

Clinical and histopathological aspects of lichenoid dermatitis in patients of retroviral diseases

Swagata A. Tambe, Uddhao S. Zambare, Chitra S. Nayak, Priyanka D. Patil, Aditi Chhonkar
Department of Skin and V.D., TNMC and BYL Nair Ch. Hospital, Mumbai, Maharashtra, India

Address for correspondence:

Dr. Uddhao S. Zambare, Department of Skin and V.D., 2nd Floor, OPD Building, TNMC and BYL Nair Ch. Hospital, Mumbai - 400 008, Maharashtra, India.
E-mail: uddhaoz1@gmail.com

Abstract

Context: Lichen planus (LP) is known to be associated with viral infections such as hepatitis B and C, but its association with HIV is rarely reported. Lichenoid drug eruptions have been implicated as the side effects of anti-retroviral therapy. **Aims and Objectives:** The aim of this study is to study demographics, clinical, histological, and immunological profile of the HIV patients presenting with lichenoid dermatitis. **Subjects and Methods:** HIV patients presenting with LP such as lesions were evaluated with complete history and physical examination. Demographic profile of patients was studied with features such as age, sex, duration of disease, distribution of the lesions, CD4 count, concomitant medications, associated comorbidities, and response to the treatment. **Results:** Twenty-one HIV patients presenting with LP such as lesions were studied. Of these, 20 patients had LP and one patient had lichenoid drug reaction. The age of the patient ranged from 40 to 60 years with no sex predilection. The duration of lesions ranged from 15 days to 7 years. Eleven patients had simultaneous cutaneous and oral involvement, five patients had only oral involvement and four patients of LP and one patient of lichenoid drug reaction had only cutaneous lesions. All the patients were on antiretroviral therapy, mainly on lamivudine, zidovudine, and nevirapine. Almost all the patients had CD4 count of more than 250 at the time of presentation. One patient was diagnosed to have lupus erythematosus and LP overlap. Patients were treated with oral medications such as corticosteroids, methotrexate, and dapsone and topical medications such as corticosteroids and calcineurin inhibitors. **Conclusions:** The appearance of LP such as lesions in HIV patients is a rare occurrence with 11 cases of LP reported till date. Our case series of 20 patients will throw light on possible etiology and difficulties in the management of LP such as lesions in HIV patients.

Key words: HIV, lichen planus, lichenoid drug eruption

Introduction

Lichen planus (LP) is an idiopathic subacute or chronic inflammatory disease of the skin, mucous membranes, and nails. The exact pathogenesis of LP is still unclear, but several hypotheses have been made regarding the role of genetic, infective, psychogenic, and autoimmune factors. HIV patients suffer from numerous dermatoses. Few of these dermatoses such as psoriasis and seborrheic dermatitis are often found to be more severe in HIV patients.

LP has been reported in association with hepatitis B and C virus infection but its association with HIV infection is rarely reported. The occurrence of LP in HIV patients can be coincidental or it can present as lichenoid drug reaction. Lichenoid dermatitis as a result of adverse cutaneous drug reaction has been reported with anti-retroviral therapy (ART) drugs, especially with zidovudine^[1] and

tenofovir.^[2] Other concomitant medications given to HIV patients such as cotrimoxazole and nonsteroidal anti-inflammatory drugs can cause similar adverse effects.

The occurrence of classical LP and its variant is quite possible in HIV patients. The exact association between these two diseases needs detailed study which cannot be conducted as there are only 11 cases reported.

Subjects and Methods

This is a retrospective observational study of HIV patients presenting with LP such as lesions. Patients with details of complete history, clinical examination, and skin biopsy were studied. The features such as age, sex predilection,

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Tambe SA, Zambare US, Nayak CS, Patil PD, Chhonkar A. Clinical and histopathological aspects of lichenoid dermatitis in patients of retroviral diseases. *Indian J Sex Transm Dis* 2022;43:59-63.

Submitted: 04-May-2020

Revised: 28-Jan-2021

Accepted: 13-Oct-2021

Published: 27-Jan-2022

Access this article online

Quick Response Code:



Website:

www.ijstd.org

DOI:

10.4103/ijstd.IJSTD_51_20

duration of LP and HIV, distribution and morphology of the lesions, histopathology findings, CD4 count, concomitant medications, ART regimen, associated comorbidities, and response to treatment were studied.

