THE EFFICACY OF LOW-MOLECULAR WEIGHT HEPARIN IN THE MANAGEMENT OF GENERALIZED CUTANEOUS LICHEN PLANUS

This dissertation is submitted to

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

In partial fulfillment of university regulations
for the award of the degree of

M.D BRANCH XX

DERMATOLOGY, VENEREOLOGY AND LEPROSY

STANLEY MEDICAL COLLEGE

CHENNAI – 600 001

APRIL 2015

DECLARATION

I solemnly declare that the dissertation titled "**THE EFFICACY OF LOW-MOLECULAR WEIGHT HEPARIN IN THE MANAGEMENT OF GENERALIZED CUTANEOUS LICHEN PLANUS"** was done by me at **Government Stanley Medical College and Hospital during 2012-2015** under the guidance and supervision of my **Chief DR.V.ANANDAN, M.D., D.C.H., D.N.B (PAED).**

This dissertation is submitted to **THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY** towards the partial fulfillment of university regulations for the award of **M.D.DEGREE (Branch XX) IN DERMATOLOGY, VENEREOLOGY AND LEPRSOY**.

Place: Chennai

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CERTIFICATE BY THE GUIDE

Certified that this dissertation entitled **"THE EFFICACY OF LOW-MOLECULAR WEIGHT HEPARIN IN THE MANAGEMENT OF GENERALIZED CUTANEOUS LICHEN PLANUS"** is a bonafide work done under my guidance by **Dr. N. SUDHAKAR**, Post-Graduate student of the Department of Dermatology, Venereology and Leprosy, Govt. Stanley Medical College, Chennai – 600 001, during the academic year 2012 – 2015.

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ACKNOWLEDGEMENT

It is with immense pleasure and gratitude that I thank ***Dr. AL. MEENAKSHI SUNDARAM****,* ***M.D, D.A.,*** ***Dean****,* ***GOVERNMENT STANLEY MEDICAL COLLEGE & HOSPITAL*** *for bestowing on me the permission and privilege of presenting this study and for enabling me to avail the institutional facilities.*

I am gratefully indebted to ***Prof. Dr. V. ANANDAN, M.D., D.C.H., DNB (PAED),*** *Professor and Head of Department of Dermatology and Leprosy for his invaluable guidance and motivation.*

I am grateful to ***Dr. A. RAMESH,*** ***M.D., D.D., DNB,*** *Additional professor of Dermatology for his support and inspiration.*

I express my deep sense of gratitude to ***Prof. Dr P.ELANGOVAN,*** ***M.D., D.V.,*** *Professor and Head of Department of Venereology and* ***Prof. Dr****.* ***S. THILAGAVATHY,*** ***M.D., D.V*** *Professor, Department of Venereology for their constant support and motivation.*

Words will not suffice the gratitude I own to my guide ***Dr. R. SOWMIYA,*** ***M.D (DVL),*** *Assistant professor, Department of Dermatology for her peerless guidance and endless patience in molding this study.*

All our Assistant professors, Department of Dermatology, ***Dr. K.P. SARADHA, M.D (DVL), Dr. B.K. AARTHI, M.D (DVL),***

Dr. T. VANATHI, M.D (DVL), Dr. M. MANI SURYA KUMAR, M.D (DVL), Dr. V. SENTHILKUMAR, D.V DNB (DERM), Dr. P.S.MOHANA SUNDARI, M.D (DVL), Dr. N.S. JAYANTHI, M.D (DVL) *are thanked for their enthusiasm in motivating me with their competency to materialize this study.*

I wish to thank ***Dr. S.SIVASUBRAMANIAM M.D., D.V.*** *Former Associate Professor Department of Venereology for his constant support.*

I wish to thank ***Dr. PARIMALAM KUMAR, M.D. D.D., Dr. P. THIRUMARAN, M.D. Dr. P.C. MYTHILI, M.D (DVL), Dr. K.RAJKUMAR, M.D (DVL), Dr. NITHYAGAYATHRIDEVI, M.D (DVL),*** *former Assistant professors, Department of Dermatology for their constant support and motivation.*

I am inclined to thank, ***Dr. B. AMUTHA M.D (DVL), Dr. V. KAYALVIZHI MD (DVL), Dr. CHITRA MD (DVL), Dr. RENJINI M.D (DVL),*** *Assistant professors, Department of Venereology for their help and suggestions.*

I also wish to thank ***Dr. DEEPA, M.D (DVL), Dr. SUDHA, M.D (DVL), Dr. K. VENKATESAN, DV DNB (DERM),*** *Former Assistant professors, Department of Venereology for their help and suggestions.*

I am also inclined to express my deep sense of gratitude to Late ***Dr. R. SANTHARAMAN, MD, DD*** *Former Senior Assistant professor for his valuable suggestions given to me.*

I duly acknowledge the paramedical staff and my colleagues for their help and favours.

I also thank wholeheartedly my parents, wife and my daughters who constantly made me aware of the values of this noble profession.

I also express my thankfulness to my batch mates for having helped me in constructing this study.

Last but not the least I thank all my patients for their cooperation and participation in this study.

CONTENTS

ABSTRACT

Background and objectives: To assess the efficacy of low molecular weight heparin in the management of generalized cutaneous lichen planus.

Materials and methods: This is a one year open label prospective randomized study from July 2013 to June 2014. About 50 cases of generalized Cutaneous lichen planus willing to participate and follow up were included in the study. A brief and relevant medical history was taken during the initial visit and physical examination done to ensure that all relevant eligible criteria are met. Patients were given Injection Enoxaparin sodium 4 mg SC once weekly for 9 weeks and later followed up for 6 months. Efficacy is assessed by monitoring Itch severity score (ISS), DLQI, and nature of old and new lesions.

Results: Clinical improvement noticed in the form of decrease in ISS with regression of cutaneous lesions within 1 to 3 weeks in 80 to 90% of cases. There was no occurrence of new lesions in 76% of cases. Improvement in DLQI was noticed in 80% and complete disappearance of itch in 66% of the patients at the end of the study. No adverse effects were observed.

Conclusion: The rapid improvement and sustained remission in these cases implies that low molecular weight heparin could be a safe, effective and alternative monotherapy in the management of generalized cutaneous lichen planus.

Key words: Lichen planus, Enoxaparin sodium, ISS, DLQI.

INTRODUCTION

Lichen planus (LP) is a common and chronic inflammatory disease affecting the skin and mucosa that exhibits distinct morphologic and microscopic features. It was first discovered in 1869 by Erasmus Wilson.

The term Lichen is derived from Greek word (Leichen),which means tree moss. The word refers to a unique group of flowerless vegetations. The word ‘planus’ in Latin means ‘flat’. It is a self-limiting condition that most commonly affects middle-aged adults. It can involve glabrous skin, mucous membrane, hair and nails[(1)]. Oral lichen planus can occur without skin lesions or skin lesions may precede, follow or appear at the same time as those in the oral cavity.

The classical cutaneous lesion of lichen planus is variable and is commonly a pruritic, polygonal, faintly erythematous to violaceous flat topped papules with flexor distribution. Less common variants include hypertrophic, atrophic, vesicular and bullous lesions. Isomorphic phenomenon is characteristic of this condition[(1)(5)]. Many agents have been implicated in the etiology. It is often associated with various autoimmune and liver disorders. Although spontaneous remission do occur in LP, the natural history is quite variable and depend on the site of involvement and clinical pattern[(43)].

Various treatment modalities exist ranging from topical to systemic therapy. Response rates vary in different individuals and with different subset of clinical lesions. Classical cutaneous lesions usually respond to existing therapy. Newer modalities of treatment do exist and these are tried either as second line therapy or for refractory lesions.

Low dose of low molecular weight heparin (Enoxaparin) was first used by Hodak et al[11] in 1988 at the dose of 3 mg in the management of lichen planus. There was regression with cutaneous lesions with no improvement in the oral lesions.

Enoxaparin Sodium was used in cases of generalized cutaneous lichen planus in this study to determine it's efficacy and also to use it as a alternative monotherapy in this condition.

Oral lichen planus responds poorly to treatment. There are chances of transition to Squamous cell carcinoma with oral lesions especially the erosive(ulcerative) variant, the frequency being 0.8%[72].

REVIEW OF LITERATURE

HISTORICAL ASPECTS

Lichen planus was first discovered in 1869 by Erasmus Wilson. The dermatosis was earlier described by Hebra as 'Leichen Ruber'[1]. Louis Fredrick Wickham described the characteristic striae in 1895 and Graham Little described scalp involvement in lichen planus in 1919.The histological findings in lichen planus were defined in 1909 by Darier and attributed Wickham's striae to an increase in granular layer[1][6].

The word "Lichen"is derived from Greek word 'Leichen', which means "to lick". In Latin it denotes a kind of plant. This word is used as a noun in Greek and Latin to denote those symbiotic forms of life (combined growth of algae and fungus) that are now called lichens[1][3].

Trautmann described the vesiculo-bullous form of lichen planus in the oral mucosa in 1911.Lichen planus has also been reported involving other mucous membranes. The occurrence of oral lesions in the absence of dermal lesions in lichen planus was first pointed out by Audry (1894).

Hebra described the condition as Leichen ruber/ Lichen ruber planus.

Hallopeau (1887) and Darier (1892) considered it as a modification of Lichen sclerosus et atrophicus[6] because of morphological similarity.

Lichen planopilaris (Pringle,1895) and follicular lichen planus (Silver et al) are terms that describe association of lichen planus with cicatrical alopecia[7].

Thyresson and Meberger demonstrated colloid bodies at dermo-epidermal junction and confirmed about it's nature to degenerating epithelial cells.

Pinkus and Mehregan (1969) proposed that damage to the basal cell layer as the basic histopathological finding[9].Zaias described histology of nail lesions in lichen planus[8].

In 1989, Perforating variant of lichen planus (Hanav and Senegal) and Grinspan syndrome[8][13] that comprises a triad of lichen planus with hypertension and diabetes mellitus were described.

Lichen planus-Lupus erythematosus overlap was described in 1970. Pelisse at al described Vulvo-vaginal gingival syndrome in 1982[10].

Glickman (1964) suggested that pallor producing Wickham's striae to the absence of capillaries in the center of the lesion. Ryan in 1966 attributed violaceous hue to the radially arranged capillaries[6][9]. Niles (1941) described actinic lichen planus[8].

Cribier et al described the male equivalent of Vulvo-vaginal gingival syndrome as Peno-genital syndrome in 1993. Association between lichen planus and hepatitis C infection was described in 1994.

Hard and Humberg used penicillin for treating lichen planus (1954). Sehgal et al demonstrated efficacy of griseofulvin in 1971 and levamisole in 1978 in cases of recalcitrant lichen planus. Other drugs like dapsone, isotretinoin, phenytoin, cyclosporine and PUVA therapy have been tried with variable degrees of success in lichen planus[8].

EPIDEMIOLOGY

Incidence:

The exact incidence and prevalence of lichen planus are not known, but the overall prevalence is believed to be somewhat less than 1% of general population. Lichen planus has a worldwide distribution with no racial predisposition. Estimates between 0.14% and 0.80% have been reported worldwide[(1)(8)].

Age:

Females are usually affected in their fifties and sixties, whereas males develop lichen planus at an earlier age. The disease is less common in very young and the elderly[(1)(8)].

Sex: No sexual predisposition is evident[(1)(8)].

Seasonal variation:

The development of lichen planus may be affected by seasonal or environmental factors. An increased incidence in December and January or from January to July has been reported[(1)(8)].

Triggering factors:

Sunlight, trauma, friction.

Genetic factors:

An increase in frequency of HLA-B7, -AW19,-B18 and CW8 haplotypes were noted in familial lichen planus.HLA-A3, -A5, -A28, -B8, -B16 and –BW35were noted in non-familial lichen planus[(1)].

HLA-B8 was common in patients of oral LP and HLA-BW35 with cutaneous lichen planus[(1)(15)].

ETIOPATHOGENESIS:

It is evident that immunologic mechanisms almost certainly mediate the development of lichen planus. Humoral immunity most likely is a secondary response in the immuno-pathogenesis. Cell-mediated immunity plays a major role in triggering the clinical expression of the disease.

Both CD4+ and CD8+ cells are found in lesional skin of lichen planus. The majority of lymphocytes in the infiltrate of lichen planus are CD8+ and CD45RO (memory) positive cells[(1)(8)].

These cells are considered responsible for the development of the most characteristic changes observed in lichenoid reactions, namely, apoptosis[1][8].

The epithelial lymphocyte interaction can be divided into three major stages: Antigen recognition, Lymphocyte activation, and Keratinocyte apoptosis[1].

Lichen Planus-Specific Antigen Recognition:

Majority of the T cells in the infiltrate of lichen planus are activated CD8+ cytotoxic lymphocytes. Evidence suggests that CD8+ lesional Tcells (within epithelium and adjacent to basal keratinocytes) recognize LP specific antigen associated with (MHC) class I on lesional keratinocytes. The antigen may be autoreactive peptide suggesting that LP may be an autoimmune disease.

Alternatively it may represent an exogenous antigen such as altered protein, drug, contact allergen, dental amalgam, viral infectious agents or unidentified immunogenic target[1]. The role of T helper cells (CD4) in the etiopathogenesis of LP is not fully understood. These cells may become activated via antigen-presenting cells such as Langerhans

cells in association with Major histocompatibility complex (MHC) class II and specific cytokines[1].

T helper (CD4) cells may also propagate CD8+ cytotoxic lymphocytes through cellular cooperation and release of cytokines.

The exact nature of antigenic stimulation is not known. Contact sensitizers such as metals which may act as haptens elicit an immunogenic response.

Low-grade chronic exposure to mercury and other metals stimulate a lymphocytic reaction manifesting as LP. The role of infections or microorganisms: Syphilis, Herpes simplex virus 2, HIV, amoebiasis, chronic infections, hepatitis virus, helicobacter pylori and human papilloma virus in the development of LP is still not clear[1].

Cytotoxic lymphocyte activation:

Activated T-lymphocytes by TH1, TH2 and cytotoxic-suppressor cells, release soluble mediators: Interleukin, IL-2, IL-4, IL-10, Interferon-(INF)-gamma, Tumor necrosis factor (TNF)-alpha,that attract lymphocytes and regulate their activities in epithelium. Both pro and anti-inflammatory cytokines are generated simultaneously. The balance

between lymphocytic activation and down regulation determines clinical behaviour of the disease.

Interferon gamma produced by T helper cells during the antigen recognition stage, induces keratinocytes to produce lymphotoxin-alpha and TNF-alpha and to upregulate MHC-II thus increasing interactions with helper T cells[1][8].

Interferon gamma also up-regulates the expression of intercellular adhesion molecule (ICAM)-I and vascular cell adhesion molecule (VCAM)-I by basal keratinocytes, Langerhans cells, and other macrophage-dendritic cells[1].

Laminin-5 and collagen types IV and VII, are increased in lesional LP and serve as ligands for β_1-intergrins on the surface of lymphocytes, thus allowing for enhanced association of lymphocytes with the basement membrane[1]

This close interaction between lymphocytes and basement membrane, targets metalloproteinases to alter extracellular matrix proteins and integrins, thus causing apoptosis, BM disruption, reduplication and subepidermal cleft formation.

Keratinocyte apoptosis[1][8]:

The exact mechanisms that trigger apoptosis are not known. Possible mechanisms are-

1) T cell secreted TNF-alpha binding to TNF-alpha R1 receptor on keratinocyte surface.

2) T cell surface CD95L binding CD95 on keratinocyte.

3)T cell secreted granzyme-B entering keratinocyte via perforin-induced membrane pores.

Basement membrane disruption may trigger apoptosis through the loss of basement membrane-derived cell survival signals that normally prevents the onset of apoptosis mediated by recruited lymphocytes.

CLINICAL FEATURES

Lichen planus affects the skin, mucous membranes, hair and nails[1].

The classical cutaneous lesions are flat-topped, faintly erythematous to violaceous polygonal pruritic papules of varying sizes, may be asymptomatic in some. A thin, transparent and adherent scale may be present over the papules.

Fine, whitish puncta or reticulated networks referred to as "Wickham's striae", are present over the surface of many papules, which are easily observed after placing mineral or immersion oil over the lesions[1][8].

Lesions are classically distributed symmetrically and bilaterally over flexural areas of wrists, arms, legs and lower back[1][8].

In active disease, scratching, injury or trauma may induce an isomorphic response (KOEBNER PHENOMENON). The lesions usually heal with hyperpigmentation[1][15].

Classification of Lichen Planus Variants[1]:

Configuration

- Annular
- Linear

Morphology of lesion

- Hypertrophic
- Atrophic
- Vesiculobullous
- Erosive/Ulcerative
- Follicular
- Actinic
- Lichen planus pigmentosus

Other forms: Perforating or Guttate.

Sites of involvement

- Palms and Soles
- Mucous membrane
- Nails and Scalp

Special forms

Drug induced (Lichenoid drug eruptions)

Lichen planus-Lupus erythematosus overlap

Lichen planus pemphigoides

Keratosis lichenoides chronica

Lichen planus and malignant transformation

Lichenoid reaction of graft versus host disease

Lichenoid keratosis

Lichenoid dermatitis

CONFIGURATION

Annular Lichen Planus

They occur approximately in 10% of cases and commonly develop as arcuate grouping of individual papules that develop rings or peripheral extension of clustered papules with central clearing. Characteristically seen over penis and scrotum and more commonly in blacks[(1)(16)].

Linear Lichen Planus

Linear lesions as a result of koebner's phenomenon are frequently found in LP but isolated linear lesions, usually made up of small papules in close apposition extending the whole length of a limb may occur. This type is usually seen in childhood. This variant must be distinguished from linear naevi and other dermatoses with linear variants. A zosteriform pattern of LP has also been described and LP can develop in the site of healed herpes zoster. Multiple linear LP was documented in a human immunodeficiency virus (HIV) patient have been reported[(1)(15)].

MORPHOLOGY OF LESION:

Hypertrophic Lichen Planus (LP Verrucosus)

These lesions are usually confined to the extremities, especially shins and interphalangeal joints and tend to be most pruritic variant. Lesions are thickened and elevated, purplish or reddish-brown in colour, hyperkeratotic with occasional verrucous plaque. The lesions heal with atrophic scar or hyper-or hypopigmentation. Chronic venous insufficiency is commonly present[(8)(15)].

Atrophic Lichen Planus:

This variant is rare and is characterized by few well-demarcated, white-bluish papules and plaques with central superficial atrophy. Commonly seen on lower extremities and trunk[1][15].

Vesiculo-bullous Lichen Planus

Two types are seen:

a) Bullous lichen planus.

b) Lichen planus pemphigoides

Bullous Lichen Planus:

Rare variant. Characterized by development of vesicles and bullae on pre-existing lesions of lichen planus[1][8].

Lichen planus pemphigoides:

This is a controversial entity with co-existence of lichen planus and bullous pemphigoid. Clinically, it consists of bullae on lesional and non-lesional skin, often on the extremities. These lesions can appear during flare-up of disease and may be associated with mild constitutional symptoms[1][8]. Histologically, the typical changes of LP are seen along with sub-epidermal separation[1].

Erosive and Ulcerative Lichen Planus

This rare variant has been described in oral cavity and the soles. Characterized by painful bullae and ulceration of the feet. Permanent loss of toe nails and cicatricial alopecia of scalp are common. Progression to squamous cell carcinoma has been reported in few cases of chronic ulcerative lesions of LP. The rare associations of erosive lichen planus are Castleman's lymph node hyperplasia and malignant lymphoma[(1)(8)].

