CUTANEOUS MANIFESTATIONS OF HIV-INFECTION IN RELATION WITH CD4 CELL COUNTS IN HADOTI REGION

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ABSTRACT: BACKGROUND: Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) are frequently associated with mucocutaneous manifestations. However, there is paucity of data on skin disorders and association with CD4 cell counts from India. **OBJECTIVE:** To evaluate the occurrence of mucocutaneous disorders and their relationship with CD4 count. **METHODS:** A cross-sectional study was performed at Government Medical College Kota from January 2011 to January 2012. Collected information included demographic data, HIV-associated mucocutaneous disorders, CD4 cell count and highly active antiretroviral therapy (HAART). **RESULTS:** One hundred cases (male: female, 1.7: 1) were enrolled. The most common mode of HIV transmission was heterosexual (89%), followed by homosexual/bisexual contacts (5%), perinatal (5%) and blood transfusion (1%). The distribution of patients in terms of CD4 cell counts was as follows: 30% with less than $200 \times 10^6 /L$, 55% with between 200 and $500 \times 10^6 /L$, and 15% with more than $500 \times 10^6 /L$. Most common skin disorders were fungal infection (46%), followed by bacterial infection (30%), viral infection (26%). Pruritic papular eruption (13%) was most common non infectious dermatoses followed by seborrheic dermatitis (8%). A CD4 cell count of less than $200 \times 10^6 /L$ was significantly associated with a higher number of mucocutaneous disorders ($P = 0.005$) and the development of oral candidiasis [$P = 0.005$] and generalized seborrheic dermatitis ($P = 0.005$). There was no case of cutaneous malignancy in our study. **CONCLUSION:** A wide range of mucocutaneous disorders were observed in HIV-infected cases which are the indicator of AIDS and overall survival. A preponderance of infectious and inflammatory dermatoses with an absence of skin tumors characterized this study.

INTRODUCTION: AIDS is acronym for acquired immune deficiency syndrome caused by retrovirus known as human immunodeficiency virus (HIV).¹ At the end of 2010, an estimated 34 million people were living with HIV worldwide.² The HIV prevalence among high risk groups, i.e., female sex workers, injecting drug users, men who have sex with men and transgender is higher. Based on HIV Sentinel Surveillance 2008-09, it is estimated that 23.9 lakh people are infected with HIV in India, of whom 39% are female and 4.4% are children. The first AIDS case in India was detected in 1986. The most common route of transmission is heterosexual/homosexual activity, transfusion of contaminated blood and its products, intravenous drug users, perinatal via breast feeding. The incidence and severity of several common cutaneous diseases are increased in patients with HIV and this correlates in many instances with the absolute number of CD4 T-helper cells. The cutaneous manifestations can occur in all stages of HIV disease and it is a prognostic indicator of development of AIDS.

Skin and mucosal diseases are often the initial manifestation of asymptomatic HIV infection, indicative of underlying degree of immunosuppression, systemic opportunistic infections or malignancy.³ After the introduction of highly active antiretroviral therapy (HAART), there has been a decrease in the incidence and severity of HIV-associated mucocutaneous lesions that were commonly seen in the pre-HAART era. However, HAART itself has brought additional skin problems, such as drug-related adverse reactions and immune reconstitution syndrome (IRS)-related skin diseases.^{4, 5} In this cross-sectional study, we assessed the prevalence of mucocutaneous manifestation in HIV-infected patients and their relationship with CD4 cell count.

MATERIAL AND METHOD:

Patients and setting: This study was conducted from January 2011 to January 2012 at Government Medical College, Kota in Hadoti region. Study included 100 HIV seropositive patients attending skin Out Patient Department. Patients on immunosuppressive drugs and corticosteroids were excluded from study. Informed consent was obtained from all participants, and the study was approved by the local ethical committee. The participating team of doctors comprised two dermatologists. Information was collected on demographic data, current skin problems, most recent CD4 count, antiretroviral therapy, modes of HIV transmission. Careful search was done for any atypical cutaneous manifestation or any unusual site of involvement. General physical examination was done to rule out systemic illness.