Results

We found 21 HIV patients presenting with LP like lesions over the last few years in our outpatient department. Ten patients in our study were in the fifth decade with a male:female ratio of 1.1:1. The duration of LP like lesions ranged from 15 days to 7 years with maximum patients having duration of <1 year. The duration of seropositive status ranged from 1 month to 23 years with 8 of 21 patients having duration of 6–10 years. Aggravating factor like photosensitivity was seen in two patients. Addiction to tobacco and smoking was seen in six patients with oral lichenoid lesions. Medication as an aggravating factor was seen in only one patient. Of the 21 patients, 11 patients had simultaneous cutaneous and oral involvement; five patients had only oral involvement while four patients of LP and one patient of lichenoid drug reaction had only cutaneous lesions.

The distribution of cutaneous lesions was almost generalized in seven patients of LP and one patient of lichenoid drug reaction. Two patients had actinic LP localized to the face, neck, and lower lips. Four patients had hypertrophic lesions of LP on the lower extremities. One patient had hypertrophic lesion on photo-exposed distribution [Figure 1a-c] while one patient had violaceous and hyperpigmented patches on the face and neck suggestive of LP pigmentosus [Figure 1d-f]. Majority of cutaneous lesions had classical morphology of LP except for one patient of lichenoid drug eruption showing larger scaly lichenoid plaques with severe involvement of photo-exposed areas [Figure 2a-c]. Another patient with hypertrophic LP had scaly fissured annular plaques on soles [Figure 2d].

Of the 16 patients of LP with mucosal involvement, the buccal mucosa was most commonly affected in all 16 patients. Tongue, hard palate, and lower lip were the other affected areas. Genital mucosal involvement was seen in one male and two female patients. In the morphology of oral lesions reticular or lacy pattern was the most common (seen in 8 of 15 patients) followed by erosive LP (seen in 7 of 15) and plaque like form (seen in 3 of 15) patients. The combination of these patterns was seen in few patients simultaneously [Figure 3].



Figure 1: (a-c) Multiple violaceous hypertrophic papules and plaques on forehead, upper back and hands, (d-f) multiple violaceous patches on forehead, cheek, ear pinna and neck

One patient of LP with the duration of 4 years, later developed changes in the morphology of lesions as depigmented hypertrophic plaques and erosive and reticulate lesion on the buccal mucosa suggestive of discoid lupus erythematosus.

Nail involvement was seen in 6 of 21 patients. The common clinical features observed were longitudinal ridging and pitting. Pterygium of the nail was seen in only one patient.

On histopathology, 18 patients showed the features of LP, one patient was diagnosed as LP pigmentosus, one patient was diagnosed with lichenoid drug eruption and one patient showed features of LP-lupus erythematosus overlap [Figure 4].

Direct immunofluorescence was done in only one patient of LP-lupus erythematosus overlap which showed granular band with IgM and C3 at the basement membrane zone with colloid bodies in the papillary dermis, staining with IgM, IgA, and C3. Diffuse nuclear staining in epidermal cells with IgG (ANA in vivo) suggesting the diagnosis of LP lupus erythematosus overlap. Patient's ANA was positive in the speckled pattern with titer of 1:1000.

All patients were screened for hepatitis B, hepatitis C virus infection, and syphilis with hepatitis B antigen (HbsAg) anti-HCV antibodies and Venereal disease research laboratory (VDRL). All three tests were nonreactive in all the patients.

Of these 21 HIV patients with LP like lesion, CD4 count at the time of presentation was available in 20 patients [Table 1]. Baseline CD4 count and CD4 count at the time of presentation was available in 16 patients.



Figure 2: (a-c) Multiple violaceous patches and plaques on face, neck, forearm and legs, (d) multiple fissured scaly and pigmented plaques on both soles and ankle area

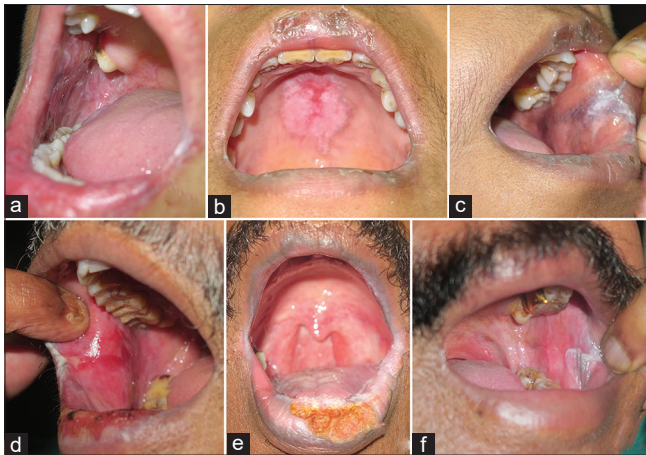


Figure 3: (a-f) Multiple erosive lacy-white lesions on oral mucosa and plaques on lips