Follicular Lichen Planus (Lichen Planopilaris, Lichen planus acuminatus, Peripilaris)

This form may occur alone or in association with other forms of lichen planus. Keratotic follicular papules are present commonly over trunk, proximal extremities, may affect scalp by producing cicatricial alopecia. The triad of follicular lichen planus of skin with cicatrical alopecia of scalp and non-scarring alopecia of axilla and pubic area is known as Graham Little-Piccardi-Lasseuer Syndrome[(1)(8)].

Other variants of follicular LP include the Pseudopelade of Brocq, lichen planus follicularis tumidus form, post-menopausal frontal fibrosing alopecia and Lichen planoporitis[(1)(8)(10)].

Actinic Lichen Planus:

This variant is also known as lichen planus subtropicus, summer time actinic lichenoid eruptions, lichen planus actinicus and lichenoid melanodermatosis. It is more common in Middle-East countries in the spring and summer. Lesions are limited to sun-exposed areas and are hyperpigmented with violaceous-brown colour and a thread, rolled edge showing well-defined borders with minimal pruritus and scaling[(1)(8)(13)].

Lichen Planus Pigmentosus:

This is a pigmentary disorder, which may not be associated with typical LP papules. It is an uncommon variant and is characterized by hyperpigmented, dark-brown macules in sun-exposed areas and flexural folds[(1)(15)].

The mucous membranes, palms and soles are never involved. Erythema dyschromicum perstans (ashy dermatosis) that occurs in sun-exposed areas bears similarity to this form of LP[(1)(8)].

Other Variants

Guttate Lichen Planus

It is characterized by widely scattered discrete lesions that seldom become chronic[1].

Exfoliative and Exanthematous forms

These are very rare and may represent manifestations of lichenoid drug reactions[1].

Invisible Lichen Planus

Lesions that are not perceptible with visible light illumination but become apparent with Wood's lamp examination. Pruritus is present and this entity may be a minimal variant of lichen planus "invisible de Gougerot"[1][8].

SITE OF INVOLVEMENT

Palmo-plantar Lichen Planus

This acral, localized variant is rare. Characteristic lesions are very pruriginous, erythematous, scaly plaques with or without hyperkeratosis and are often seen on internal plantar arch. Yellowish, compact keratotic

papules or papulonodules are seen on the lateral margins of the fingers and hand surfaces. They appear like callosities with an inflammatory, erythematous halo[1].

Mucosal lichen planus

Lichen planus involves mucosal surfaces of mouth, vagina, esophagus, conjunctiva, urethra, anus, nose and larynx. Its prevalence is approximately 1% of adult population. It may be the only manifestation in 20-30% of patients[1][8].

Oral Lichen Planus

Oral lichen planus affects primarily middle aged adults and the prevalence is greater among women. Children are rarely affected. 30% to 50% of patients with oral lichen planus also have cutaneous involvement. Most common sites include posterior buccal mucosa, tongue, gingiva, retromolar area, vestibule, palate, floor of mouth and lips[1][8].

The World Health Organisation recognizes different forms of Oral Lichen Planus.

(1) Reticular type

(2) Erosive type

(3) Plaque type

(4) Atrophic type

(5) Papular type

(6) Bullous type

Reticular type is the commonest presentation. It presents as interlacing white keratotic lines, also known as Honiton lace or Wickham's striae. The striae are typically located bilaterally on the buccal mucosa, mucobuccal fold, gingival and less commonly the tongue, palate and lips[(1)(8)]. This type is usually asymptomatic.

Erosive type is the second most common type of oral LP. It presents as a mix of erythematous and ulcerated areas surrounded by finely radiating keratotic striae. The erosion may be covered by a pseudomembrane.

Patients present with symptoms ranging from episodic pain to severe discomfort. The triad of erosive or desquamative lichen planus involving vulva, vagina and gingiva is known as Vulvo-Vaginal-Gingival Syndrome. Malignant transformation is common with this variant.

Plaque type appears as a multiple, diffuse, raised white plaques commonly over buccal mucosa and tongue. This type of lichen planus is usually asymptomatic[(1)(8)].

Atrophic type presents as diffuse, erythematous patches surrounded by fine white striae. This can cause severe discomfort and burning sensation.

Papular type of lichen planus is rare and it consists of small whitish papules, about 0.5 mm in diameter. They may also precede Wickham's striae and they are usually asymptomatic.

Bullous type is the least frequent form of oral lichen planus. The lesion appears as vesicles or bullae of variable size, that easily bursts leaving behind painful erosions.

It occurs mainly in the buccal mucosa, in particular in the area next to the second and third molar teeth.

70% of patients with cutaneous lichen planus develop oral lichen planus. Lichen planus can involve eyelids and conjunctiva also. It causes a foreign body sensation. They can be seen as fine, white lacy pattern in the tarsal conjunctiva. Rarely, Keratoconjunctivitis sicca may be seen. Inflammatory meatal fibrosing otitis can be seen in the ears.

Genital Lichen planus:

Involvement of genitalia with cutaneous LP has been reported in 25% of men with typical lesions. They present with pruritus and burning sensation. Lesions consist of violaceous papules, commonly on glans penis. Annular lesions are frequently reported on the scrotum. Female genital involvement consists of patches of leukoplakia or erythroplakia, sometimes with erosions and generalized desquamative vaginitis. Anal lesions of mucosal lichen planus present with leukokeratosis, hyperkeratosis, fissuring and erosions[(1)(8)].

Lichen planus of nails

Nail involvement occurs in 10% to 15% of patients. Usually only a few finger nails or toe-nails are involved. Thinning, longitudinal ridging and dorsal slitting of nail plate (Onychoschizia) are the most common findings. Onycholysis, longitudinal striations (Onychorrhexis), subungual hyperkeratosis or even absence (anonychia) of nail plate can also be seen.

Twenty-nail dystrophy (Trachyonychia) may be an isolated finding. Pterygium or forward growth of the eponychium with adherence to the proximal nail plate is a classical nail finding in lichen planus of the nail.

Pup-tent or tenting sign is observed as a result of nail bed involvement that elevates the nail plate and may cause longitudinal splitting[1][8][15].

Lichen planus of scalp

Lichen planus affects the scalp. Typically individual keratotic follicular papules that coalesce and merge over the scalp to form patches are seen, affecting women more than men. Patients present with unifocal or multifocal hair loss that may be extensive and involve the entire scalp. Perifollicular erythema and acuminate keratotic plugs are characteristic features. End-stage disease is characterized by scarring alopecia that has led to the use of several clinical terms describing the entity like lichen planopilaris, folliculitis decalvans et atrophicus, lichen spinulosus et folliculitis decalvans and Graham-Little Syndrome[1].

Inverse lichen planus

It is a rare variant characterized by red-brownish, discrete papules and nodules occurring in flexures like the axillae, groins, inframammary region and less likely, popliteal and antecubital area. Erosive flexural LP has also been reported[1][8].

SPECIAL FORMS OF LP

Lichenoid eruptions or Drug-induced Lichen planus:

It is a group of cutaneous reactions identical or similar to lichen planus. Lichenoid drug eruptions develop after contact, ingestion, or inhalation of certain chemicals. The eruptions usually appear symmetrically on the trunk and extremities, with pattern restricted to photo distributed areas. Mucosal involvement is less common[(1)].

Lichen planus-Lupus erythematosus overlap syndrome

It is an overlap between LP and Lupus erythematosus. Atrophic plaques and patches with hypopigmented and a livid red to blue-violet colour with telengiectasiae and minimal scaling are characteristic. Lesions are most commonly seen on the extremities. Some patients may progress to SLE. In others, laboratory evaluation may reveal only a weakly positive antinuclear antibody. This disease variant is characterized by a prolonged course and lack of response to treatment[(1)(8)].Histologically, features of LP and LE are usually seen in the same biopsy specimen. On DIF, features of LP with linear to granular deposits of IgM and C3 are seen as in LE[(1)].

Lichen planus pemphigoides:

In this rare variant, there is an acute onset of generalized lesions of LP followed by the appearance of tense vesicles and bullae on and around those lesions as well as on uninvolved normal looking or erythematous skin. Extremities are usually involved. Oral lesions are rare. It can be differentiated from bullous LP, where vesicles appear only on and around lichen planus lesions for a brief duration[(1)].

Keratosis Lichenoides Chronica (Nekam's Disease):

It is a rare dermatosis characterized by violaceous papular and nodular lesions, arranged in a linear and reticulate pattern on the dorsum of hands and feet, extremities and buttocks[(1)(8)].

Lichen Planus and Malignant Transformation:

Malignant transformation of oral lichen planus is controversial. Risk factors for development of oral cancer in LP are long-standing disease, erosive or atrophic types and tobacco use. Only 0.5-5% of patients develops squamous cell carcinoma. The most common site for malignant change is the tongue, followed by buccal mucosa, gingiva and rarely the lips. The lesions appear as indurated, non-healing ulcers or exophytic lesions with a keratotic surface[(1)(8)].

Lichenoid Reaction of Graft-Versus-Host Disease (GVHD):

It may present as lichenoid eruptions over the trunk, buttocks, hips, thighs, palms, and soles. In oral mucosa, xerostomia and oral ulcerations are occasionally seen. Histologically, infiltrating CD3 + T lymphocytes are present in larger number in oral LP than in lichenoid lesions of oral GVHD[(1)(8)].

Lichenoid Keratosis:

It is commonly seen on sun-exposed areas of the extremities. Clinically presents as brown to red, scaling maculo-papules. Histology shows features of lichen planus with additional features of focal parakeratosis.

ASSOCIATED CONDITIONS: Idiopathic Lichen planus has been reported to be associated with disease of altered immunity[(8)].

- Alopecia areata
- Vitiligo
- Morphea
- Dermatomyositis
- Systemic lupus erythematosus

- Lichen sclerosus et atrophicus
- Pemphigus vulgaris
- Paraneoplastic pemphigus

In association with thymoma:

- Myasthenia gravis

With gastrointestinal diseases:

- Primary sclerosing cholangitis
- Primary biliary cirrhosis
- Ulcerative colitis
- Chronic hepatitis

LP has also been associated with Diabetes mellitus, Hypertension.

Association with HCV:

The prevalence of HCV infection in lichen planus has been reported to be 3.4% to 38%[51], and that with oral lichen planus is 0% to 62%. In HCV infected individuals the association with oral LP is 1.6% to 20%[(52)].

Syndromes associated with LP:

- Grinspan's Syndrome[35]: Association of Oral LP with diabetes mellitus and hypertension.
- Graham-Little-Piccardi-Lasseur Syndrome[1][54]: It is a triad of multifocal cicatricial alopecia of scalp with non-cicatricial alopecia of axilla and groin with follicular LP on the body, scalp or both.
- Good's Syndrome[40]: Oral erosive lichen planus associated with Thymoma.
- Jolly in 1972 found a defect in carbohydrate tolerance in oral LP cases[36].
- Lichen planus as a part of Multiple Auto immune Syndrome.
- Turner's Syndrome with LP
- Polyglandular Auto-immune Syndrome type II with Oral LP
- Lichen planus with Vulvo-vaginal-gingival Syndrome[41]**.**
- Ulcerative LP with Sjogren's Syndrome.

HISTOPATHOLOGY OF LICHEN PLANUS[6][18]

- Compact orthokeratosis
- Wedge shaped hypergranulosis
- Vacuolar alteration of the basal layer

- Band-like dermal lymphocytic infiltrate in close approximation to the epidermis.

The earliest finding is an increase in epidermal Langerhans cells, associated with a superficial infiltrate of lymphocytes and histiocytes, impinging on the dermo-epidermal junction [DEJ]. Mild spongiosis followed by vacuolar alteration, clefting along the dermal-epidermal junction, with accumulation of necrotic keratinocytes [colloid bodies].[18]

Hyperkeratosis: The cornified layer shows compact orthokeratosis and contains few parakeratotic cells,which are important for diagnosis.[18]

Focal hypergranulosis: The thickening of granular layer is uneven and wedge shaped. The granular cells appear increased in size and contain coarse and abundant keratohyaline granules.[18]

Acanthosis: It is irregular and affects the spinous layer and suprapapillary plates. Keratinocytes of spinous layer appear larger and eosinophilic, possibly because of advanced keratinization.

The rete ridges show irregular lengthening and some are pointed at lower end giving a saw-toothed appearance.

Alteration of basal cell layer: The cells are not clearly visible in early lesions, because the dense dermal infiltrate obscures dermo-epidermal

junction with vacuolar alteration and necrosis of these cells. In fully developed lesions, basal cells appear as flattened squamous cells[18].

Band-like dermal lymphocytic infiltrate: The infiltrate in the upper dermis is band-like and sharply demarcated at its lower border, comprising entirely of lymphocytes and macrophages .

Few eosinophils and or plasma cells may be seen. Melanophages are seen in upper dermis with subsequent pigment incontinence.

Colloid bodies: Necrotic keratinocytes also referred to as colloid, hyaline, cytoid or civatte bodies are present in the lower epidermis and especially in papillary dermis. These are 20µ in diameter, homogenous, eosinophilic, and may occur in any interface dermatitis[18].

Max-Joseph Space: They are small areas of artefactual separation between the epidermis and dermis.

Variations of LP-histopathology:

Hypertrophic LP: Epidermis shows irregular acanthosis, papillomatosis and hyperkeratosis. In the center of the lesion the follicles may be expanded and at times have a "cyst-like" appearance. Long standing cases will be dermal fibrosis adjacent to the inflammatory changes[(6)(18)].

Atrophic LP: The epidermis may be greatly thinned almost to the level of granular layer, although relative compact hyperkeratosis remains. The rete ridges are usually completely effaced with relatively few colloid bodies. The papillary dermis shows fibrosis.

Lichen Planopilaris: Infiltrate extending around, and may permeate the base of the hair follicle epithelium, with follicular keratin plugging[(6)(18)].

Actinic LP: Epidermis shows orthokeratosis and hypergranulosis. The prickle cell layer at the center of lesion is thin and atrophic with loss of rete pegs, at borders it is acanthotic with saw-tooth appearance. The upper dermis shows classical band of lymphocytic infiltrates hugging epidermis[(6)(18)].

Lichen planus pigmentosus: It is similar to classical lichen planus, except for the stratum granulosum which looks normal and there is pigment incontinence that extends deep in to reticular dermis[(6)(18)].

In oral LP: The classical diagnostic features of oral lichen planus include parakeratosis alternating with both types of keratinization with presence of granular layer. The epithelium is often atrophic[6][18].

ELECTRON MICROSCOPY[6][18]:

1. The basal keratinocytes with their desmosomes and hemidesmosomes, show degenerative changes.

2. Tonofilaments are decreased in early lesions, increased in late lesion.

3. The dermal infiltrate, on invading the epidermis causes damage to the lamina densa such as fragmentation. This may be followed by duplication and irregular folding of the lamina densa. The dermal infiltrate contains lymphocytes and macrophages.

4. Necrotic keratinocytes or colloid bodies are located in papillary dermis.

IMMUNOFLUORESCENCE[6]

In Lichen planus, fibrinogen deposition can be demonstrated by Direct Immunofluorescence(DIF) as shaggy deposits at dermo-epidermal junction. There are also granular deposits of IgM or linear deposits of C3 or both IgG and C3 in basement membrane zone. Necrotic keratinocytes are seen by DIF in 87%.They stain mainly for IgM but also for IgG, IgA, C3 and fibrin[6][20].

In Lichen planopilaris, DIF shows deposits of IgM and or IgA, IgG and rarely C3 at the level of infundibulum and isthmus. The shaggy pattern of fibrinogen are seen around affected follicles[18].

In Lichen planus pemphgoides, DIF of perilesional skin shows IgG, C3 arranged linearly along the basement membrane zone[18].

IMMUNOCYTOCHEMICAL STUDIES

The infiltrating cells in lichen planus are chiefly T lymphocytes with very few B lymphocytes. Around 90% are activated T lymphocytes expressing HLA-DR antigen and some interleukin-2 receptor. It is likely that both subsets participate in immunologic reaction in the epidermis adjacent to the infiltrate, basal keratinocytes express HLA-DR surface antigen and ICAM-1, both of which are implicated in the enhancement of

the interaction between lymphocytes and their epidermal targets resulting in keratinocyte destruction. Probably these surface antigens are induced by cytokines released by lymphocytes from the infiltrate[18].

COMPLICATIONS

Hair fall: Patches of atrophic cicatricial alopecia develop over the scalp. It results from follicular destruction by the inflammatory infiltrate with scarring[1][15].

Pterygium unguis: Adhesion between the epidermis of the dorsal nail fold and the nail bed may cause partial destruction of the nail, rarely nail may be permanently lost[1][15].

Malignant transformation: Risk of malignant transformation is very low. Risk factors for the development of oral cancer are long standing disease, erosive or atrophic lichen planus and use of tobacco. There is a possibility of 0.5-5% of LP patients developing Squamous cell carcinoma. Risk of skin malignancy in cutaneous LP is very low[1][8].

Erythroderma– Generalised lichen planus

DIFFERENTIAL DIAGNOSIS:

Lichenoid eruptions: The only differential diagnosis to be considered in classical LP is that of lichenoid eruptions. Lichenoid drug eruptions have been reported after ingestion, contact, inhalation of certain chemicals or drugs[(1)(8)]. These reactions have also been described as a reflection of chronic graft-versus-host disease in patients after bone-marrow transplantation. Lichenoid eruptions may be typical or atypical for classic LP, with localized or generalized eczematous papules and plaques. The salient features of differentiation are as follows[(1)]

	Classic LP	**Lichenoid eruptions**
Lesion	Smaller	Larger and scaly
Wickham's striae	Usually present	Usually absent
Residual hyperpigmentation	Possible	Common
Alopecia	Uncommon	Common
Predilection	Flexures/extremities	Sun-exposed areas
Mucous membrane involvement	Very common	Less common
Colloid bodies in granular layer	Very common	Common
Parakeratosis	Not seen	Common

Papular lesions of LP should be differentiated from other papulo-squamous lesions especially psoriasis[1][5].

Annular lesions may resemble granuloma annulare[1].

Linear LP should be differentiated from nevus unius lateris, lichen striatus and epidermal nevus[1].

Hypertrophic LP may resemble lichen simplex chronicus, prurigo nodularis, lichen amyloidosis, warts and Kaposi sarcoma[1].

Atrophic LP may mimic lichen sclerosis et atrophicus. Follicular LP may resemble lichen nitidus and lichen spinulosus[1].

Lichen plano-pilaris should be differentiated from other causes of cicatricial alopecia such as lupus erythematosus, inflammatory folliculitis and cicatricial pemphigoid[1].

Nail involvement may resemble psoriasis, alopecia areata and onychomycosis.

Oral lesions should be differentiated from candidiasis, lupus erythematosus and mucous patches of secondary syphilis, paraneoplastic pemphigus and oral pemphigus[1].

TREATMENT

Lichen planus is essentially a benign and self-limiting condition. Current treatment modalities consist of topical and systemic therapy for cutaneous lichen planus.