Clinical data and diagnostic criteria: Chronic mucocutaneous disorders were diagnosed by clinical manifestation. Skin scraping and culture for fungal infections were performed to confirm dermatophytes and candida infection. Deep mycosis was confirmed by skin biopsy and culture. The diagnosis of bacterial infection is made with Gram's stain and culture. Diagnosis of HSV infection is confirmed by Tzanck smear. Diagnosis of verruca vulgaris and condyloma acuminata were made clinically and correlated with histopathology.

Seborrheic dermatitis is a marker of early HIV infection. Clinically it presents as yellow-white greasy scales on erythematous patches predominantly on the face, scalp, chest, back and intertriginous areas. HIV-infected patients may have two coexisting patterns of psoriasis simultaneously (eg - guttate and psoriasis vulgaris). Prominent involvement of groin, axillae and scalp occur. HIV related psoriasis has histologic features similar to typical psoriasis but, Munro-microabscesses are seen less frequent, with more irregular acanthosis and less discernible thinning of the suprabasal plate.⁶

Pruritic papular eruption (PPE) was defined as presentation of pruritic, discrete papules on trunk, extremities, head and neck for greater than 1-month duration, absence of other definable causes of itching with sparing of the mucous membranes, palms, soles and digital web spaces.⁷ Eosinophilic folliculitis (EF) is a chronic, intensely pruritic condition occurring predominantly over head and neck area.^{4,6} Lipodystrophy is defined as presentation of Cushingoid features, lipomatosis, facial thinning, central obesity, buffalo hump and peripheral lipoatrophy. The drug eruptions were defined as follows: (i) the suspected drug was used in temporal relation to symptoms; (ii) the skin and mucosal manifestations were typical for the suspected drug; and (iii) the eruptions were improved after withdrawal of the suspected drug.

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Statistical analysis : The statistical analysis was done using Chi-square test for non parametrical data and if $p < 0.005$, then the test was considered statistically significant and a Student T- test while comparing two groups of unequal variance. Descriptive statistics were used to summarize the clinical characteristics and skin disorders of the subjects.

RESULTS:

Demographic characteristics: Among 100 HIV-positive patients, 63 (63%) were male and 37 were female. Ages ranged from 2.5 to 60 years with a mean 33.8 years. Most of the patients (74%) were young and middle-aged, sexually active people (20-40 years). Among 100 patients, 79% were married and 9 % patients were widow/widower. Majority of the patients (58%) were unskilled labourers, which included guards, daily wage workers, hotel/bar servants, sweepers and construction workers. The most common mode of HIV transmission was heterosexual (89%), followed by homosexual/bisexual contacts (5%), perinatal (5%) and blood transfusion (1%). (Table 1).

Table 1: Demographic and clinical characteristics of 100 HIV-infected patients enrolled in the study.

Demographic and clinical characteristics	No. of patients (%) (n=100)
Age (mean, years)	33.8 (range 2.5 -60 years)
Sex	
Male	63
Female	37
Marital status	
Married	79
Unmarried	5
Widow/widower	9
Divorced	2
Not applicable	5
Transmission	
Heterosexual	89
Homosexual/Bisexual	5
Perinatal	5
Blood transfusion	1
Antiretroviral therapy	
Combination therapy	85
None	15
Current CD4 cell count (cells/cumm)	
<200	30
200-500	55
>500	15

The mucocutaneous manifestations of HIV infection are very frequent and also tend to appear at a specific stage in the progression of the disease. Frequency of skin manifestations increased with fall of CD4 count.

- Mucocutaneous manifestation divided in 2 broad categories: infective and non infective dermatoses. Fungal infection was most common among infectious dermatoses comprising 46%. *T. cruris* was the commonest infection followed by Candidiasis which caused oropharyngeal, vaginal candidiasis, and chronic paronychia. In upto 10% of patients it is the first manifestation of HIV infection, occurring when the CD4 counts are < 400cells/cumm.^{4, 5} Other fungal infections which can be seen in HIV patients are histoplasmosis, cryptococcosis, coccidioidomycosis, and penicilliosis.