Table 1: CD4 count and antiretroviral therapy details of all the patients

Patient number	CD4 count before initiation of ART	CD4 count at the time of presentation of lichen planus	ART regimen	Duration of ART
1	200	1164	ZLN	12 years
2	154	415	ZLN	7 years
3	12	370	ZLN	10 years
4	156	489	ZLE	7 years
5	NA	NA	ZLN	1 year
6	234	568	ZLE	4 years
7	NA	822	ZL + Indinavir	10 years
8	191	1189	TL + ATZ/Rv	23 years
9	273	511	TLE	10 years
10	253	459	TLE	7 months
11	261	1011	ZLN	5 years
12	311	441	ZLN	10 years
13	241	405	ZLN	7 years
14	NA	109	ZLE	16 years
15	267	252	ZLN	3 years
16	64	632	ZLN	8 years
17	285	663	TLE	4 months
18	340	330	ZLN	4 years
19	NA	686	ZLN	9 years
20	NA	294	TLE	8 years
21	314	974	ZLE	7 years

Z=Zidovudin; L=Lamivudin; N=Nevirapine; E=Efavirenz; T=Tenofovir; ATZ=Atazanavir; Rv=Ritonavir; NA=Not available; ART=Antiretroviral therapy

Except for one patient, majority of them had CD4 count more than 250 at the time of presentation with lichenoid lesions. Comparison of baseline CD4 count and CD4 count at the time of presentation revealed that except for two patients there was significant increase in CD4 count at the time of presentation with LP like lesions.

Lamivudine was the most common ART medication taken by all 21 patients in our study. Fifteen patients were on zidovudine, 11 patients were on nevirapine, 8 patients were on efavirenz, 5 patients were receiving tenofovir and 2 patients were on protease inhibitors like indinavir and combination of atazanavir and ritonavir. In 1 patient of lichenoid drug reaction nonsteroidal anti-inflammatory medication was the causative drug.

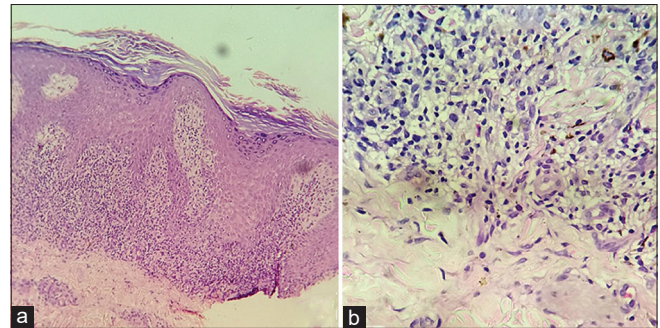


Figure 4: (a) Wedge shaped hypergranulosis in epidermis with lichenoid infiltrate in upper dermis suggestive of lichen planus (H and E, $\times 100$), (b) eosinophils in upper dermis infiltrate in case of lichenoid drug eruption (H and E, $\times 400$)

Table 2: Inflammatory skin diseases in human immunodeficiency virus

Inflammatory diseases in HIV	Clinical presentation
Seborrheic dermatitis	Seborrheic dermatitis can affect up to 85% of the HIV-positive population Presence of SD could indicate rapid progression of HIV It may occur at any CD4 cell count, (>500 cells/ mm^3) but usually becomes extensive and refractory as CD4 cell counts decline (<100 cells/ mm^3) Progression to erythroderma is known in HIV-positive patients HAART therapy can lead to significant improvement in the severity of disease
Psoriasis	Psoriasis affects up to 2% of the HIV population Psoriasis in HIV patients tends to be more severe, acral, extensive, destructive, and recalcitrant It may be a poor prognostic indicator for HIV-positive patients Higher prevalence of psoriatic arthritis in HIV patients HAART regimens containing antiretroviral drugs such as zidovudine, emtricitabine, tenofovir, atazanavir, and ritonavir are found to be successful in treating psoriasis in HIV patients
Reiter's syndrome	Clinical severity, including increased incidence of incapacitating arthritis pose special problems in therapeutic management of Reiter's disease Only one-third of RS in AIDS patients presented with prior genital or enteric infection
PPE of HIV	One of the earliest manifestations of HIV seen in 25%-50% of patients PPE is regarded as a cutaneous marker of advanced HIV ($\text{CD4} < 50/\text{mm}^3$) It can also present as IRIS
EF	EF is seen in the late stage of HIV commonly at CD4 cell count below 250 cells/ mm^3 , thus it may be considered as an important marker of HIV Eosinophilia, leucocytosis, and elevated IgE levels are often present