TOPICAL	SYSTEMIC	PHOTO-THERAPY	MISCELLANEOUS
Topical steroids Intralesional steroids Tacrolimus Pimecrolimus Psoralens Photochemo-therapy	**1st line:** Systemic steroids Acitretin Etretinate Isotretinoin **2nd line:** Cyclosporine Dapsone Azathioprine Hydroxychloroquine Mycophenolate mofetil	PUVA NB-UVB Balneotherapy	Doxycycline Tetracycline Nicotinamide Interferon alpha 2b Metronidazole Cyclophosphamide Methotrexate Griseofulvin Low molecular weight heparin

Treatment of oral Lichen Planus:

TOPICAL	SYSTEMIC	PHOTO-THERAPY	MISCELLANEOUS
1st line: Topical steroids Intralesional steroids Lidocaine Tretinoin gel Isotretinoin gel Tacrolimus Pimecrolimus **2nd line:** Cyclosporine mouth wash Extracorporeal photochemotherapy PDT	**1st line:** Anti candidal drugs Systemic steroids Etretinate Isotretinoin Acitretin **2nd line:** Cyclosporine Griseofulvin Azathioprine Thalidomide Cyclophosphamide Hydroxychloroquine Mycophenolate mofetil	PUVA	6-thioguanine Azathioprine Sulfasalazine Tacrolimus Pimecrolimus Photodynamic therapy Lasers-excimer (308nm)

Corticosteroids :

Corticosteroids are the first line of treatment of LP. Depending on the extent of involvement and type of lesions steroids can be used as topical, systemic or intralesional forms[1].

Topical steroids: They can be used for limited cutaneous and mucosal disease. Potent topical preparations like Flucinonide 0.05% and Clobetasol propionate 0.05% under occlusion may cause regression of cutaneous lesions in most instances. Oral lesions can be treated with triamcinolone acetonide oral lozenges, betamethasone aerosols and pellets[15].

Systemic steroids: Indicated for[15]

1) Extensive lesions interfering with patient's normal life

2) Nail atrophy and pterygium formation

3) LP with extensive ulcerative lesions on oral or vaginal mucosa

4) Follicular LP of scalp

5) Bullous LP.

Prednisolone, methylprednisolone and triamcinolone have been used.

The effective dose of prednisolone is 5 to 20 mg/day for 4 to 6 weeks and then gradually tapered for another 6 weeks[15].

Intralesional: Triamcinolone acetonide 5 to 20 mg/ml is used to treat hypertrophic, oral and nail LP.

Retinoids:

Topical retinoids: 0.1% Isotretinoin gel has shown to improve the lesions of oral LP, but relapses are common with discontinuation of the drug[1][8].

Systemic retinoids: Acetretin in a dose of 30 mg/day for 8 weeks in severe cutaneous LP and 30-35 mg/day daily for 2 weeks in patients with LP and LE overlap syndrome[22]. Etretinate or isotretinoin 0.6-1 mg/kg/day three times daily for 2 months.

Photochemotherapy: Psoralen and ultraviolet A photochemotherapy is useful in generalized cutaneous LP and refractory erosive oral LP.

Initial dose is 0.5 – 2 J/cm^2. The maximum dose not to exceed 7 J/cm^2 in a single session, treated 3 times per week with an interval of 48hrs between each session[1][20].

Immunosuppressive drugs:

Cyclosporin A is used in recalcitrant LP in the dose of 3-10 mg/kg/day. Pruritus disappears in 1-2 weeks and rash disappears in 4-6 weeks[(1)(25)].

Tacrolimus 0.1% ointment improves refractory erosive oral LP. It is very effective in controlling the symptoms[(1)(26)].

Pimecrolimus 1% cream cleared oral LP in 4 weeks.

Azathioprine is used in refractory generalized cutaneous LP and LP Pemphigoides[(1)].

Mycophenolate mofetil at a dose of 1500mg/day is used in oral, hypertrophic and bullous LP[(27)].

Miscellaneous:

Antimalarials- Hydroxychloroquine 200 to 400mg/day is used in actinic LP and erosive LP[(1)].

Thalidomide-can be used in erosive LP refractory to other treatment.

Dapsone- 200 mg/day is used in bullous and erosive LP for 4 – 6 weeks

Phenytoin- 100 to 200 mg orally daily for 2 – 8 weeks in cutaneous and oral LP.

Metronidazole- 500 mg orally twice daily for 1 to 2 months also reportedly clears the majority of cases of lichen planus[28].

IFN-α2b has been administered for the treatment of generalized lichen planus with improvement, but this biologic response modifier is also associated with exacerbation of LP.

Surgery: Split thickness skin grafting has been used to cover ulcerative lichen planus of the feet that is recalcitrant to other treatments.[1][15]

Course and prognosis:

Lichen planus is an unpredictable disease that persists for one to two years, but may at times follow a chronic relapsing course for many years. The duration varies according to the morphology and extent of involvement of the lesions. Generalized lichen planus tend to regress faster than limited lesions. Spontaneous regression is often a uncommon feature of oral lichen planus. The mean duration for oral lichen planus averages about 5 years.

Chances of conversion into malignancy is more so with oral LP. Relapse of the disease is common in 15 to 20 percent of the cases and tends to occur in same locations. Reccurences are more common in generalized

lichen planus and tend to be of shorter duration. Hair loss is usually permanent[1][4].

Low-Molecular weight Heparin[11]:

Low-molecular weight Heparin is one among the optional treatments available for the management of cutaneous lichen planus.

Mechanism of action:

Low dose of low-molecular weight heparin devoid of anti-coagulant activity inhibits T lymphocytes heparanase enzyme activity, which is crucial in T cell migration to the target tissues[11].

Enoxaparin has been proven to inhibit the expression of heparanase enzyme (endoglycosidase) that is synthesized by CD4 cells, allowing them to penetrate into subendothelial basal lamina of the epidermis by cleaving the heparin sulfate side chains of the extracellular matrix that is yet again crucial in the migration of the T-cells to the target tissues[17].

Low doses of low molecular weight heparin also inhibit delayed type hypersensitivity responses. Sulfated disaccharides in the heparin moiety contribute to the immunomodulatory effect by inhibiting the cytokines mainly the TNF-α[33].

Enoxaparin is being widely used in the prevention and treatment of thromboembolic disorders. It does not affect the activated partial thromboplastin time and there is no significant microvascular bleeding when compared to conventional heparins. The recommended dose of enoxaparin in these conditions range from 20 to 80mg/day by subcutaneous injection.

It can be effectively used as a monotherapy in cutaneous lichen planus[2][11]. It can lead to significant periods of remissions with consequent reduction in the relapse rates. It's anti-pruritic effect is evident within a week of onset of the treatment.

Enoxaparin was used for the first time in the treatment of Lichen planus in 1988 by Hodak et al.[11] It was given at the dose of 3mg subcutaneously to 10 cases of LP. Regression of cutaneous lesions were observed with the disappearance of the itch. There was no improvement with the oral lesions.

Enoxaparin sodium[11]:

Enoxaparin sodium is a low-molecular weight heparin. It is a sterile aqueous solution containing enoxaparin. The pH of the solution is

5.5 to 7.5. It is obtained from the porcine intestinal mucosa by alkaline depolymerisation of heparin benzyl ester[4][11].

MOA: It causes its effect by inhibition of factor Xa. It also has antithrombotic properties.

Low-molecular heparin has a longer half-life, easier to use and more reliable than conventional heparins. Risk of heparin induced thrombocytopenia is lower.

Other uses:

1. Prophylaxis and treatment of deep vein thrombosis.
2. Treatment of acute pulmonary embolism.
3. Prophylaxis of ischemic complications of unstable angina.
4. Prophylaxis of Non-Q-Wave Myocardial infarction
5. Treatment of acute ST elevation Myocardial infarction.
6. Patients undergoing abdominal surgery and Hip and Knee replacement surgery.

Preparations: Enoxaparin sodium is available as-

Prefilled syringes: 20 mg/0.2 ml, 30 mg/0.3 ml, 40 mg/0.4 ml

Graduated prefilled syringes:60 mg/0.6 ml, 80 mg/0.8 ml,100 mg/1 ml.

Dosage: Injection Enoxaparin sodium 4 mg given subcutaneously once weekly. Therapy is continued for nine weeks.

Contraindications:

1) Patients with renal impairment (creatinine clearance < 30 ml/min)

2) Patients with active major bleeding.

3) Patients with thrombocytopenia.

4) Known hypersensitivity to enoxaparin sodium.

5) Known hypersensitivity to heparin or pork products.

6) Pregnancy Category B drug.

7) Used with caution in elderly patients.

PHARMACOLOGICAL PROPERTIES:

Pharmacodynamic properties: Enoxaparin is a low molecular weight heparin with a high anti-Xa activity(100 I.U./mg), and with a low anti-IIa or antithrombin activity (28 I.U./mg).At doses required for the various indications, enoxaparin does not increase the bleeding time. At

preventive doses, enoxaparin causes no notable modification of APTT. It neither influences platelet aggregation nor binding of fibrinogen to platelets.

Pharmacokinetic properties: The pharmacokinetic parameters have been studied in terms of the time course of plasma anti-Xa activity.

Bioavailability: After subcutaneous injection, enoxaparin is rapidly and completely absorbed. The bioavailability of the drug is close to 95%.

Distribution: After subcutaneous injection, the maximum plasma activity is obtained three hours after the administration. The anti-X a activity is located in the vascular space.

Biotransformation: Enoxaparin is primarily metabolized in the liver.

Elimination: The elimination half-life of anti-Xa activity is approximately 4.4 hours after administration of 40 mg of enoxaparin and 4 hours for an administration of 60 mg or 80 mg of enoxaparin.

Excretion: Enoxaparin is eliminated in the urine. In the elderly, the elimination is slightly decreased.

Dosage and method of administration: 1 mg (0.01 ml) of enoxaparin corresponds approximately to 100 anti-Xa I.U. It should be injected by

deep SUBCUTANEOUS ROUTE in prophylactic and curative treatment and by INTRAVASCULAR ROUTE during hemodialysis.

Subcutaneous administration technique: The prefilled syringes are ready-to-use. **The air bubble from the syringe should not be expelled before the injection.** The SC injection should preferably be made when the patient is lying down. It is given in the anterolateral or posterolateral abdominal wall, alternately on the left and the right side. The injection itself consists in introducing the needle perpendicularly and not tangentially throughout its entire length into a fold of skin held between the thumb and the index finger. The skin fold should be held throughout the injection.

In generalized cutaneous lichen planus, a dose of 4 mg is given subcutaneously every week for nine weeks.

Elderly: No dose adjustment is necessary in prophylactic therapy. Anti-Xa activity measurement is done in cases of curative therapy.

Children: Enoxaparin is not recommended for use in the children.

Renal impairment: No dose changes needed at prophylactic therapy. Dose adjustment is mandatory at curative doses.

Enoxaparin should be used with extreme degree of caution in patients with history of heparin induced thrombocytopenia.

This drug is inadvisable in the following situations:

- ❖ Severe impaired renal functions
- ❖ Hemorrhagic vascular cerebral stroke
- ❖ Uncontrolled arterial hypertension

Precautions for use:

- If a significant decrease in platelet count occurs (30 to 50% of the initial count), the drug should be discontinued.
- Use with caution in hepatic or renal insufficiency.

Drug interactions:

- Acetylsalicylic acid
- NSAID

Undesirable effects:

- Hemorrhage: This may occur during co-treatment with any anticoagulant.
- Bluish marks at injection sites.
- Localized or generalized allergic reactions.
- Thrombocytopenia
- Increased transaminase levels.

AIMS AND OBJECTIVES OF THE STUDY

1) **To assess the efficacy of low molecular weight heparin in the management of Generalised cutaneous lichen planus.**

2). **To look for adverse effects of the drug during the treatment.**

3). **To assess the period of remission.**

MATERIALS AND METHODS

Place of study: Department of Dermatology, Government Stanley Medical College and Hospital, Chennai.

Type of study: Randomized, Prospective, Open Label Study.

Time duration: One year **(July 2013 To June 2014)**

Sample size: 50 patients of Generalised cutaneous lichen planus.

Study procedure:

This study was conducted in accordance with the ethical committee approval obtained in June 2013 (**Annexure 1).** A brief and relevant medical history was taken at the initial visit and physical examination was done to ensure that all the relevant eligibility criteria (given below) are met. Informed and written consent was obtained (**Annexure 3**). Consent was also obtained for taking photograph of the patient during the study procedure and follow up.

Patients who satisfy the inclusion criteria (given below) and willing to take part in the trial were hospitalized and administered Inj. Enoxaparin Sodium 4 mg subcutaneously, every week for 9 weeks. Later patients were followed up for a period of 6 months. No antihistamines were used during this study period.

Efficacy of the treatment is assessed by monitoring Itch Severity Score (ISS), DLQI and reduction in number of old lesions and appearance of new lesions if any every 3 weeks during the study and monthly during the follow up for 6 months. Safety and tolerability is monitored by regular clinical examination and bi-weekly monitoring of relevant blood parameters.

Skin biopsy was done in selected cases before and after the treatment to assess the histopathological response.

INCLUSION CRITERIA

- Patients with generalized cutaneous lichen planus.
- Age > 20 years.
- Patients selected with no history of any previous treatments.
- Patients willing for follow up and to take photographs.
- Patients with no contraindication to therapy with low molecular weight heparin.

EXCLUSION CRITERIA

- Known contraindications to heparin therapy.
- Congenital or acquired haemostatic defects.
- Uncontrolled hypertension.
- Active peptic ulcer , recent stroke, liver and renal diseases.
- History of drugs inducing lichenoid eruptions
- Elderly and paediatric patients.
- Pregnant and nursing mothers.
- Patients with body weight < 50kg.
- Patients on oral anticoagulants, platelet inhibitors.

INVESTIGATIONS

- Complete Blood Count (Including platelet count)
- Coagulation Profile (PT with INR, APTT).
- Renal and Liver Function Tests.
- Stool occult blood tests.
- HBV and HCV antibody tests.
- ICTC, VDRL Tests.
- Chest X-Ray, ECG.
- Skin biopsy in selected cases.

Withdrawal of patients was done under following conditions:

1. Request of the patient.
2. Patient lost to follow up.
3. Adverse event/reactions/intercurrent illness
4. `4. Patients who develop signs and symptoms of hypersensitivity.

CLINICAL EFFICACY PARAMETERS:

Parameters monitored during each visit:

1. Disappearance of itch in weeks after start of the treatment.
2. Regression of skin lesions consistent with disappearance of itch.
3. Nature of the old lesions – Grading of response to treatment by measurement of reduction in the extent of skin lesions.
4. Appearance of any new lesions during the course of therapy and 6 months after therapy.
5. DLQI before and after the treatment.
6. Adverse effects of the drug during the study period.
7. Periodical monitoring of laboratory parameters.

Assessment of clinical efficacy: The efficacy, safety and tolerability of Enoxaparin sodium is assessed by the following clinical parameters.

1. Itch severity score (ISS):

Grade '0' -No itch

Grade '1' - Mild itch

Grade '2' - Moderate itch

Grade '3' - Severe itch

Grade '4' - Very severe itch

Grade '5' - Worst possible itch that interferes with daily activity.

Itch severity score was assessed periodically every 3 weeks after the start of treatment along with nature of regression of the cutaneous lesions.

2. Dermatology life quality index (DLQI):

0-1 : No effect at all on patient's life.

2-5 : Small effect on patient's life.

6-10 : Moderate effect on patient's life.

11-20 : Very large effect on patient's life.

21-30 : Extremely large effect on patient's life.

Series of Questionnaire is used for assessment of DQLI. It includes

1). Over the last week, how itchy was his/her skin.

2). How embarrassing is this skin condition to them.

3). How much has this skin disease interfered with their shopping or any leisure activities.

4). Has this condition prevented them from working or studying.

5). Experiencing any problem with the partner and other family members.

Responses interpreted as ‘Very much’, ‘A lot’, ‘A little’, ‘Not at all’ and ‘Not relevant’. Scoring is done based on these responses.

3. Grading of response to treatment by measuring reduction in skin lesions as follows:

Grade 0 (no response) : same number of lesions.

Grade 1 (mild response) : less than one third of lesions reduction.

Grade 2 (moderate response) : more than third and less than two thirds reduction.

Grade 3 (dramatic response) : more than two third of lesion reduction.

STATISTICAL ANALYSIS

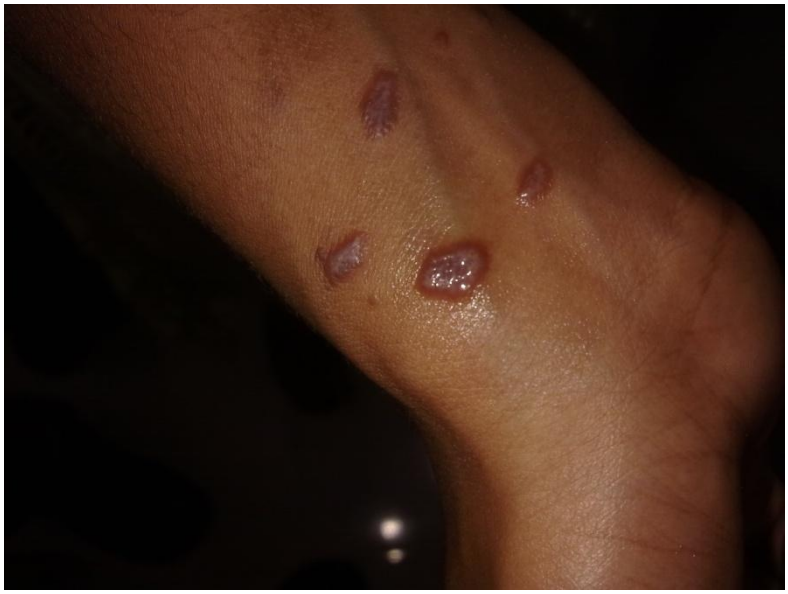
The collected data was analysed with SPSS 16.0 version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and for continuous variables the mean and S.D were used. To find the significance difference between the bivariate samples in Paired groups Wilcoxon signed rank test was used & for Independent groups (Male & Female) Independent t test was used. For the multivariate analysis in repeated measures (ISS -Baseline & week 3, 6 & 9) the Friedman test was used. To find the significance in categorical data Chi-Square test was used. In all the above statistical tools the probability value .05 is considered as significant level.

