among enrolled subjects (N=55).

Dermatoses	**Number**	**%**	**Number**	**%**
	CD4<200/µL (n=41)		**CD4≥200/µL (n=14)**	
Pruritic papular eruption of HIV	15	36.59	5	35.71
Eosinophilic folliculitis	3	7.32	1	7.14
Prurigo nodularis	2	4.88	0	0.00
Leukocytoclastic vasculitis	2	4.88	1	7.14
Acute exanthemata of HIV	0	0.00	1	7.14
Inter-phase dermatitis	1	2.44	0	0.00
Seborrhoeic dermatitis	2	4.88	1	7.14
Urticarial vasculitis	1	2.44	0	0.00
Dermatitis herpetiformis	1	2.44	0	0.00
Lichen planus	1	2.44	0	0.00
Verruca	5	12.20	2	14.29

Molluscum contagiosum	6	14.63	3	21.43
Scabies	2	4.88	0	0.00

DISCUSSION

The present clinico-pathological study was conducted to elucidate the causes of various papular and nodular eruptions in HIV, which could be indigenous to HIV infection or could have been sequelae to profound immunosuppression. In present study majority of the patients presenting with cutaneous manifestation had a low CD4 count, ranging from 6 to 199/µL (average 106.43/µL). This is in consonance with various other studies where cutaneous manifestations are an indicator of low immunity [14,15,16]. In present study, most of the cases had non-infective dermatoses (37 cases, 67.27%) compared to infective dermatoses (18 cases, 32.73%). This could be explained due to advent of HAART and prior therapy at referral hospitals. A similar study conducted by Goh et al., reported identical findings [17].

Pruritic papular eruption formed the majority of the cases (20, 54.05%), fifteen of them had a low CD4 count <200/µL (Mean CD4 count was (126/µL). This is in conformity with various studies where the incidence has ranged 33-37% in Thailand to 46% in Haiti and is inversely related to the CD4 count [16,17,18,19]. Most of our cases had extensive excoriated papules over the trunk and extremities and had been treated presumptively for scabies at the referral centers. Majority of the cases responded to HAART and symptomatic therapy with topical steroids and anti-histaminics. Histopathological examination of these cases revealed dense superficial and deep perivascular and interstitial infiltrate of lymphocytes and eosinophils often extending into the subcutis and associated with epidermal hyperplasia. Reneck et al., reported similar histopathological findings [20].

In our study, few of the cases revealed a superficial and mid-dermal mixed perivascular and peri-follicular infiltrate of lymphocytes and eosinophils with variable degrees of follicular damage. Hevia et al., study showed similar findings [21]. Bouscarat et al., has proposed that PPE could be as a result of initial rise of specific memory cells directed against pathogens that are already present which may explain the occurrence of this condition after HAART [22]. In present study, eosinophilic folliculitis was found in 4 cases, of which 3 had a low CD4 count <200/µL (mean 72/µL). This is in consonance with the study by Goldstein et al., where eosinophilic folliculitis correlated with a more advanced degree of immunosuppression with CD4 counts below 75/µL [14]. In our study, leukocytoclastic vasculitis was seen in 3 patients, 2 of whom had a CD4 count of less than 200/µL (mean 190/µL). The manifestations of human immunodeficiency virus (HIV) infection are protean and vasculitides are one of the less common but nonetheless important consequences [23]. A wide range of vasculitides can be encountered, ranging from vasculitis resulting from specific infective agents to a non-specific vasculitis. There are cases of vasculitis related to HAART. This is probably related to the immune dysregulation and the propensity toward allergic phenomena found in Human Immunodeficiency Virus infection [24]. Cytomegalovirus and tuberculosis are probably the most common among the infective causes of vasculitis. Hypersensitivity vasculitis resulting in several patterns of vasculitis and angiocentric immunoproliferative vasculitis are well recognised. Non-specific vasculitides not fitting into any of the characteristic pattern's accounts for the residue of vasculitides associated with HIV [23].

In our study, neoplasms like Kaposi`s sarcoma were not observed. In a study conducted by Goh et al., the relative proportion of homosexual individuals is significantly lower in Asian population as compared to western population. This difference together with a low prevalence of HHV-8 infection in Asians, may explain the apparent absence of this neoplasm in our study [17,25].

LIMITATIONS

Limitations of this study were small sample size, immunohistochemical markers could not be done due to resource limited settings. Further studies were needed to get the clear consensus on the aetiology of papulonodular dermatoses.

CONCLUSION

Patients with infective and non-infective cutaneous manifestations are significantly immuno-suppressed than HIV-positive asymptomatic controls. The absolute CD4 count is inversely related to the number of HIV positive patients with papulonodular eruptions of skin. Pruritic papular eruption is

a very common cause of papular eruption in HIV positive patients with severe immunosuppression. Majority of the patients respond to HAART and those who are not on HAART, respond to symptomatic therapy with anti-histaminics and topical steroids. Eosinophilic folliculitis is also a very common entity in severely immunosuppressed patients. 75% of our cases were associated with peripheral blood eosinophilia. Respond to HAART with complete regression of lesions. Leukocytoclastic vasculitis is also a rare form of presentation in HIV patients. This could be per se because of HIV infection and HAART induced. Hence, there is a need for histopathology examination to separate these closely related entities for precise diagnosis and proper management in HIV patients.

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