Bacterial infections were seen in 30 patients. *Staphylococcus aureus* is the most common bacterial pathogen in HIV- infected adults.^{8,9} It is seen in seropositive patients with CD4+ count < 500 cells / cumm.^{9,10} Folliculitis was the most common pattern of Staphylococcal pyoderma, occurring on the trunk, face or groin. Viral infections were seen in 26% of patients. The mean CD 4 count was 278.77 + 176.69. Herpes genitalis was the most common viral infection and also most common cause of genital ulcer disease comprising 9% of cases. Early in the course of HIV infection, HSV usually presents as it does in immuno- competent patients, with recurrent, painful ulcerations at mucocutaneous junctions such as the genital, perioral or perianal areas.¹¹ With more advanced infection, lesions can be larger, more widespread or necrotic.¹² In parasitic infestation, scabies and pediculosis were seen in 7 and 1 patients respectively.

In non infective dermatoses papulosquamous disorders and pruritic papular eruptions were seen most commonly. In papulosquamous disorders, Seborrheic dermatitis is a marker of early HIV infection and most common non-infectious skin disorder. It is mostly seen in patients who have CD4+ counts >200 cells / cumm. It presents as yellow-white greasy scales on erythematous patches usually affecting sebaceous areas on face, scalp, chest, back and intertriginous areas. Other papulosquamous disorders were psoriasis, ichthyosis. Majority of patients who had pruritic papular eruption (PPE) had a CD4 cell count below 50 cells / cumm, suggesting that PPE should be regarded as a cutaneous marker for advanced HIV infection. Eosinophilic folliculitis (EF) is a chronic, intensely pruritic condition seen when CD4 count is below 75 cells / cumm.⁶

In adverse drug reactions, maculopapular rash, urticaria and SJS were seen usually with CD4 count 200-500 cells / cumm. Hair changes included telogen effluvium, diffuse alopecia, graying of hair seen with CD4 count <200. In Nail changes, onychomycosis were most common, rest were melanonychia, bluish discoloration, koilonychia, leuconychia seen with CD4 count <200. In oral manifestation, candidiasis were most common followed by pigmentation, aphthous ulcers, herpes labialis, oral hairy leucoplakia which were seen with CD4 count < 200 cells/ cumm. Lipodystrophy is seen in 1 patient having count <200. It is change in the body fat distribution observed in patients receiving HAART. Patient appear Cushingoid with visceral fat accumulation, lipomatosis, facial thinning, central obesity ('protease pouch', 'crix belly'), buffalo hump and peripheral lipoatrophy.

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Table 2: Distribution of Cases according to type of bacterial skin infections & CD4 count.

Infection	CD4 counts (Cells/ cumm)			Total
	< 200	200-500	> 500	
Folliculitis	9	4	4	17 (17%)
Abscess	2	0	0	2 (2%)
Furuncle	1	4	0	5 (5%)
Carbuncle	0	1	0	1 (1%)
Cellulitis	0	1	0	1 (1%)
Leprosy	0	1	0	1 (1%)
Chancroid	0	1	0	1 (1%)
Chancre	0	1	0	1 (1%)
Ecthyma	1	0	0	1 (1%)
Total	13	13	4	30 (30%)

Table 3: Distribution of Cases according to types of viral infections and CD4 Count

Viral Infections	CD4 counts (Cells/ cumm)			Total
	< 200	200-500	> 500	
Herpes zoster	2	3	0	5 (5%)
Herpes genitalis	2	5	2	9 (9%)
Molluscum contagiosum	1	2	0	3 (3%)
Genital Wart	1	4	0	5 (5%)
Herpes labialis	0	2	0	2 (2%)
Plane wart	0	1	0	1 (1%)
Common wart	0	1	0	1 (1%)
Total	6	18	2	26 (26%)

Table 4: Distribution of Cases according to Fungal infection & CD4 Count

Fungal Infection	CD4 counts (Cells/ cumm)			Total
	< 200	200-500	> 500	
T. Cruris, corporis, pedis	12	8	3	23 (23%)
Intertrigo	0	0	1	1 (1%)
Oral Candidiasis	12	2	0	14 (14%)
Vulvovaginal candidiasis	2	0	1	3 (3%)
Candidal Balanoposthitis	1	1	0	2 (2%)
T Capitis	0	0	1	1 (1%)
Pityriasis Versicolor	1	0	0	1 (1%)
T Manum	1	0	0	1 (1%)
Total	29	11	6	46 (46%)