P-Value	Highly Significant at P ≤ .01
P-Value	Significant at P ≤ .05
P-value	Not Significant at P >.05

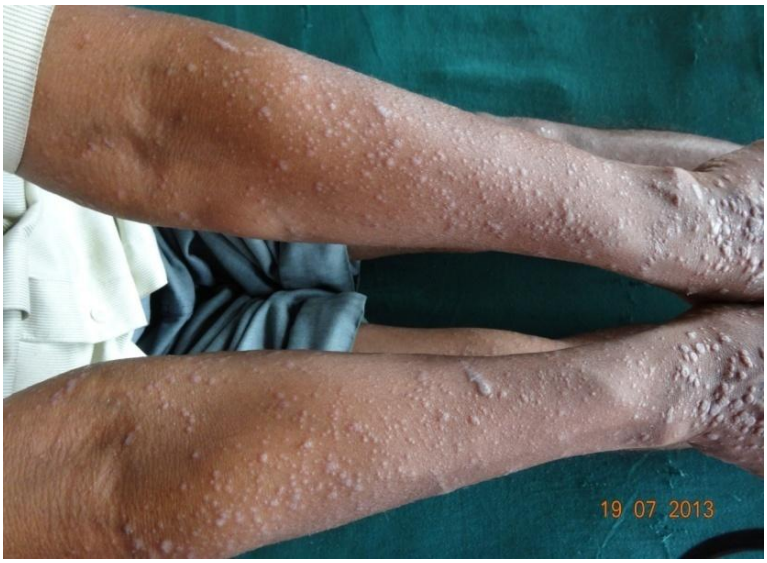
CLINICAL PHOTOS

Classical Lichen Planus

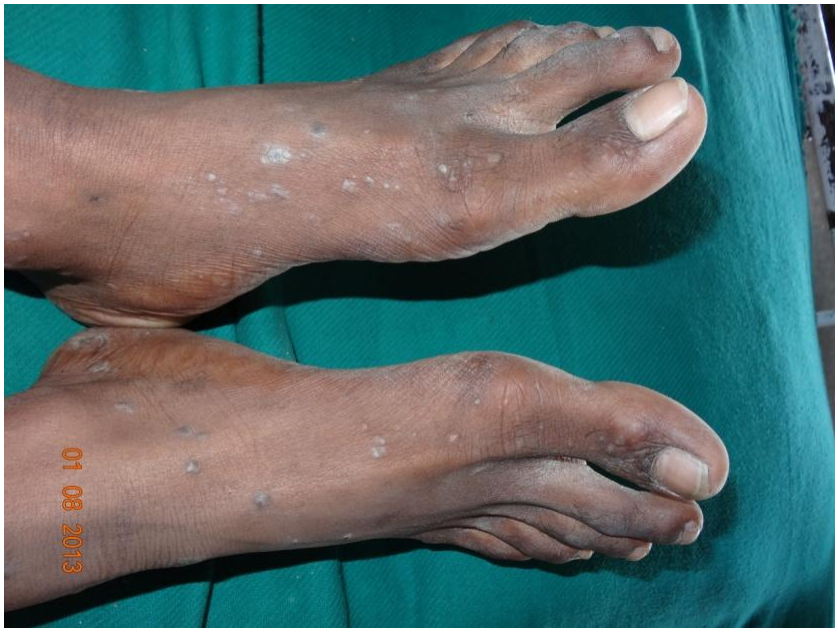
(Typical Violaceous Papule)