HIV=Human immunodeficiency virus; HAART=Highly active antiretroviral therapy; PPE=Pruritic papular eruption; EF=Eosinophilic folliculitis; IgE=Immunoglobulin E; RS=Reiter's syndrome; SD=Seborrheic dermatitis; IRIS=Immune reconstitution inflammatory syndrome

Associated comorbidities in these patients were vitiligo vulgaris, recurrent herpes genitalis, perianal warts and pulmonary tuberculosis.

All the patients were treated with emollients, oral antihistamines. Topical steroids and tacrolimus 0.1% ointment were preferred topical agents for cutaneous lesions. For oral involvement topical triamcinolone acetonide paste and tacrolimus ointment 0.03% was preferred. Patients with extensive involvement and those not responding to topical treatments were considered for

Table 3: Reported cases of human immunodeficiency virus and lichen planus association in the literature

Authors and years	Age/sex of patient	Duration and CD count	Type of lichen planus	Drug history	Treatment
Pardo and Kerdel 1988 ^[3]	40-year-old black male	4 months CD4 count: 38 cells/mm ³	Hypertrophic Lichen Planus Distribution: Extensor surfaces of the arms, forearms, pretibial areas, and dorsal aspects of the feet, neck	ART details not mentioned	Oral etretinate
Rippis <i>et al.</i> , 1994 ^[3]	41-year-old African-American male	1 year CD4 count: 33% CD4-positive cells, (NL 30-60%)	Extensive hypertrophic LP Distribution: Face, trunk, and upper and lower extremities	ART: Details not mentioned	Topical steroids
Rippis <i>et al.</i> , 1994 ^[3]	33-year-old African-American male	1 year CD4 count: 4% CD4 positive cells (NL 30-60%)	Extensive hypertrophic LP Distribution: Face extensor surfaces of the arms, legs, and fingers	ART: Details not mentioned Other medications: pyrimethamine and Dapsone	Topical steroids
Rippis <i>et al.</i> , 1994 ^[3]	28-year-old African-American male	2 months CD4 count: 5% CD4-positive cells (NL 30-60%)	Extensive hypertrophic LP Distribution: Face, trunk, arms, scrotum, and thighs	ART: Details not mentioned Other Medications: Dapsone and sulfa drugs	Topical steroids
Fitzgerald <i>et al.</i> , 1995 ^[4]	33/male Black	CD4 count: 8% (176 cells/ μ l)	Photodistributed hypertrophic LP Distribution: Face, ears, neck, chest, arms	ART: Dideoxycytidine (Zalcitabine), Zidovudine Other medications: Cotrimoxazole	Sunscreen Intralesional steroids
Ruiz Villaverde <i>et al.</i> , 2002 ^[8]	22 year/male	15 days CD4 count: 756 cells/ μ l	Multiple linear lichen planus Distribution: Left side of his chest, right arm, left back	ART: Zidovudine, lamivudine and nevirapine Other medications: Risperidone (schizophrenia)	Antihistamines
Kumari <i>et al.</i> , 2009 ^[9]	37 year/female Indian	1 month CD4 count: 250/mm ³	Widespread Hypertrophic and eruptive lichen planus Distribution: Lips, face, forearms, dorsum of hands, trunk, thighs, lower legs, feet, palms soles Oral and genital mucosae	ART: Zidovudine, lamivudine and nevirapine (initiated after diagnosis and treatment of LP)	Systemic steroids and oral acitretin topical steroids and tretinoin
Emadi <i>et al.</i> , 2010 ^[10]	40/Kenyan male	Exact duration not mentioned CD4 count: 140/mm	Extensive hypertrophic LP Distribution: Face, lower lip, trunk, lower and upper limbs, and the dorsal surfaces of both hands	ART: Stavudine, lamivudine, nevirapine Since 4 years	Topical steroids under occlusion
Patil <i>et al.</i> , 2016 ^[11]	40/female Indian	5 years CD4 count: 682 cells/ μ l	Lupus erythematosus Lichen planus overlap Distribution: Extremities and back, Lip, buccal mucosa	ART: Tenofovir, lamivudine, and efavirenz	Methotrexate, chloroquin and topical steroids and tacrolimus
Wilson <i>et al.</i> , 2016 ^[12]	75 year/male Caucasian	4 years CD4 count: 300 cells/ μ l	Unilateral, linear, hypertrophic LP Distribution: Right leg	ART: Efavirenz, emtricitabine, and tenofovir	Topical clobetasol ointment
Shah and Dhakre <i>et al.</i> , 2017 ^[13]	36/male	3 years CD4 count: 336 cells/ μ l	Hypertrophic LP on legs and oral lesions: buccal mucosa	ART: Zidovudine, lamivudine, and nevirapine	Not mentioned