Table 5: Distribution of STD's cases according to CD4 count

S NO	Sexually transmitted disease (STD)	Male	Female	Total
1	Herpes genitalis	9 (9%)	0	9 (9%)
2	Genital wart	5 (5%)	0	5 (5%)
3	Genital Molluscum contagiosum	0	2 (2%)	2 (2%)
4	Chancroid	1 (1%)	0	1 (1%)
5	Syphilis	2 (2%)	1 (1%)	3 (3%)
Total		17 (17%)	3 (3%)	20 (20%)

Table 6: Non-infective Dermatoses in relation to CD4 count

Non infective dermatoses	<200	200-500	>500
Papulosquamous disorder	3	5	0
Pruritic papular eruption	6	6	1
Papular urticaria	3	1	1
Eosinophilic folliculitis	2	2	1
Adverse drug reaction	1	3	0
Hair changes	3	2	0
Nail changes	11	6	2

DISCUSSION: HIV-infected patients commonly have various mucocutaneous manifestations at all stages of HIV infection. Certain mucocutaneous disorders can be considered as markers of disease progression. HAART has been proven to inhibit viral replication and to induce recovery of CD4 cells with immune reconstitution. The prevalence of certain mucocutaneous diseases has decreased in HIV/ AIDS patients ever since HAART became more accessible to the patients.¹³ The results in our study also confirmed such an improvement.

A total of 100 HIV seropositive patients were evaluated to know the correlation between mucocutaneous manifestations and CD4 cell count in Hadoti region of Rajasthan state. Number of males and females accounted to about 63% and 37% respectively. The male predominance in the study can be explained by the fact that there is a greater involvement of male patients in 'high risk' activities predisposing to HIV infection. Also about 45% of total patients were in 31-40 yr age group which is also sexually active group.

Majority of the patients in our study were unskilled labourers group which included guards, daily wage workers, hotel/bar servants, sweepers and construction workers. This group comprised about 58% and their higher proportion in our study can be explained by the fact that our hospital renders free supply of medicines from both free medicine scheme and from PLWHA (patients living with HIV and AIDS) group. Also majority of these patients stayed away from home and hence there was lack of restraint against high risk activities. Majority of females were also unskilled workers followed by widows who were infected by their live and late seropositive husbands respectively. Also majority of males (52%) got infected by multiple, polygamous, unprotected, heterosexual exposure. Although history of blood transfusion was present in 9% of patients, only 1 patient was affected due to it and rest 8 patients were seropositive before transfusion. Perinatal transmission

was present in 5% of patients indicating lack in the quality of medical services present in this part of the state. Mucocutaneous manifestations were divided into two categories – infectious and non-infectious.

A] Infectious mucocutaneous manifestation:- Cutaneous fungal infections were most common (46%) infectious dermatoses. Dermatophytic infections were most prevalent fungal infection in 25% of patients. About half (13%) of these were having CD4 count < 200/cumm, which is slightly more than that reported by Goh et al.⁸ Higher prevalence in our study can be attributed to increased sweating due to hot climate in this part of state. Majority of the patients suffering from dermatophytoses had extensive infection. *T. cruris* was the commonest (17%) followed by Candidiasis affecting 17% and 14% respectively of all manifestations. The incidence of Candidiasis increased significantly as the CD4 count fell and was higher when CD4 counts were less than 200 cells / cumm. The mean CD4 count was 256.41 + 222.84.

About 30% of patients had bacterial infections in our study. Bacterial folliculitis (17%) was the most common presentation followed by furuncle (5%), abscess (2%), and 1% each of carbuncle, cellulitis, leprosy, chancroid, chancre, ecthyma. The prevalence of folliculitis in Indian studies was 1.7 - 3.6%.^{10, 14} The mean CD4 count for bacterial infection was 262.17 + 165.97. The incidence of staphylococcal infections is much higher compared to other studies from India. This could possibly be because being a tertiary care centre; patients came to this hospital later after the primary lesions became complicated by secondary infection. In our patients, Impetigo and folliculitis were recurrent and persistent and more resistant to treatment requiring higher doses of antibiotics for longer duration.