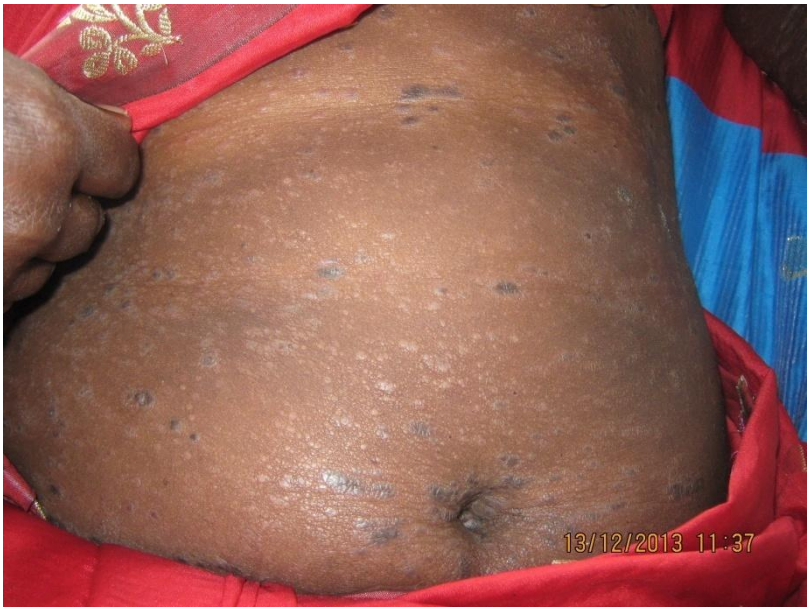
Upper limb involvement



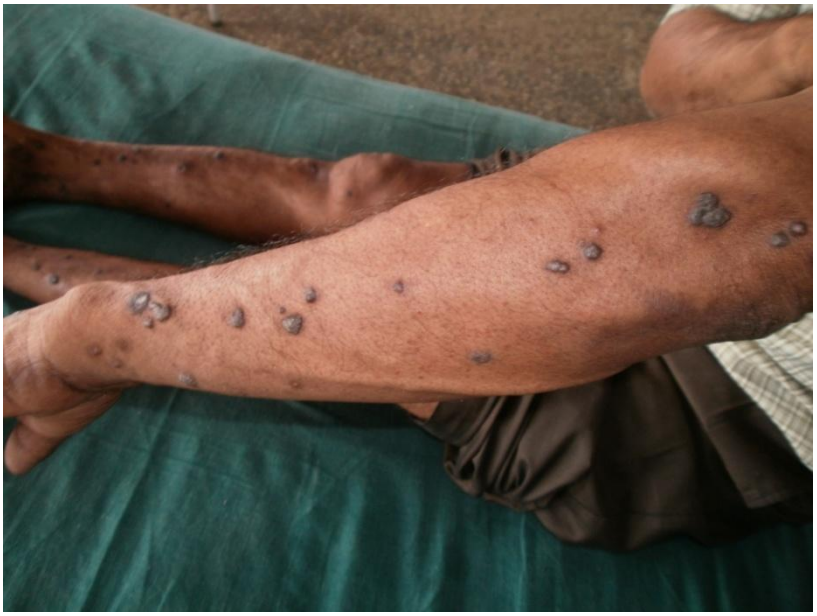
Lower limb involvement

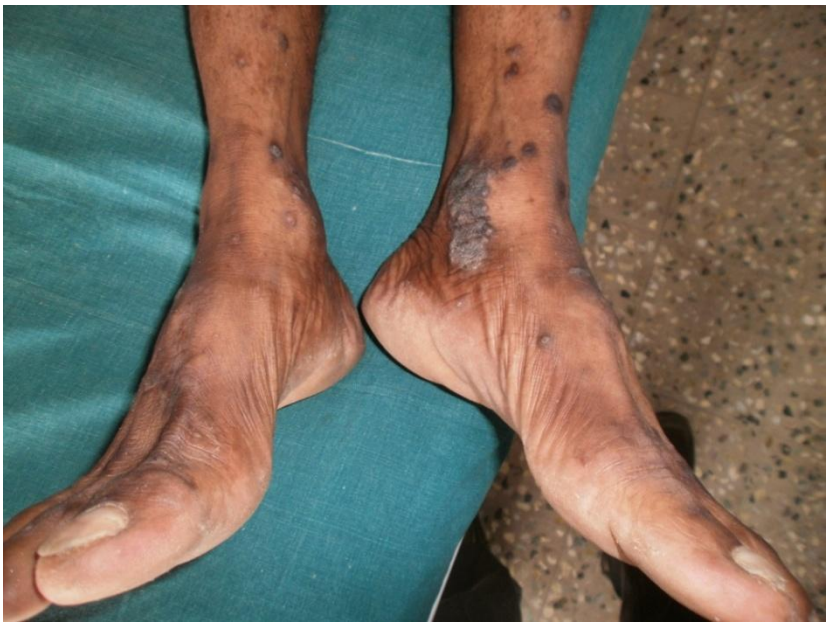


Trunk Involvement

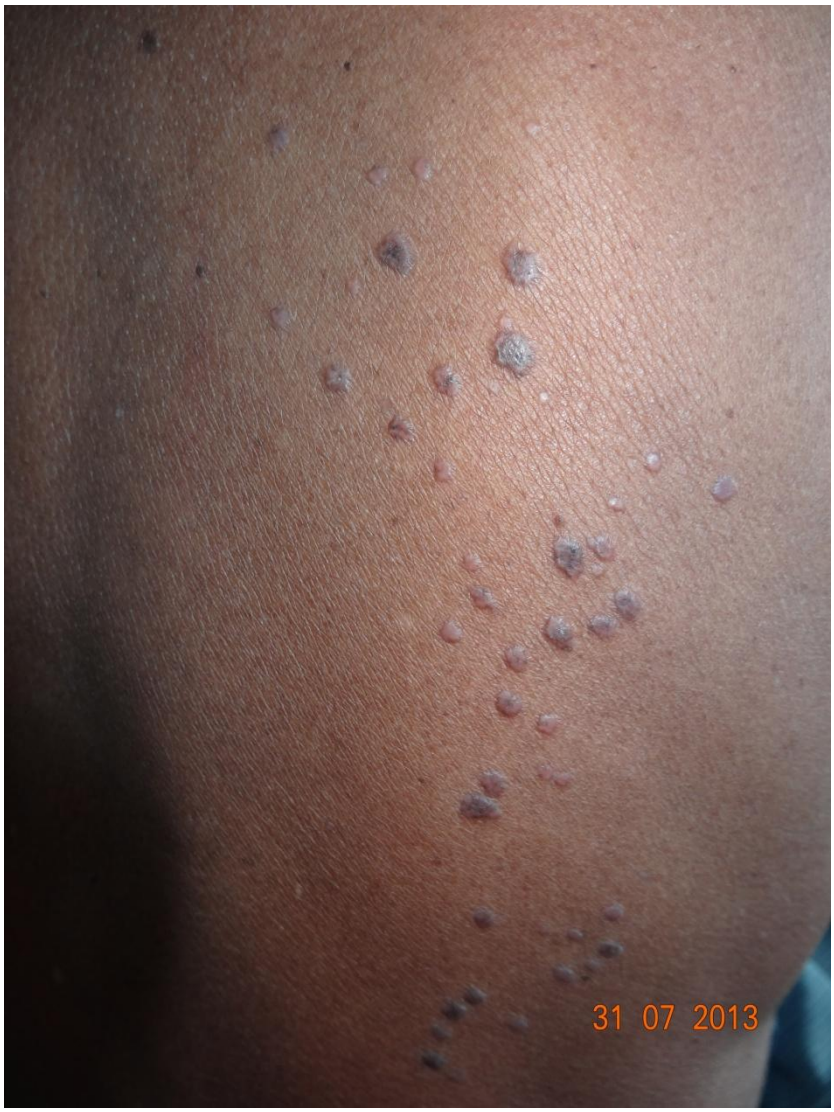


Hypertrophic lichen planus

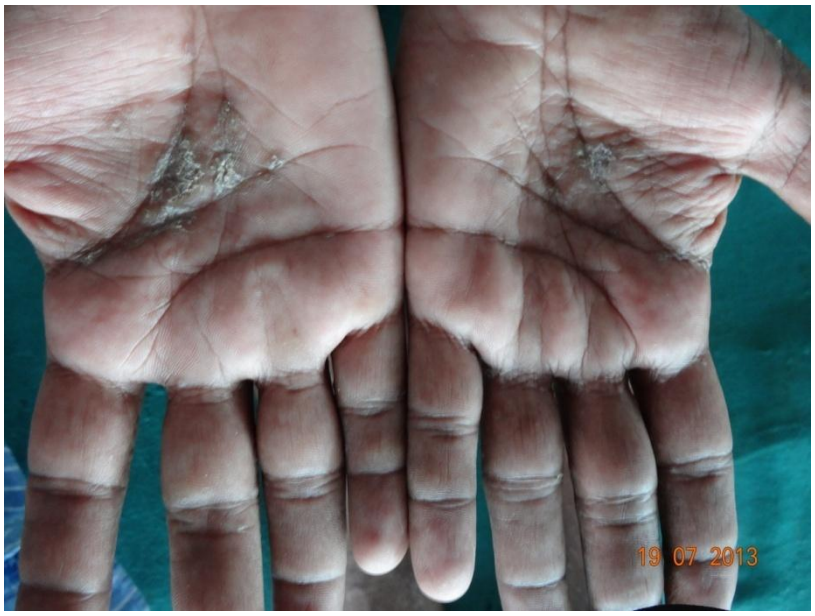


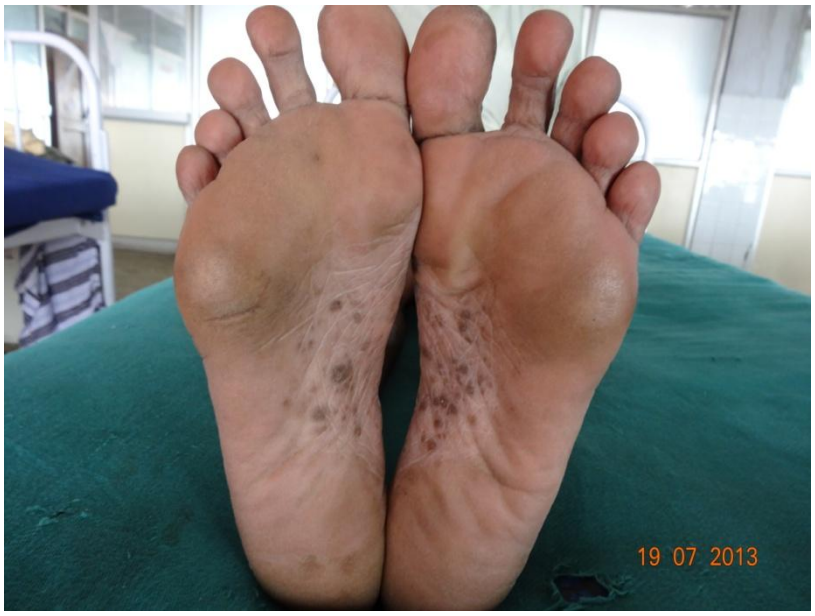


Linear lichen planus

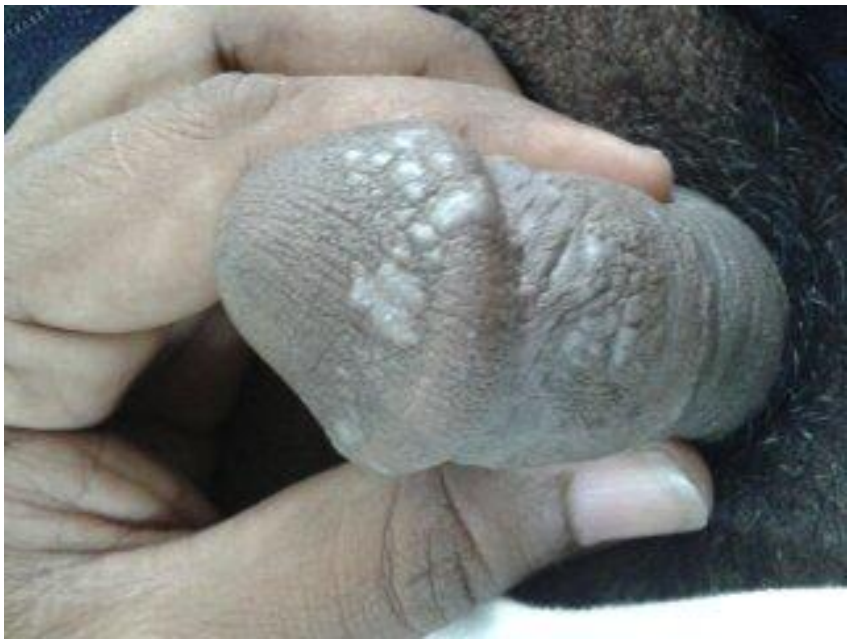


Palms and Soles



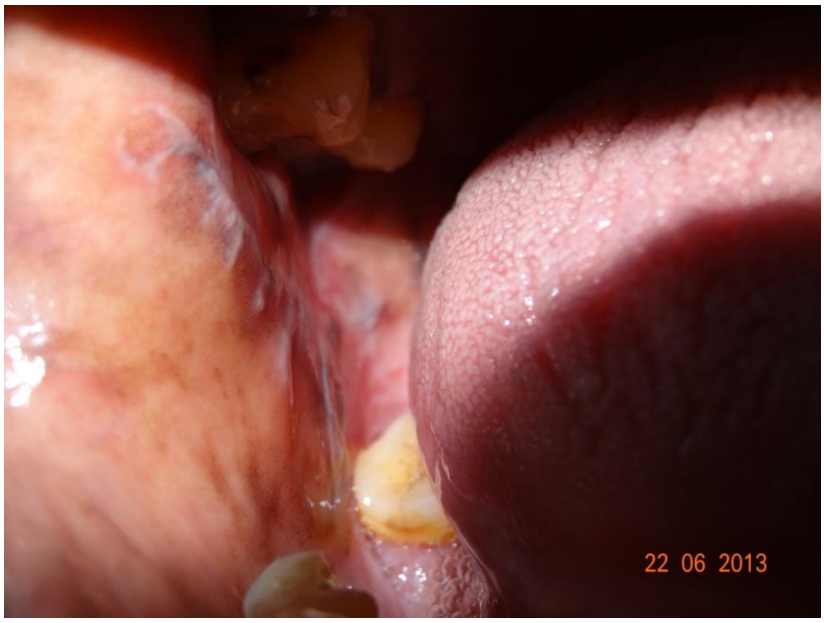


Genital lichen planus



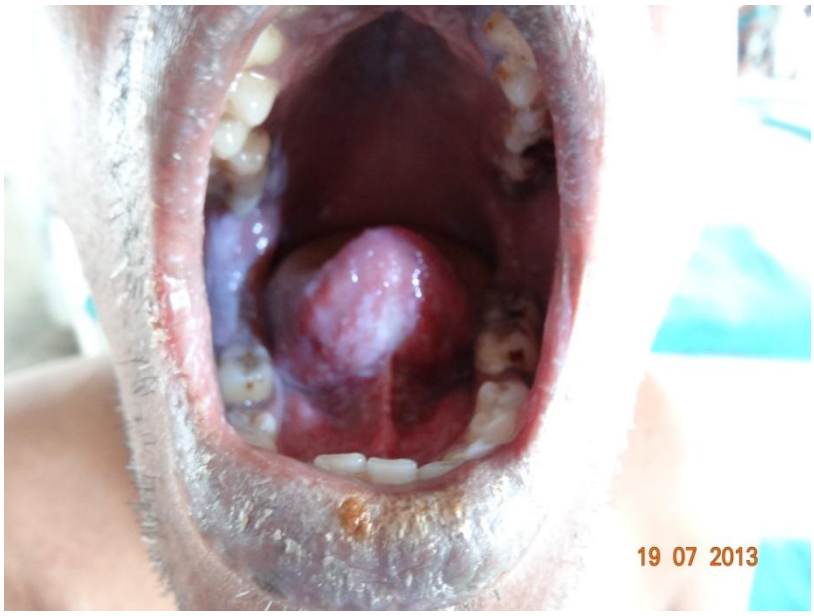
Oral lichen planus

Reticular subtype

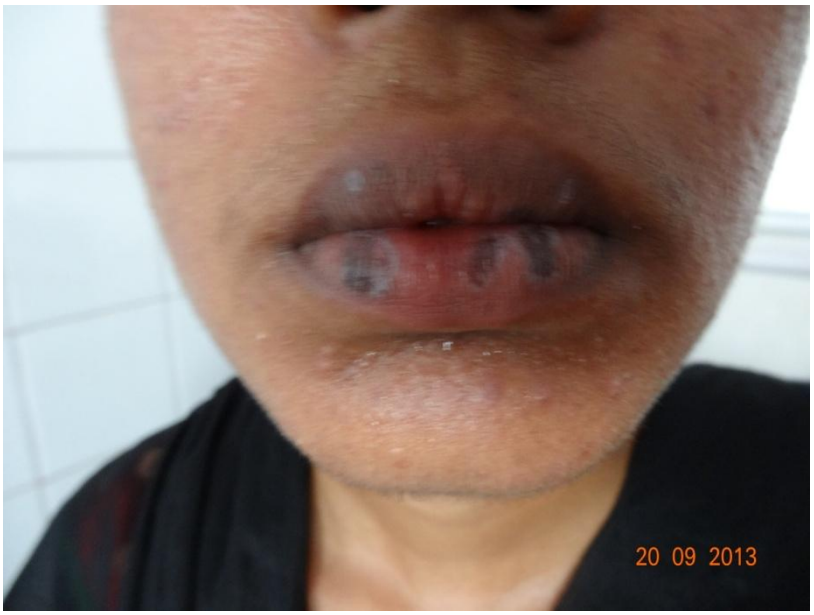


Lace-like white streaks on the buccal mucosa

Oral lichen planus



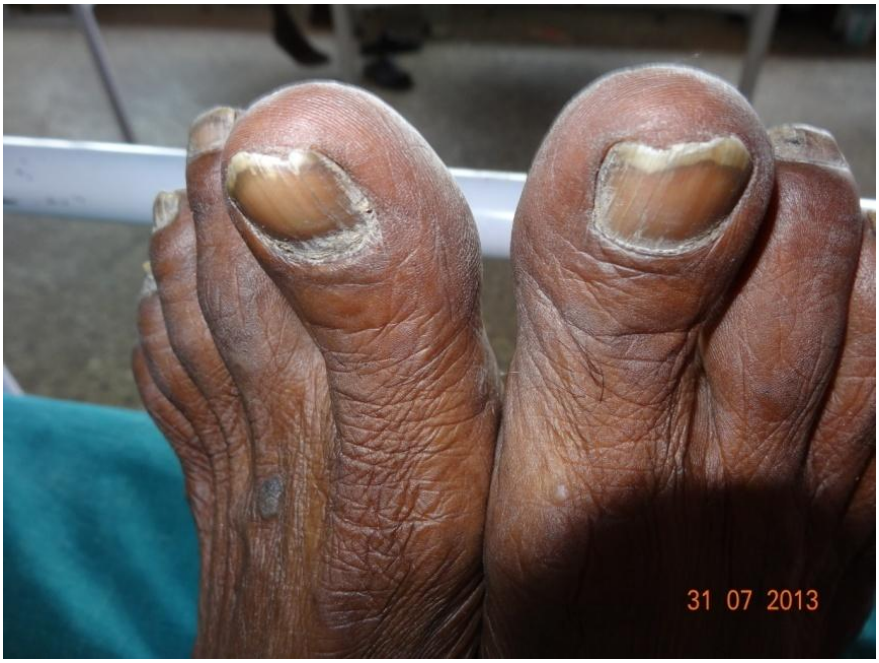
Violaceous plaque on the tongue



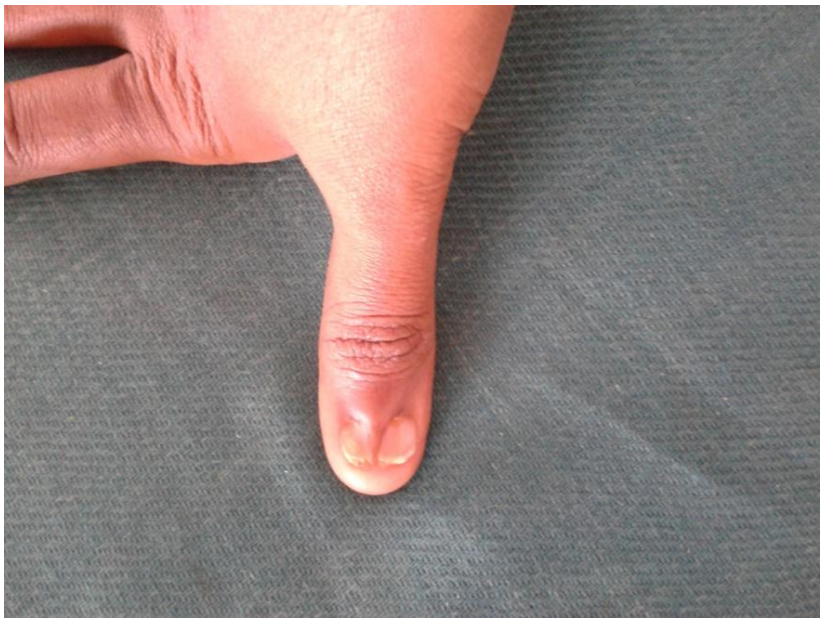
Violaceous plaque on the lower lip

Nail changes

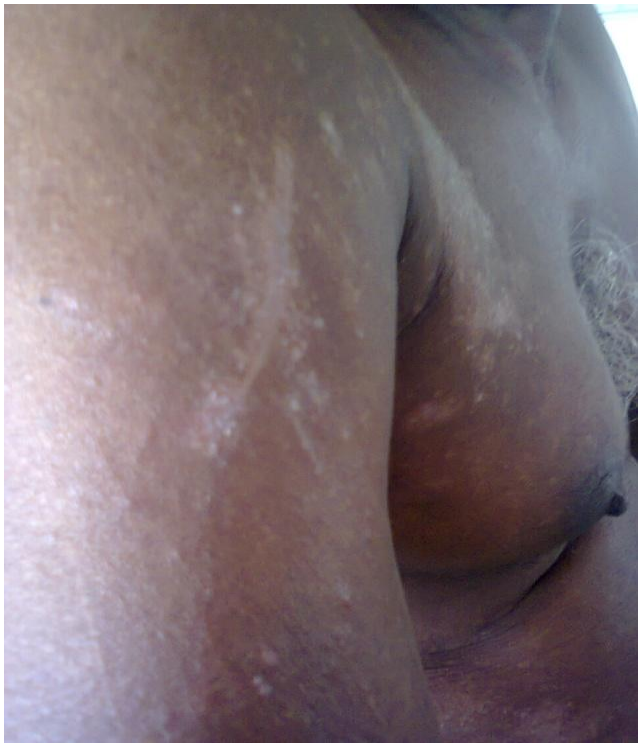
Longitudinal striations

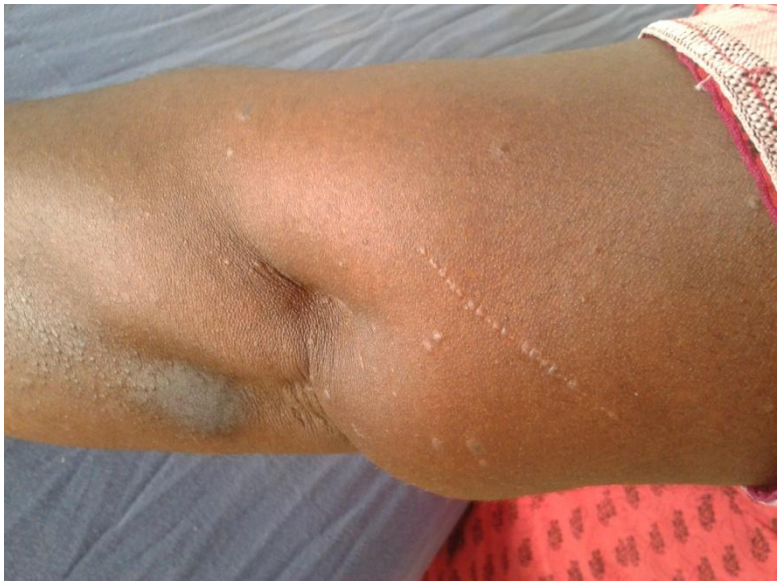


Pterygium



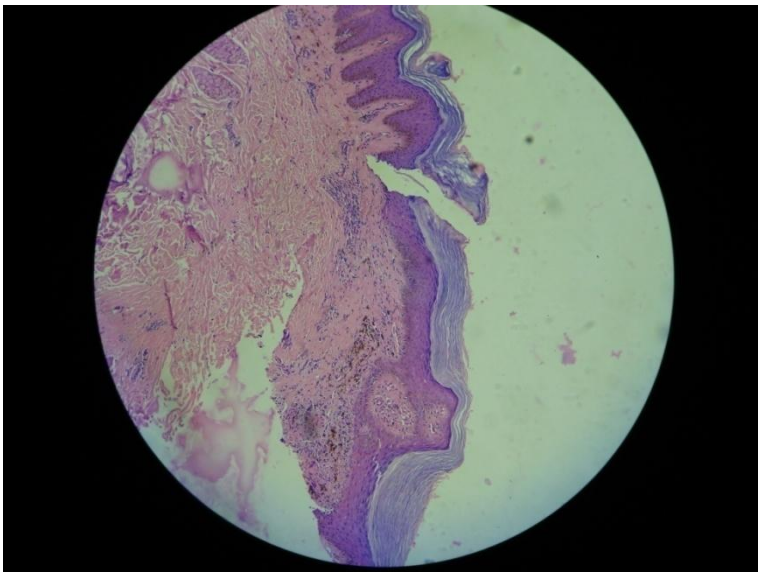
Association with koebnerisation

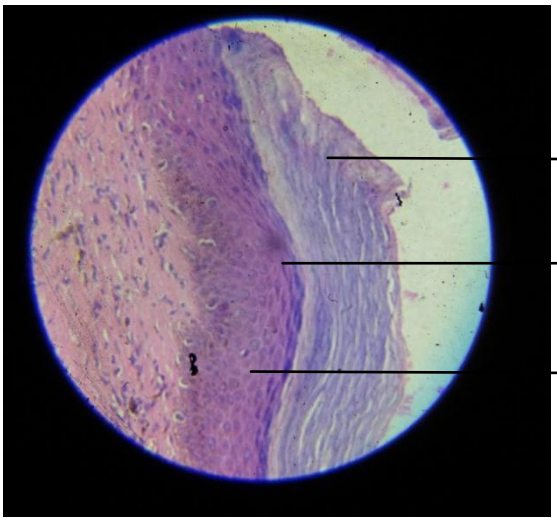




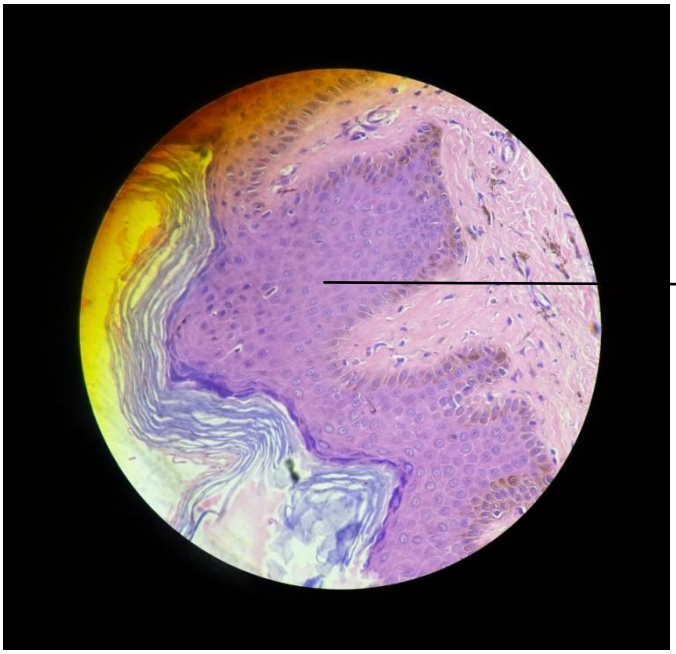
HISTOPATHOLOGY OF LICHEN PLANUS

Low power view

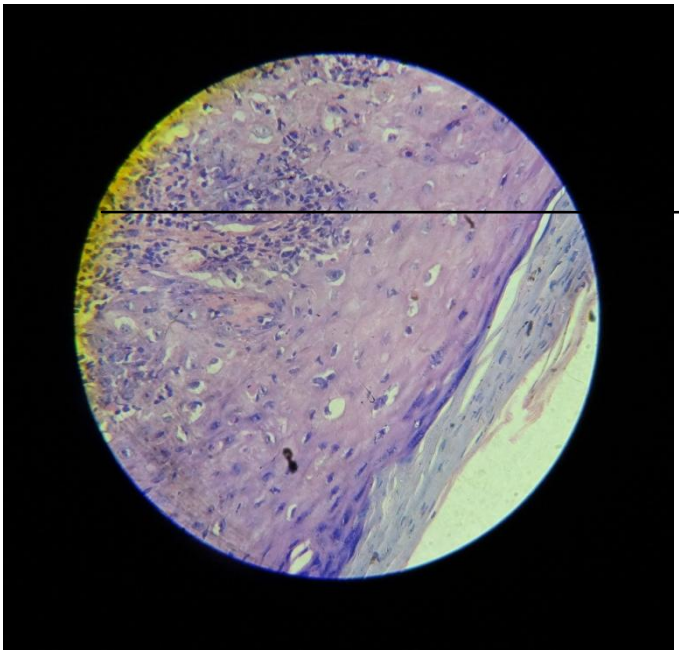




HISTOPATHOLOGY

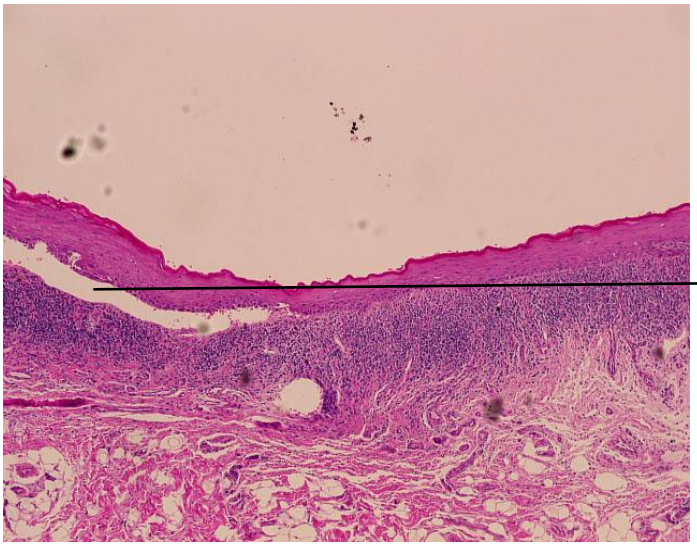