ART=Antiretroviral therapy; LP=Lichen planus; NL=Normal level

systemic therapy. Six patients received treatment with oral prednisolone, four patients received oral dapsone, two patients of actinic LP responded very well to oral antimalarial agents while one patient of widespread LP and one patient of LP and one patient of LE-LP overlap syndrome received oral methotrexate with regular monitoring of CD4 count. As stated earlier, majority of these patients had CD4 count more than 250 at the time of presentation. Patients on oral immunosuppressive therapy were monitored regularly for CD4 counts and other concomitant infections. All the patients showed excellent response to the treatment with discontinuation of systemic immunosuppressive medications after improvement and maintenance on topical steroids and tacrolimus ointment.

Discussion

IP is a chronic inflammatory papulosquamous skin disorder. It may occur in immunocompromised hosts such as patients with graft versus host disease and those with tumor-induced immunodeficiency, abnormal humoral immunity. However,

there are a few case reports of LP, especially a severely hypertrophic form, occurring as an associated feature of HIV infection.^[3-5]

Rippis *et al.*^[3] have reported the three cases of hypertrophic LP in HIV-positive patients, in which they have studied alteration in the immune status in HIV-positive hosts by proportion of T-helper and T-suppressor cells in the inflammatory infiltrate. They found majority of the infiltrating lymphocytes in the dermis were of the T-helper phenotype and epidermal lymphocytes were of the T-suppressor phenotype.

The depletion of CD4+ T-cells and the associated disruptions of immune homeostasis result in greatly elevated susceptibility to numerous pathologies in HIV-positive persons. Infected persons also suffer from an elevated incidence and severity of dermatophytes, seborrheic dermatitis, herpes simplex, Ofuji disease, psoriasis, molluscum contagiosum, and other dermatoses and infections.^[6]

Inflammatory skin disease in HIV infected can have different clinical presentation compared to non-HIV patients^[7] [Table 2].

There is a paucity of literature on the occurrence of LP in HIV with only 11 cases of LP reported in HIV patients. These cases are summarized in Table 3.^[3-5,8-13]

We have compared the findings in our study with reported cases of LP.

Most of the patients of LP-HIV reported in the literature and cases in our study were in the fifth decade. In literature, cases of LP-HIV showed male preponderance, while in our study, no sex preponderance was seen. The duration of the LP in our study ranged from 15 days to 7 years, whereas the duration of LP in reported literature ranged from 15 days to 5 years.

Higher number of patients in our study showed generalized distribution of the disease, actinic and hypertrophic lesions compared to available literature.

Mucosal involvement was predominantly seen in our patients compared to cases reported in literature.^[3-5,8-13] Buccal mucosa was the most commonly affected mucosa, and reticulate type of LP was the most common.

In reported literature, almost 50% of LP patients had CD4 count <250 cells/mm³. This finding was not seen in our study.

In reported cases, majority of patients were treated conservatively with topical steroids and antihistamines while two patients with extensive involvement were treated with oral etretinate and oral methotrexate. Higher number of patients in our study had generalized distribution requiring treatment with systemic agents such as prednisolone, dapsone, antimalarial drugs, and methotrexate along with topical steroids and calcineurin inhibitors.

In HIV-positive patients, zidovudine^[1,14] and tenofovir,^[2,15] cotrimoxazole, NSAIDs, dapsone and ketoconazole are reported to cause lichenoid drug reaction. Zidovudine can cause oral lichenoid reactions while tenofovir-induced lichenoid reactions were generalized in distribution.^[2,15,16] In our study, only one patient had lichenoid drug eruption secondary to NSAIDs.