In the present study, 26% of patients had viral infections. Herpes simplex was most common (11%) [Herpes genitalis (9%) + Herpes labialis (2%)] viral infection followed by Herpes zoster (5%). The mean CD4 count for viral infections was 278.77 + 176.69. Majority of patients with Herpes simplex had CD4 count in the range of 200 – 500 / cumm. Jing et al¹⁵ reported an incidence of 2.9% in the study done in 1998. Nnoruka⁹ et al and Goh⁸ et al reported an incidence of 6.3% and 17.7% respectively, which reflects a current trend for increased HSV infection. It is now possibly the largest etiology for genital ulcer disease. The implication of this increased incidence in the setting of HIV includes a greater risk of transmission of the disease and also greater morbidity as the disease is recurrent. Issues like suppressive therapy arise which greatly add to the financial burden of the patient. Chronic ulcer from Herpes simplex virus for more than 1 month is an AIDS defining illness.

Herpes zoster was seen in 5 patients, out of these 3 patients presented with multidermatomal zoster involving > 2 dermatomes and another one with disseminated herpes zoster. The prevalence of Herpes zoster in study conducted by Shobana et al¹⁶ was 6% which is consistent with our study. Disseminated herpes zoster is defined as more than twenty skin lesions appearing outside either the primarily affected dermatome or dermatomes directly adjacent to it.¹⁷ Besides the skin, other organs, such as the liver or brain, may also be affected (causing hepatitis or encephalitis respectively), making the condition potentially fatal.¹⁵⁴ The lesions were morphologically bullous and hemorrhagic and took longer time to crust and heal. The post herpetic neuralgia associated was also more severe. All herpes zoster patients had CD4 count < 500 / cumm.

Molluscum contagiosum was seen in 4% cases in our study which was similar to the prevalence of 4% as shown in the study by Shobana et al.¹⁶ Also characteristically noted was the

multiple number of lesions (>20), the size and location. The mollusca were giant (>1cm) in 1 patient, 2 had genital mollusca and 1 had facial molluscum. Umbilication was absent and pseudo- Koebner phenomenon was observed. Genital wart was present in 5 patients (5%). All patients had CD4 counts < 500 / cumm. Confluent verrucae were noted in 4 cases and were very resistant to treatment. Kumarasamy¹⁰ et al reported a prevalence of 1.2% with mean CD4 count of 187±142 cells / cumm. Other viral infections seen were Herpes labialis (3%), plane wart (2%) and common wart in 1 patient.

In our study 21% of cases had STD's. Herpes genitalis was the most common STD in our study (9%) followed by genital wart (5%) and Molluscum contagiosum. The incidence of Herpes genitalis in various studies range from 6.3% to 17.7%^{8, 9}, which is comparable with our study signifying current trend for increased HSV infection. Although the exact incidence of genital molluscum in HIV-infected persons remains unknown, studies have estimated that 5 to 18% of untreated HIV-infected patients develop molluscum lesions at some point in their clinical course.¹⁸ A lower incidence in our study can be explained by the fact that prevalence of atopic dermatitis, which predisposes to molluscum contagiosum, is less in India as compared to developed countries.¹⁹ The incidence of genital warts in various studies involving male patients ranged from 13.8% to 21.4%.^{20,21} The lower incidence in our study may be due to reduced prevalence of homosexuality in our country.

Parasitic infestations were seen in 8 patients (8%). Scabies was seen in 7 patients (7%). Most common type was nodular scabies and one case of crusted scabies. The incidence of scabies in various other studies, were ranging from 3 to 6%.^{8, 9, 22} Scabies was most common in patients with CD4 count below 200 cells / cumm. The parasitic infections were resistant to treatment and repeated applications of anti-parasitic agents became necessary.

B] Non infectious mucocutaneous manifestation: - Pruritic papular dermatoses were the most common non infectious dermatosis. Pruritic papular eruptions were commonest (13%). Nearly 50% (6 patients) had CD4 counts <200 cells / cumm. Goh⁸ et al in 2004 found it to be three times more common in patients with CD4 counts below 200. Sanchez et al²³ found that 80% of their patient had a CD4 cell count of < 100 cells / cumm. Higher mean CD4 count in current study may be due to the fact that 90% of Pruritic papular eruptions patients were on HAART and it could be due to IRIS (immune reconstitution inflammatory syndrome).