Elongated rete ridges

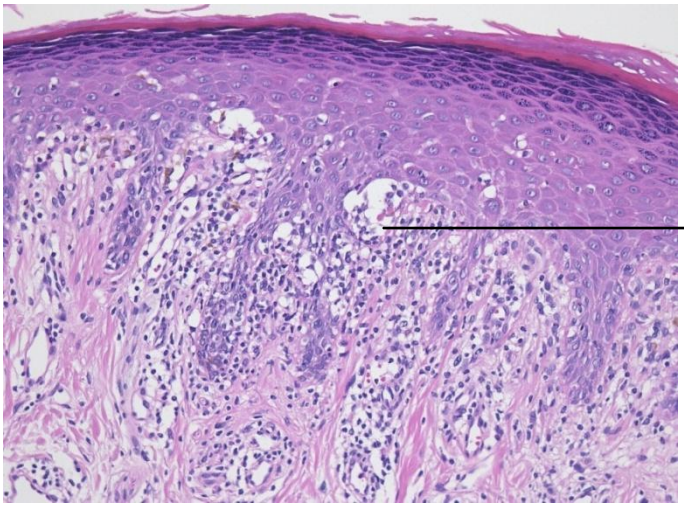


Band like inflammatory infiltrate

HISTOPATHOLOGY



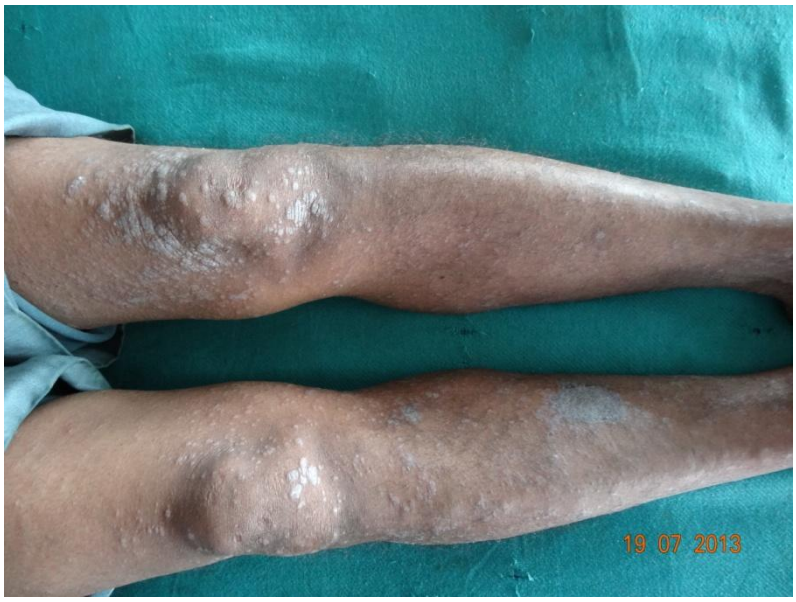
Max joseph space

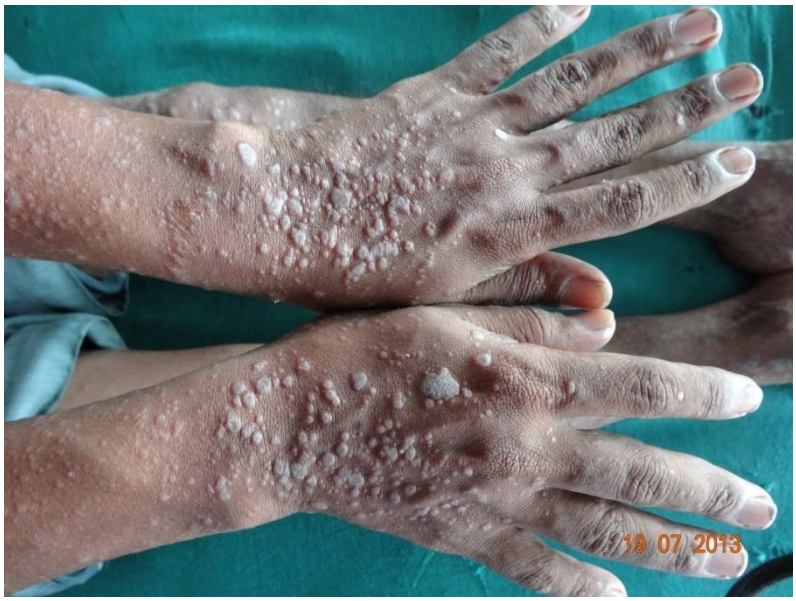


Colloid bodies

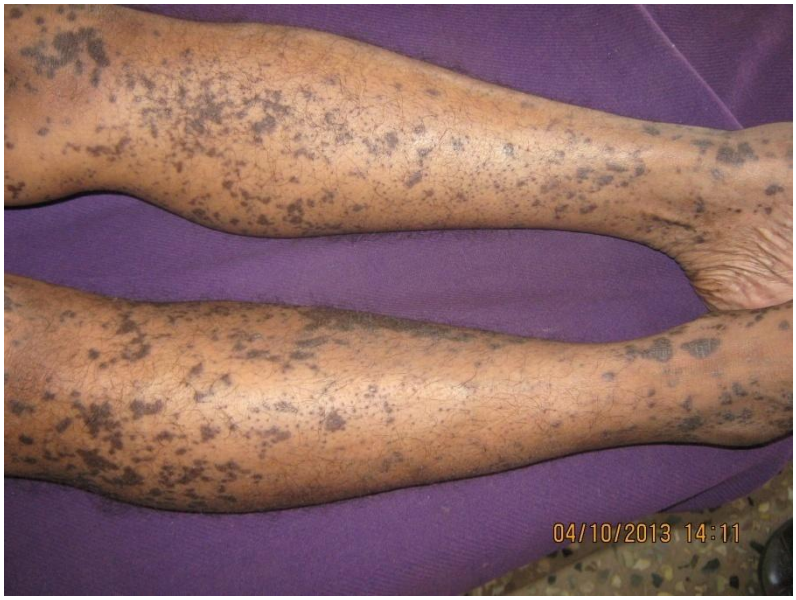
CLINICAL PHOTOS

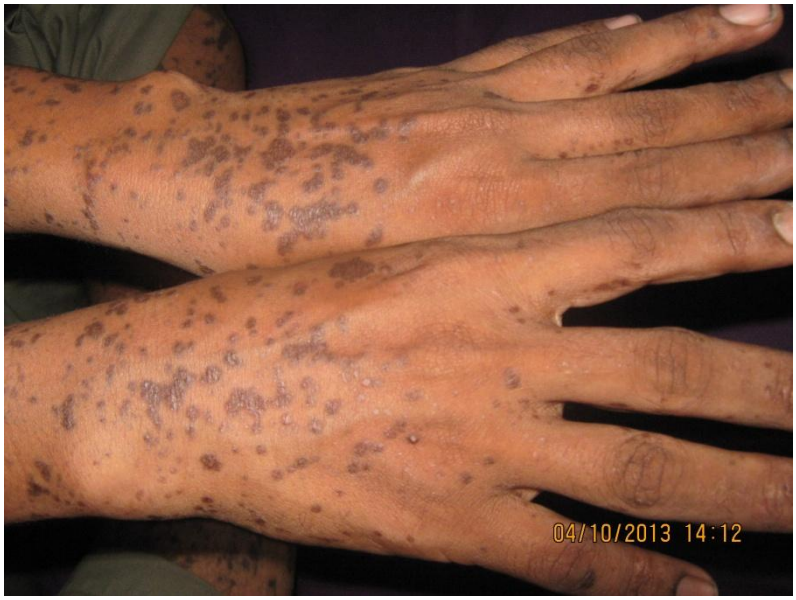
Patient1 **Before treatment**



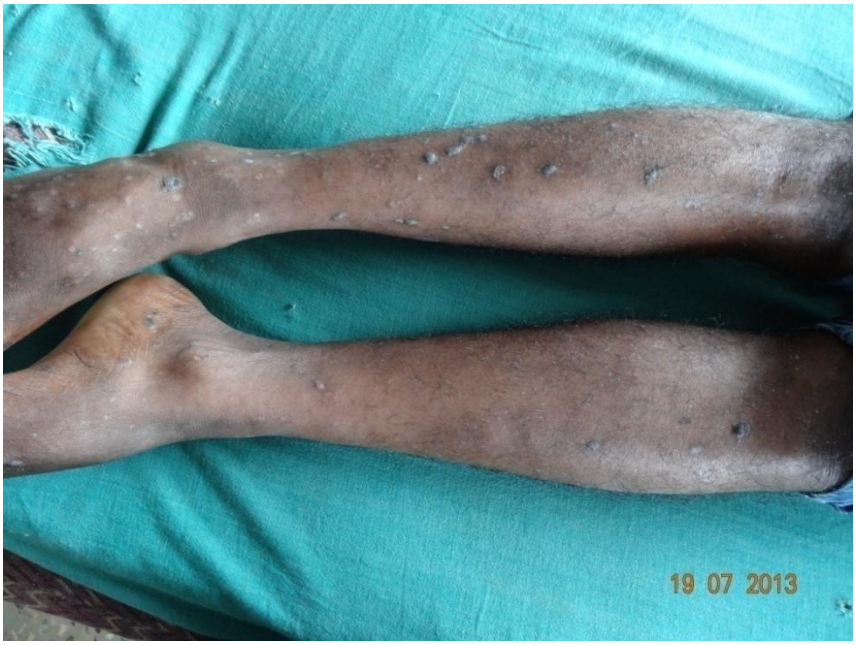


Patient 1 **After treatment**

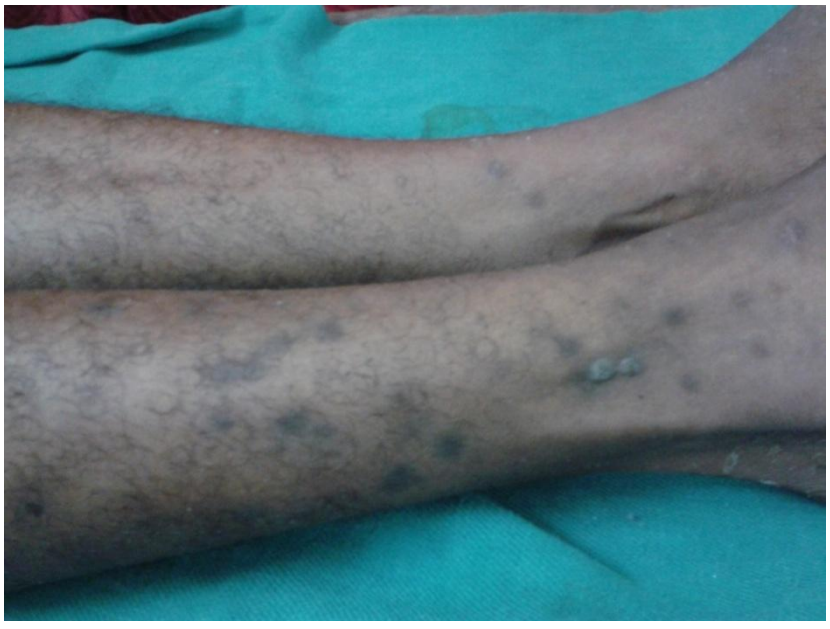




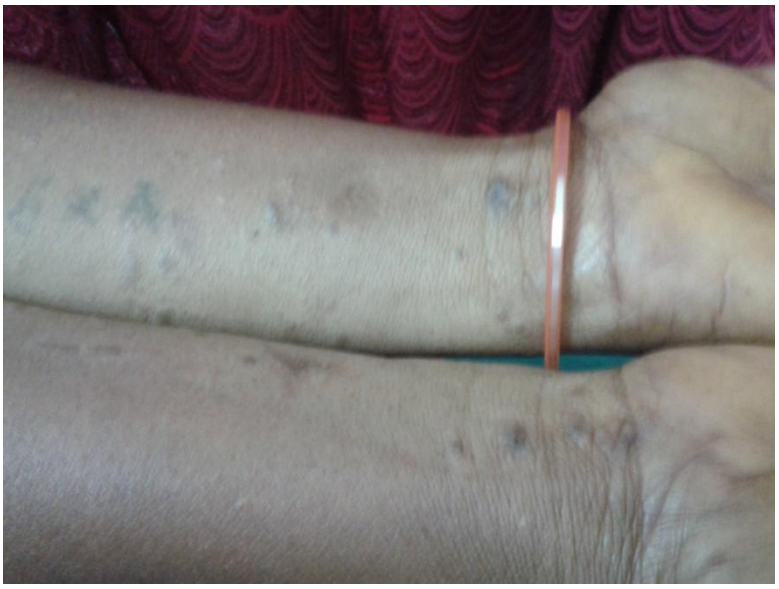
Patient 2 **Before treatment**



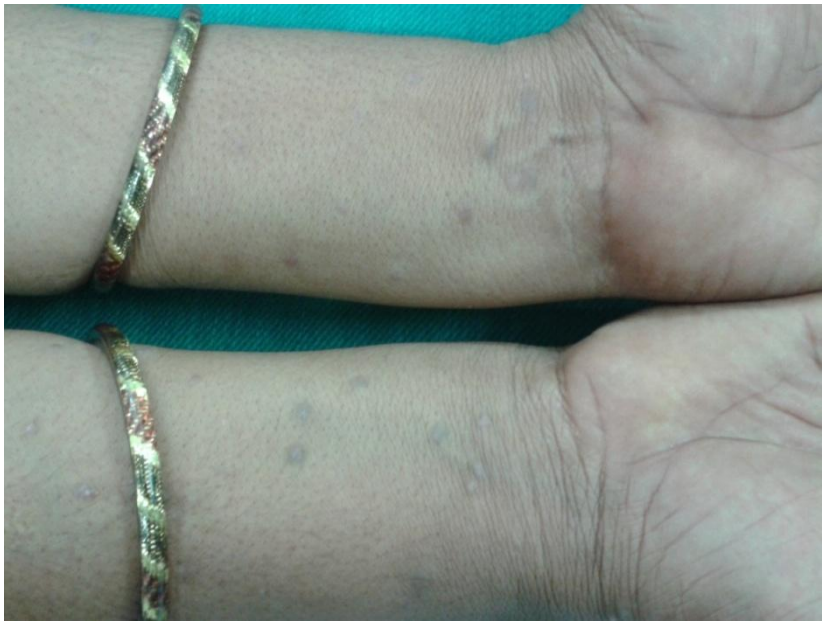
After treatment



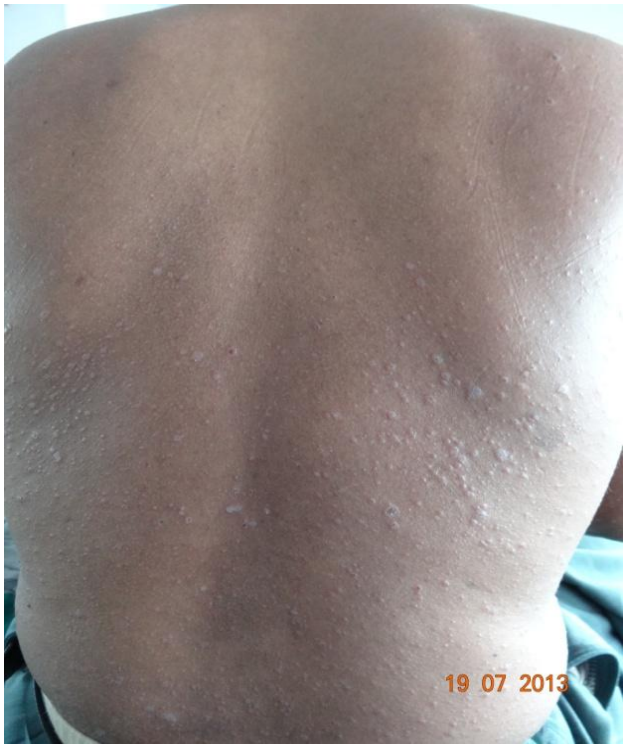
Patient 3 **Before treatment**



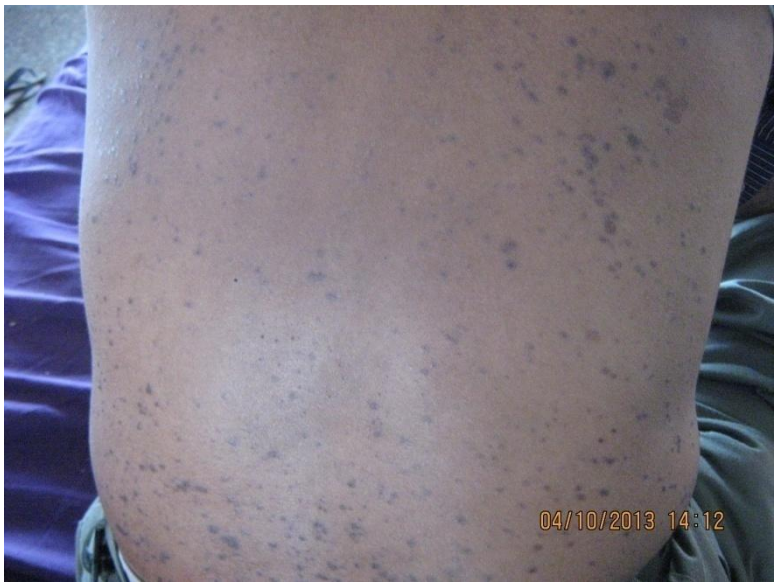
After treatment



Patient 4 **Before treatment**

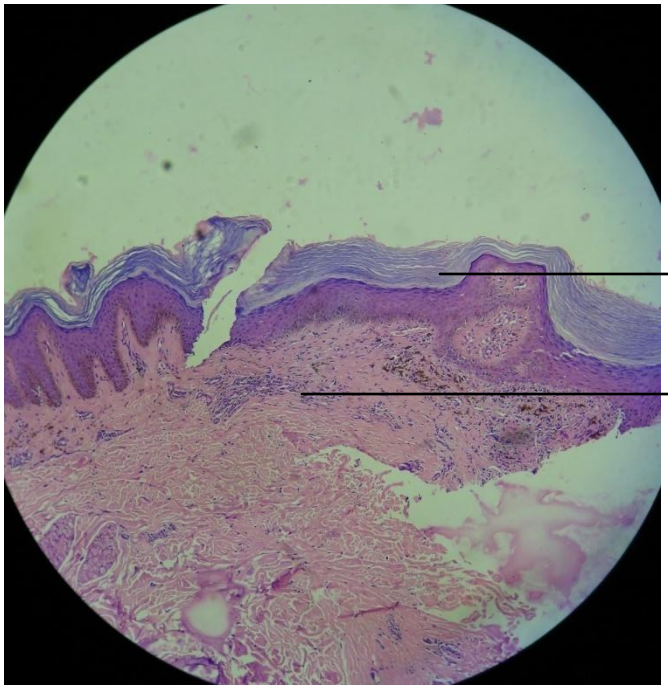


After treatment

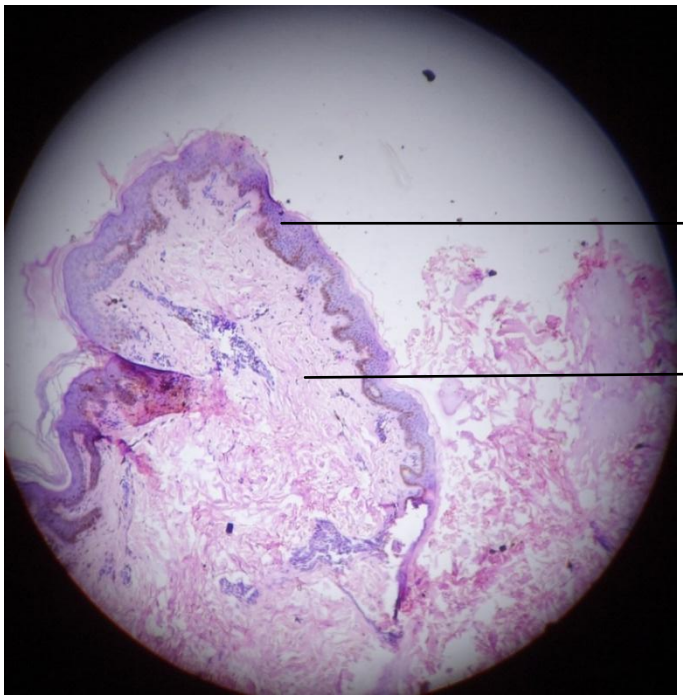


Histopathology of Lichen planus

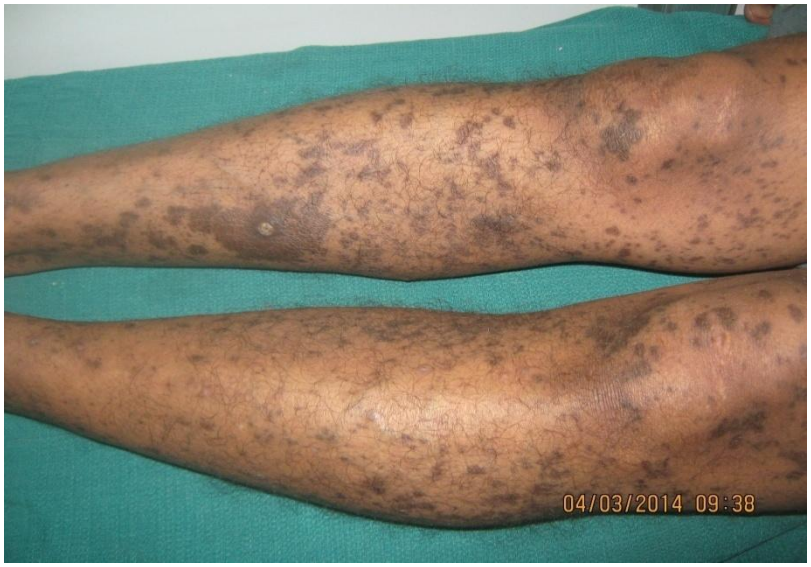
Before treatment

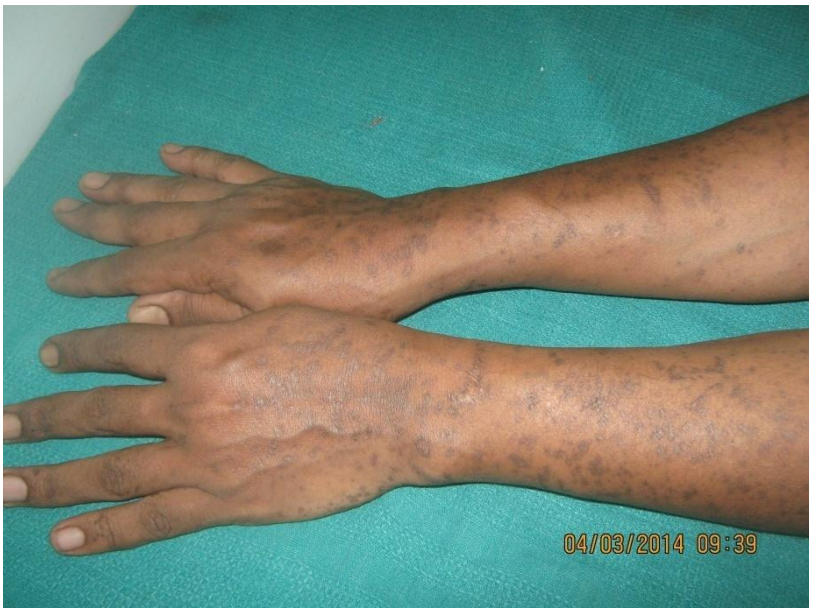


After treatment

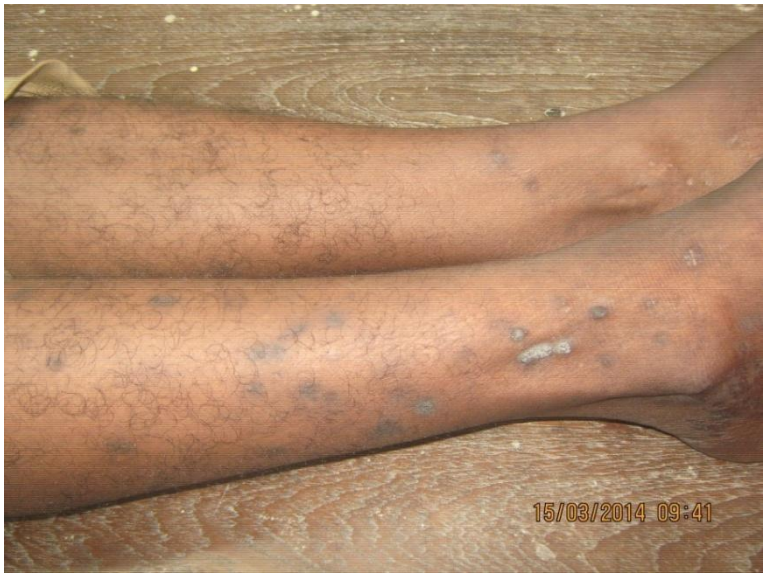


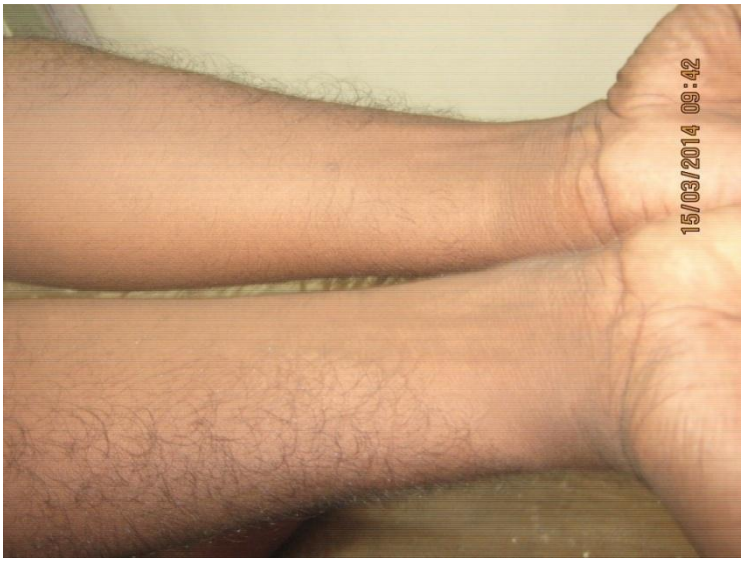
Patient 1- **6 months after treatment**





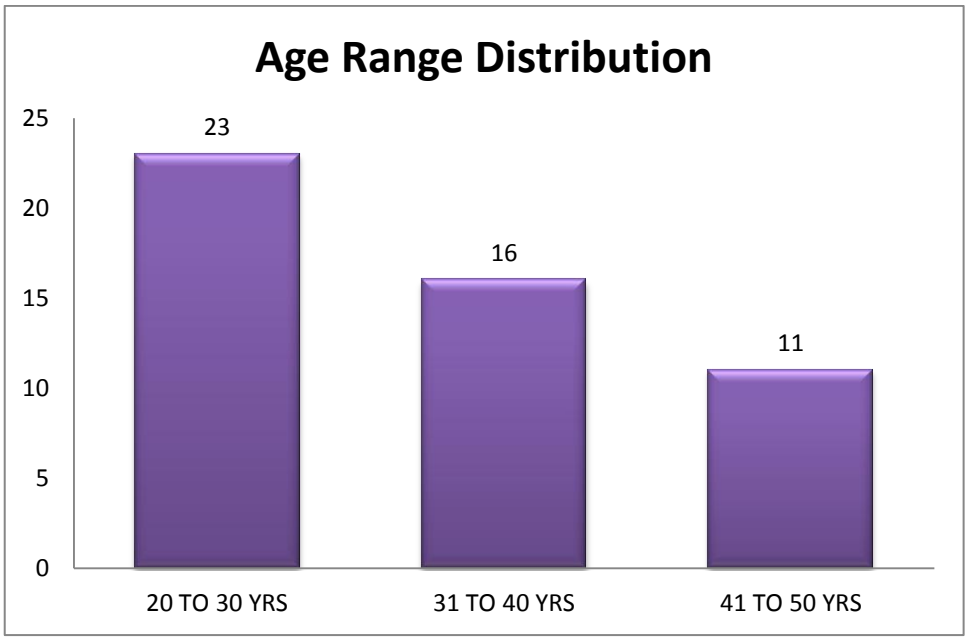
Patient 2 - **6 months after treatment**