Eruptions resembling LP are commonly encountered as a sequel of graft-versus-host disease in persons receiving bone marrow transplantation or blood transfusions. The lichenoid phase of graft-versus-host disease may be clinically and histologically identical to LP and both diseases are thought to result from the destruction of basal cells by activated lymphocytes. Disease similar to that seen in persons who have received transplants or transfusions may result from infection of lymphocytes with human immunodeficiency virus. It is typically a generalized eruption.

Adverse cutaneous drug reactions occur far more often in HIV-infected persons than in the general population.^[16] After reviewing the literature, there are more reports of lichenoid drug reactions in HIV patients than LP. The feature of photo-distribution of the lesions, especially in darkly pigmented patients indicates a need for more studies to know the relevance of this observation.

Summary

Occurrence of LP in patients of HIV can be coincidental or could be part of changed immunological profile of the patients which has also been seen in patients of psoriasis and seborrheic dermatitis. Other differentials such as lichenoid drug eruption should be ruled out by detailed clinical history

and histopathological examination. Our study of 19 patients of LP and one patient of lichenoid drug eruption is the largest series of LP reported in HIV patients.

Limitations

The small number of patients in our retrospective study could be attributed to the rare occurrence of these diseases in patients on antiretroviral drugs.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Ficarra G, Flaitz CM, Gaglioti D, Piluso S, Milo D, Adler-Storhtz K, *et al.* White lichenoid lesions of the buccal mucosa in patients with HIV infection. *Oral Surg Oral Med Oral Pathol* 1993;76:460-6.
2. Gupta M, Gupta H, Gupta A. Tenofovir induced lichenoid drug eruption. *Avicenna J Med* 2015;5:95-7.
3. Rippis GE, Becker B, Scott G. Hypertrophic lichen planus in three HIV-positive patients: A histologic and immunological study. *J Cutan Pathol* 1994;21:52-8.
4. Fitzgerald E, Purcell SM, Goldman HM. Photodistributed hypertrophic lichen planus in association with acquired immunodeficiency syndrome: A distinct entity. *Cutis* 1995;55:109-11.
5. Pardo RJ, Kerdel FA. Hypertrophic lichen planus and light sensitivity in an HIV-positive patient. *Int J Dermatol* 1988;27:642-4.
6. Sadick NS, McNutt NS, Kaplan MH. Papulosquamous dermatoses of AIDS. *J Am Acad Dermatol* 1990;22:1270-7.
7. Betkerur JB, Ashwini PK, Ranugha PS, Sachdev A. Mucocutaneous manifestations of HIV-AIDS. In: Sacchidanand S, Oberai C, Inamdar A, editors. *IADVL Textbook of Dermatology*. 4th ed. Mumbai: Bhalani Publishing House; 2015. p. 2962-96.
8. Ruiz Villaverde R, Blasco Melguizo J, Naranjo Sintes R, Serrano Ortega S, Dulanto Campos MC. Multiple linear lichen planus in HIV patient. *J Eur Acad Dermatol Venereol* 2002;16:412-4.
9. Kumari R, Singh N, Thappa DM. Hypertrophic lichen planus as a presenting feature of human immunodeficiency virus infection. *Indian J Dermatol* 2009;54, S1:8-10.
10. Emadi SN, Akhavan-Mogaddam J, Yousefi M, Sobhani B, Moshkforoush A, Emadi SE. Extensive hypertrophic lichen planus in an HIV positive patient. *Dermatol Online J* 2010;16:8.
11. Patil P, Nayak C, Tambe S, Das D. Lupus erythematosus-lichen planus overlap syndrome in an HIV-infected individual. *Int J STD AIDS* 2016;27:1117-22.
12. Wilson S, Pollinger T, Turiansky G. An atypical presentation of unilateral, linear, hypertrophic lichen planus in a patient with HIV. *Pract Dermatol* 2016;24:6.
13. Shah PM, Dhakre VW. The rare occurrence of cutaneous and mucosal lichen planus in HIV infection. *BMJ Case Rep* 2017;2017:bcr2017222625.
14. Arirachakaran P, Hanvanich M, Kuysakorn P, Thongprasom K. Antiretroviral drug-associated oral lichenoid reaction in HIV patient: A case report. *Int J Dent* 2010;2010:291072.
15. Woolley IJ, Veitch AJ, Harangozo CS, Moyle M, Korman TM. Lichenoid drug eruption to tenofovir in an HIV/hepatitis B virus co-infected patient. *AIDS* 2004;18:1857-8.
16. Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients, 1975 to 1982. *JAMA* 1986;256:3358-63.