Seborrhoeic dermatitis was seen in 8% of patients and all patients (5%) with generalized involvement had CD4 count < 200 / cumm and improved with HAART therapy and rising CD4 cell counts. The mean CD4 count is 142.12 + 115.78 cells / cumm, consistent with study of Shobana et al.¹⁶ Adverse drug reactions constituted 4% of the total manifestations and included maculopapular, urticarial rash and Stevens - Johnson syndrome. The causative agents were mainly Nevirapine followed by NSAIDS and Cotrimoxazole. The low incidence in our study can be explained by the fact that apart from HAART, relatively few drugs are used to manage minor infections as HAART itself improves the general condition of the patient.

Hair changes were seen in 5 patients (5%) of whom 2 patients had Telogen effluvium, 2 had diffuse alopecia and 1 patient had premature graying of hair. Diffuse alopecia (telogen effluvium) in various studies ranges from 3.9% to 10%.^{10, 16} Chronic, diffuse hair loss in HIV infected patients has been attributed to chronic HIV-1 infection itself and recurrent secondary infections, nutritional

deficiencies, immunologic and endocrine dysregulation and exposure to multiple drugs.²² Many cytokines including IL-1, IL-6, TNF- α , and IL-10 increase in the mid to late stages of HIV-1 disease, and these may have an effect on the follicle. In addition, in HIV-1 disease, a constant state of oxidative stress is present. Oxidative stress is a common factor in immediate anagen release telogen effluvium.²²

Nail changes were seen in 19% patients. Onychomycosis was seen in 8 patients with 3 of them having proximal subungual onychomycosis. The prevalence of onychomycosis in HIV-positive individuals in the sample of 500 patients was 23.2%.²⁴ The lower incidence attributed to in our study may be due to the fact that majority of patients attending our OPD were taking HAART and also were treated in the peripheral centre.

Oral manifestations were found in 28 patients (28%). The mean CD4 count for oral manifestations was 217.38 ± 188.76 . Oral Candidiasis was most common and was seen in 14 patients (14%) which is less than that found by Shobana et al.¹⁶ The majority of oral candidiasis patients (12) had CD4 count < 200 / cumm. The lower incidence of oral candidiasis in our study can be explained by the fact that relative number of patients with CD4 count < 200 / cumm is less than that compared in other studies. Oral hairy leukoplakia was seen in 1 (1%) patient, and the report of OHL varies from 0 to 3%.^{16, 22} In the present study, 1 case of lipoatrophy involving face and extremities was found. The CD4 count of the patient was < 200 / cumm.

No case of Kaposi's sarcoma was noted in our study which correlated with other studies and is a known fact that neoplasms are relatively uncommon in Asians. Thus the present study reinforces the fact that skin is the most common organ affected in HIV infected persons and mucocutaneous manifestations are one of the most important clinical prognostic markers and may even indicate to a diagnosis of HIV infection.

The mucocutaneous manifestations of HIV infection are very frequent and also tend to appear at a specific stage in the progression of the disease. They are an indicator of the development of AIDS and overall survival like the CD4 T cell count. The frequency of infections like dermatophytoses, oral candidiasis, folliculitis and others were higher at lower CD4 count. Frequency of skin manifestations increased with fall of CD4 count. Infectious disorders like herpes zoster, warts, scabies, molluscum contagiosum and non infectious disorders like Seborrheic dermatitis and xerosis were seen. Pruritic papular eruptions, hair change like telogen effluvium, diffuse alopecia, and graying which are the late manifestations described in HIV infected persons were also noted. There was no case of cutaneous malignancy in our study.

In conclusion, HIV-infected Indian individuals were afflicted with a wide range of mucocutaneous manifestations, which could be affected by HAART. The most common ones, oral candidiasis and PPE, were associated with a low CD4 cell count and indicated advanced HIV infection. In resource limited regions, like India where immunological monitoring is not easily available, certain mucocutaneous manifestations are of help in surmising underlying immune status and risks of disease progression. By correlating CD4 count and mucocutaneous lesions, the skin lesion itself may be sufficient to indicate the stage of the disease and for commencement of HAART, without having to wait for CD4 count.

Lipoatrophy over face and temporal region

SJ syndrome due to Nevirapine

Giant molluscum contagiosum

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