OBSERVATION AND RESULTS

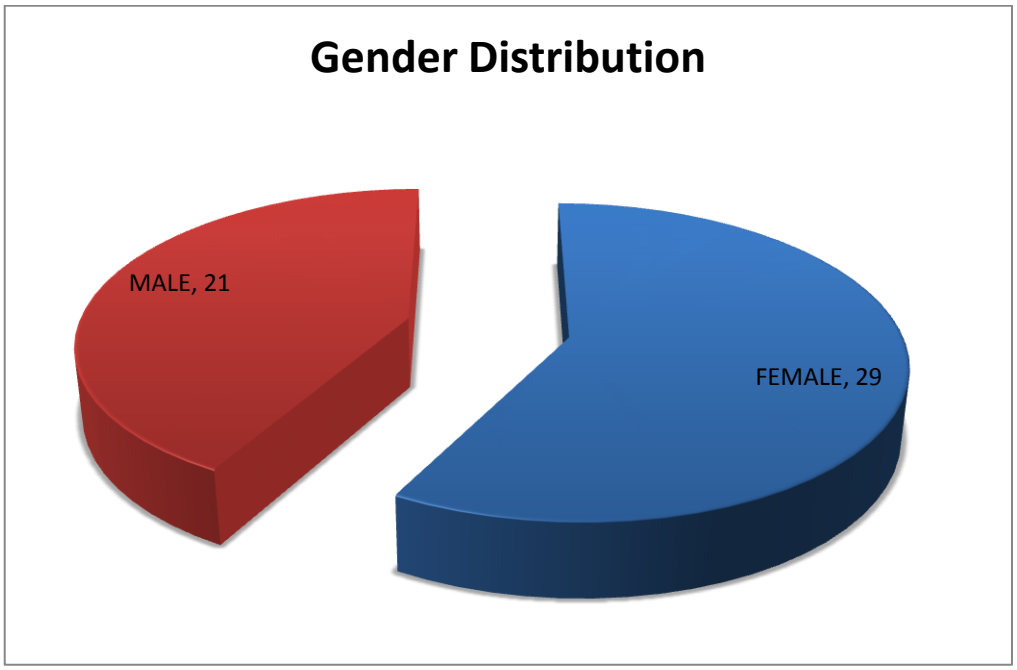
AGE DISRIBUTION



AGE RANGE

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	20 TO 30 YRS	23	46.0	46.0	46.0
	31 TO 40 YRS	16	32.0	32.0	78.0
	41 TO 50 YRS	11	22.0	22.0	100.0
	Total	50	100.0	100.0	

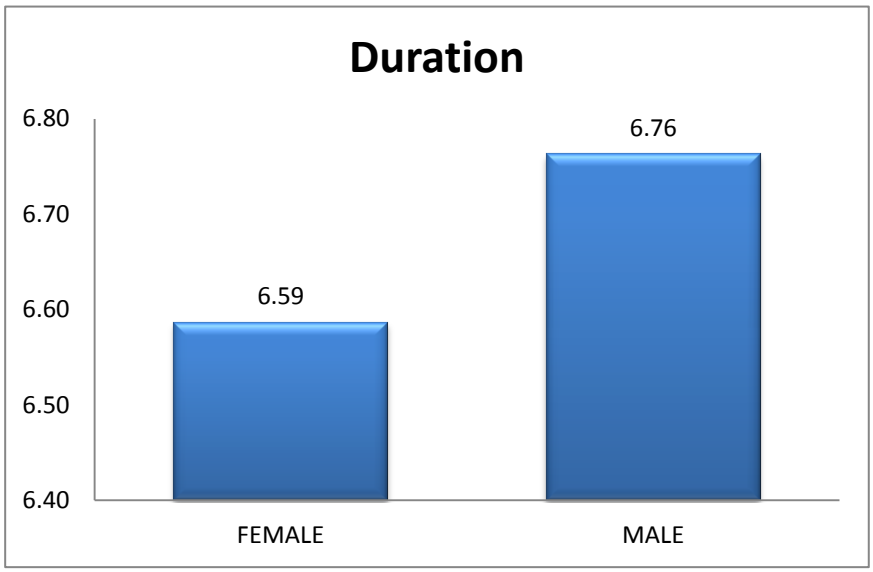
SEX DISTRIBUTION



GENDER

	Frequency	Percent	Valid Percent	Cumulative Percent
FEMALE	29	58.0	58.0	58.0
MALE	21	42.0	42.0	100.0
Total	50	100.0	100.0	

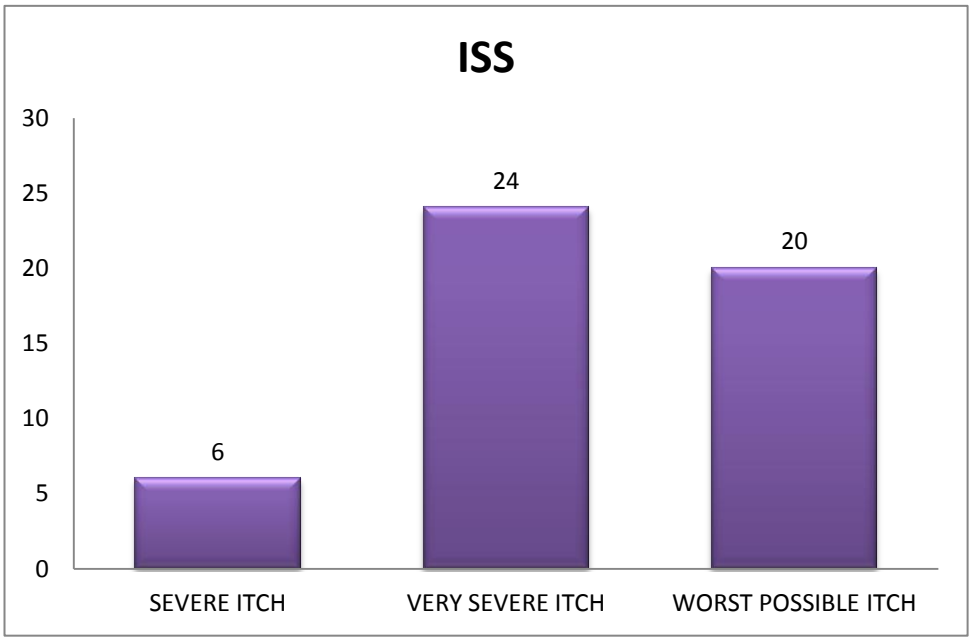
DURATION OF ILLNESS



GROUP STATISTICS

	GENDER	N	Mean	Std. Deviation	Std. Error Mean
Duration	FEMALE	29	6.59	1.323	.246
	MALE	21	6.76	1.411	.308

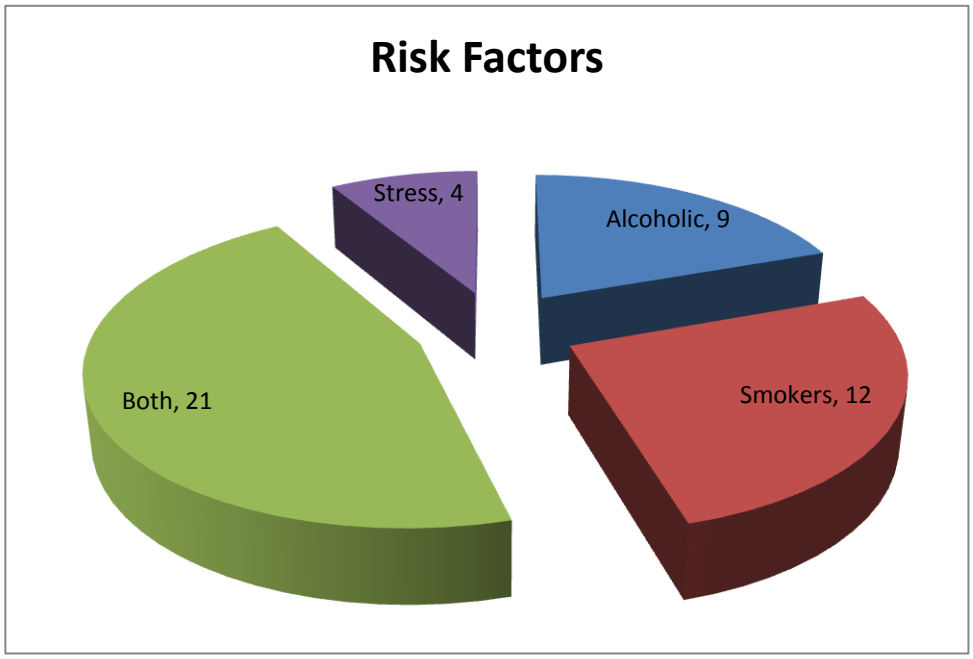
SYMPTOMS



ISS

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	3	6	12.0	12.0	12.0
	4	24	48.0	48.0	60.0
	5	20	40.0	40.0	100.0
	Total	50	100.0	100.0	

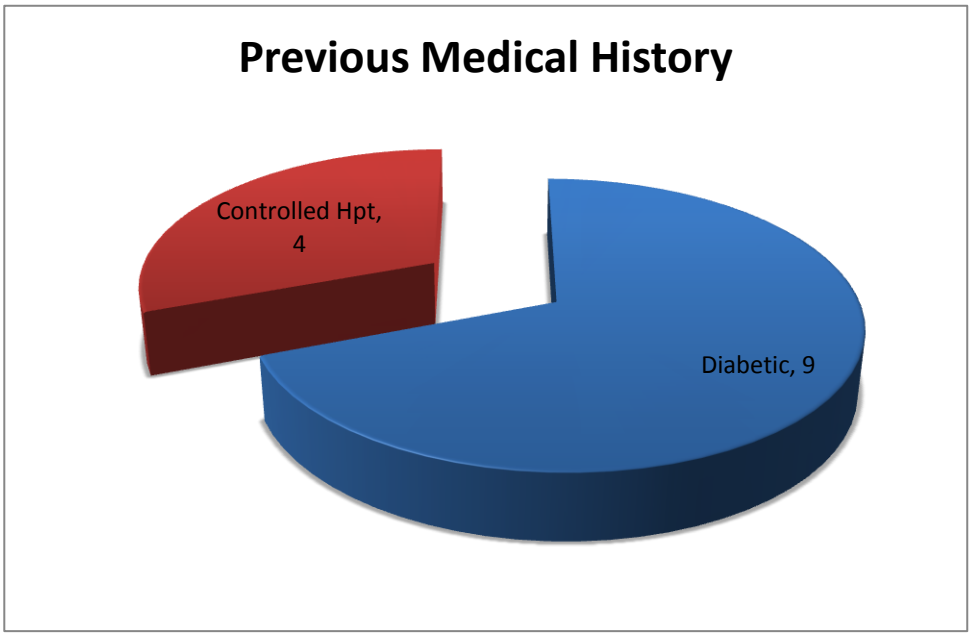
RISK FACTORS



In this study,

9 patients were alcoholic, 12 were smokers, among these 21 patients, 5were smoker as well as alcoholic, 4 patients reported stress.

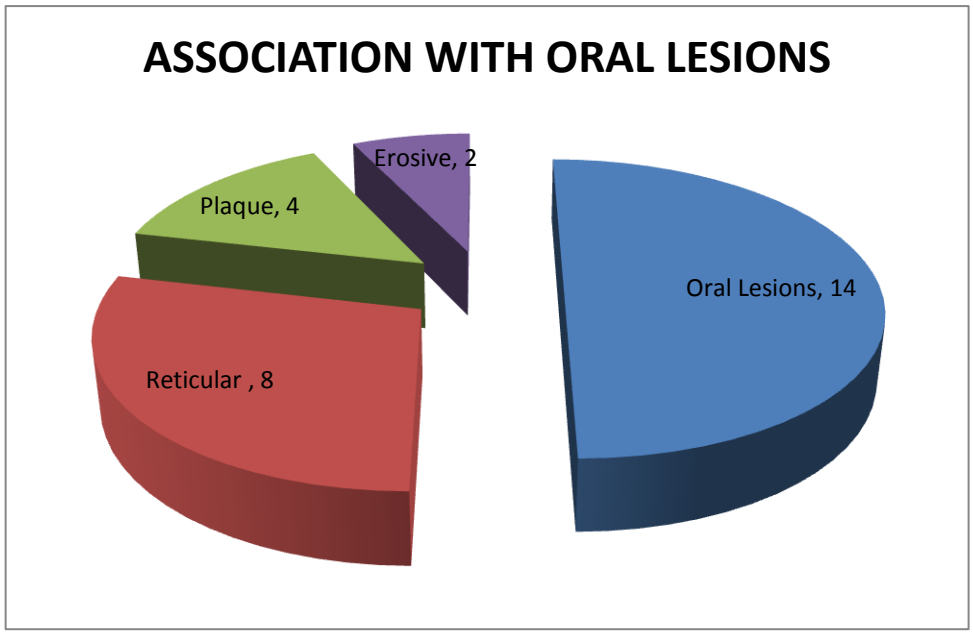
PREVIOUS MEDICAL HISTORY

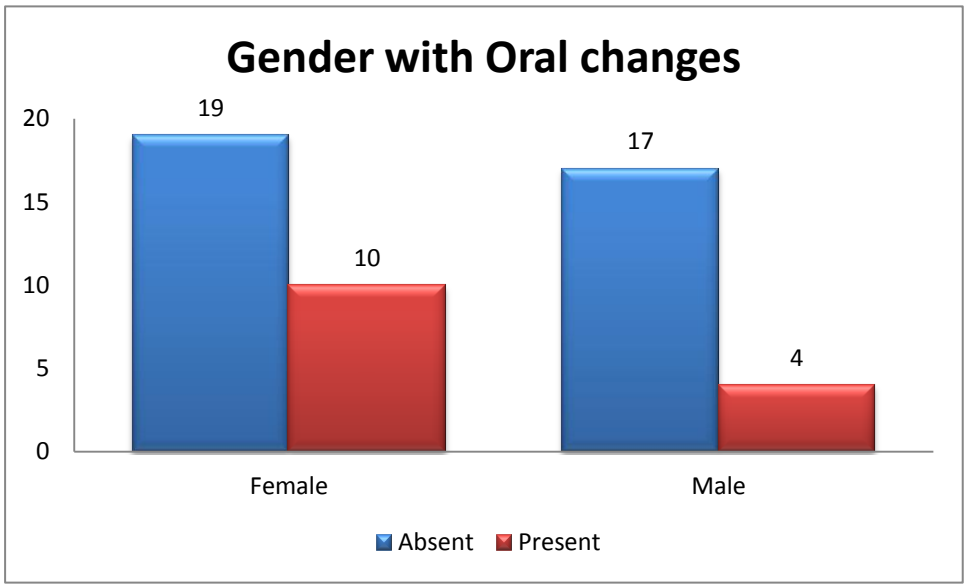


In this study,

9 patients were diabetic with good glycemic status and 5 were with controlled hypertension on drugs.

ASSOCIATION WITH ORAL LESIONS





Oral changes * GENDER

CROSSTAB

			GENDER		
			F	M	Total
Oralchanges	-	Count	19	17	36
		% within Oralchanges	52.8%	47.2%	100.0%
		% within GENDER	65.5%	81.0%	72.0%
	+	Count	10	4	14
		% within Oral changes	71.4%	28.6%	100.0%
		% within GENDER	34.5%	19.0%	28.0%
Total		Count	29	21	50
		% within Oral changes	58.0%	42.0%	100.0%
		% within GENDER	100.0%	100.0%	100.0%

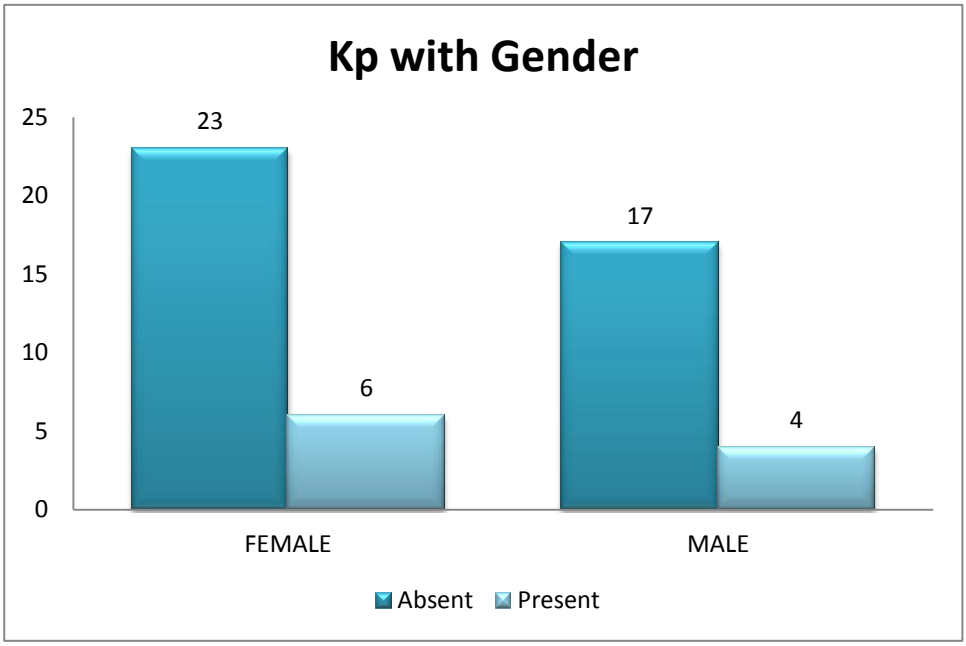
CHI-SQUARE TESTS

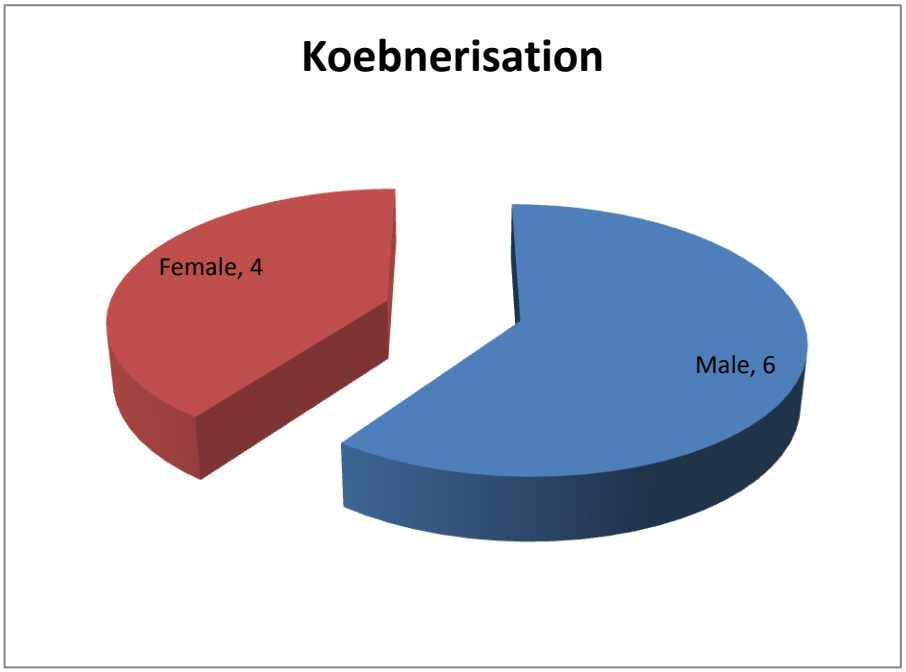
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.439[a]	1	.230		
Continuity Correction[b]	.776	1	.378		
Likelihood Ratio	1.482	1	.223		
Fisher's Exact Test				.341	.190
N of Valid Cases	50				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 5.88

b. Computed only for a 2x2 table.

ASSOCIATION WITH KOEBNERISATION





KOEBNERISATION

			GENDER		
			FEMALE	MALE	Total
KP	-	Count	23	17	40
		% within GENDER	79.3%	81.0%	80.0%
	+	Count	6	4	10
		% within GENDER	20.7%	19.0%	20.0%
Total		Count	29	21	50
		% within GENDER	100.0%	100.0%	100.0%

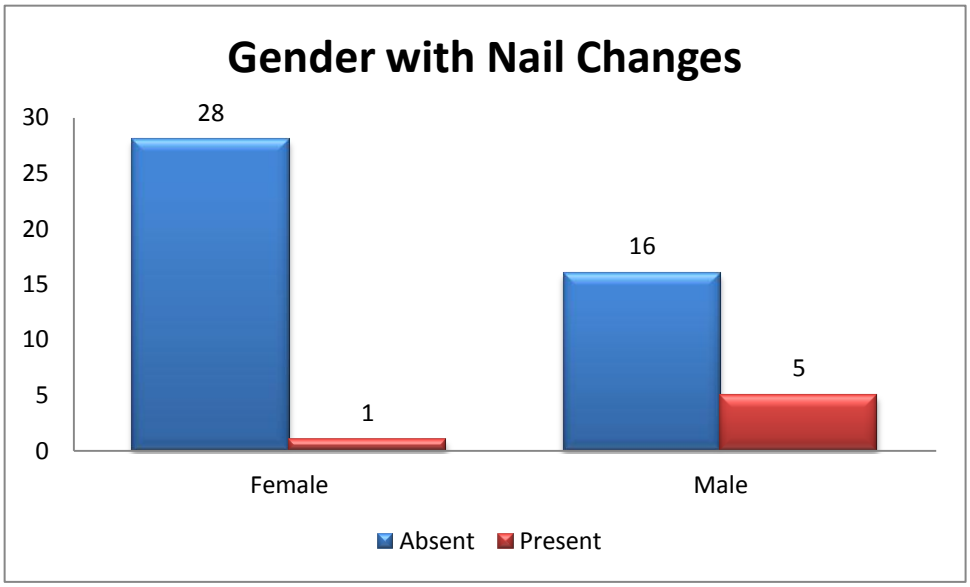
Chi-Square Tests

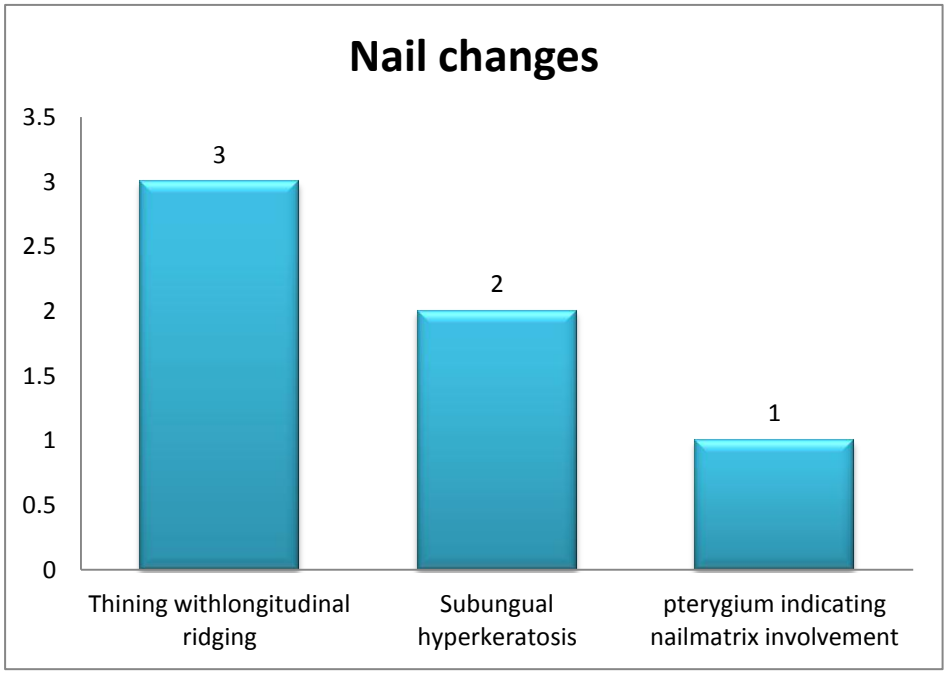
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.021[a]	1	.886		
Continuity Correction[b]	0.000	1	1.000		
Likelihood Ratio	.021	1	.886		
Fisher's Exact Test				1.000	.589
N of Valid Cases	50				

a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 4.20.

b. Computed only for a 2x2 table

ASSOCIATION WITH NAIL CHANGES





Nail changes * GENDER

Crosstab

			GENDER		
			F	M	Total
Nailchanges	-	Count	28	16	44
		% within Nailchanges	63.6%	36.4%	100.0%
		% within GENDER	96.6%	76.2%	88.0%
	+	Count	1	5	6
		% within Nailchanges	16.7%	83.3%	100.0%
		% within GENDER	3.4%	23.8%	12.0%
Total		Count	29	21	50
		% within Nailchanges	58.0%	42.0%	100.0%
		% within GENDER	100.0%	100.0%	100.0%

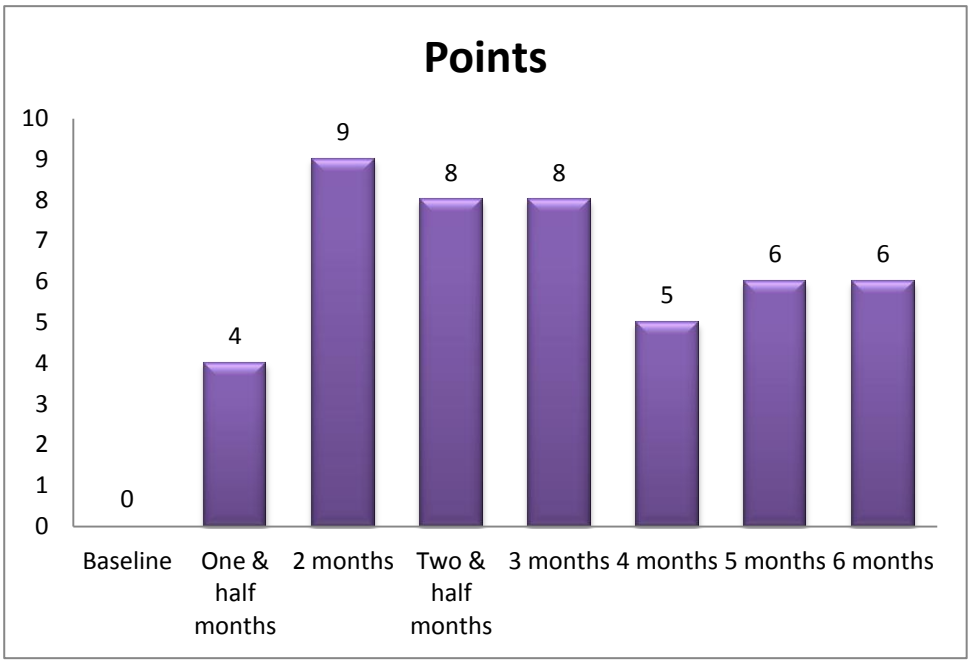
CHI-SQUARE TESTS

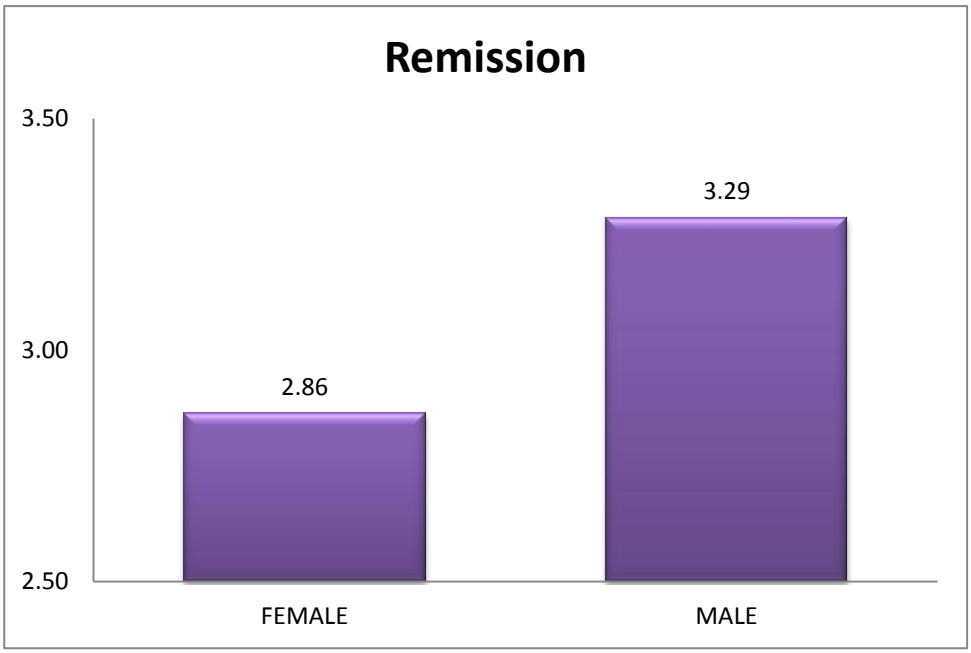
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.782[a]	1	.029		
Continuity Correction[b]	3.048	1	.081		
Likelihood Ratio	4.940	1	.026		
Fisher's Exact Test				.070	.041
N of Valid Cases	50				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 2.52.

b. Computed only for a 2x2 table.

DURATION OF REMISSION





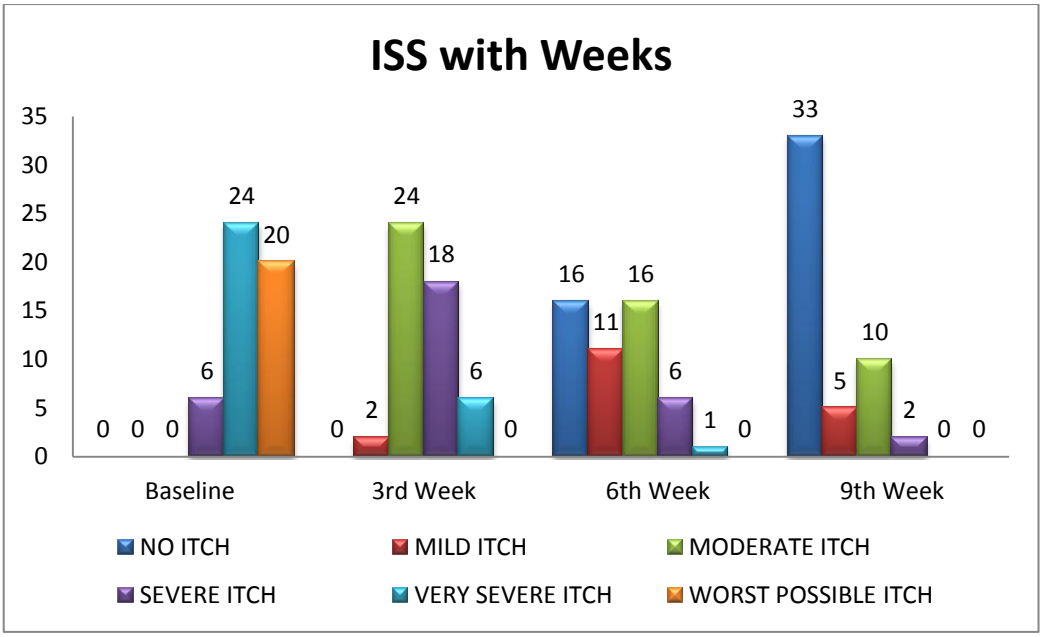
Group Statistics

GENDER		N	Mean	Std. Deviation	Std. Error Mean
Remission	FEMALE	29	2.86	1.505	.280
	MALE	21	3.29	1.927	.421

Independent samples test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	T	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Remission	Equal variances assumed	1.904	.174	-.873	48	.387	-.424	.485	-1.400	.552
	Equal variances not assumed			-.839	36.488	.407	-.424	.505	-1.447	.600

ITCH SEVERITY SCORE (ISS)



STATUS * WEEKS Cross tabulation

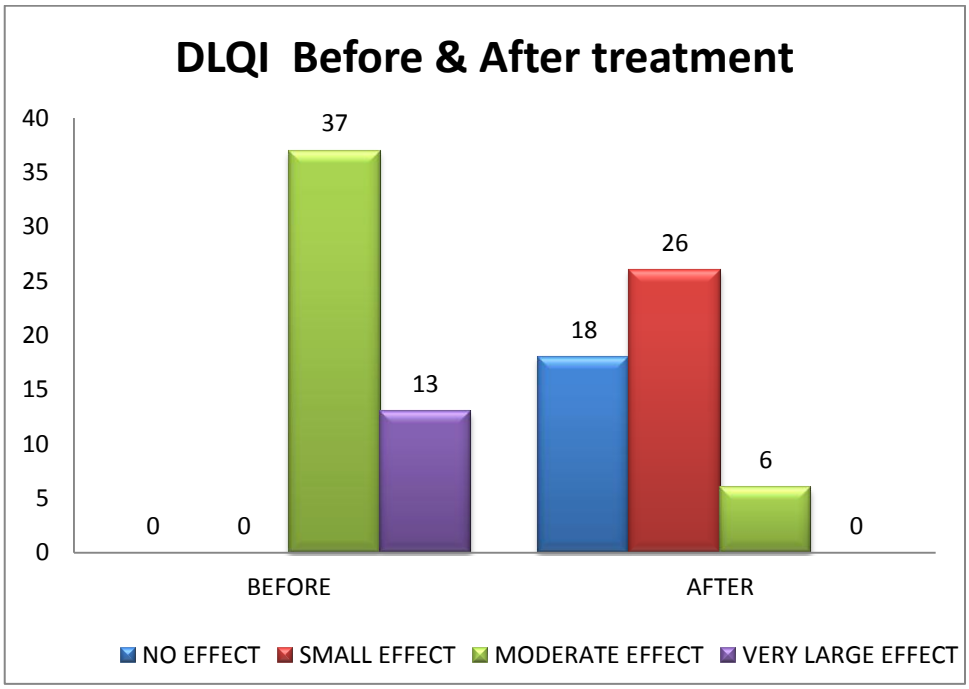
		WEEKS				
		BASELINE	3RD WEEK	6TH WEEK	9TH WEEK	Total
NO ITCH	Count	0	0	16	33	49
	% within STATUS	0.0%	0.0%	32.7%	67.3%	100.0%
	% within WEEKS	0.0%	0.0%	32.0%	66.0%	24.5%
MILD ITCH	Count	0	2	11	5	18
	% within STATUS	0.0%	11.1%	61.1%	27.8%	100.0%
	% within WEEKS	0.0%	4.0%	22.0%	10.0%	9.0%
MODERATE ITCH	Count	0	24	16	10	50
	% within STATUS	0.0%	48.0%	32.0%	20.0%	100.0%
	% within WEEKS	0.0%	48.0%	32.0%	20.0%	25.0%
SEVERE ITCH	Count	6	18	6	2	32
	% within STATUS	18.8%	56.2%	18.8%	6.2%	100.0%
	% within WEEKS	12.0%	36.0%	12.0%	4.0%	16.0%
VERY SEVERE ITCH	Count	24	6	1	0	31
	% within STATUS	77.4%	19.4%	3.2%	0.0%	100.0%
	% within WEEKS	48.0%	12.0%	2.0%	0.0%	15.5%
WORST POSSIBLE ITCH	Count	20	0	0	0	20
	% within STATUS	100.0%	0.0%	0.0%	0.0%	100.0%
	% within WEEKS	40.0%	0.0%	0.0%	0.0%	10.0%
Total	Count	50	50	50	50	200
	% within STATUS	25.0%	25.0%	25.0%	25.0%	100.0%
	% within WEEKS	100.0%	100.0%	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	226.786[a]	15	.000
Likelihood Ratio	245.459	15	.000
Linear-by-Linear Association	137.319	1	.000
N of Valid Cases	200		

4 cells (16.7%) have expected count less than 5. The minimum expected count is 4.504 cells (16.7%) have expected count less than 5. The minimum expected count is 4.50

DERMATOLOGY LIFE QUALITY INDEX (DLQI)



DLQI SCORE * BA Cross tabulation

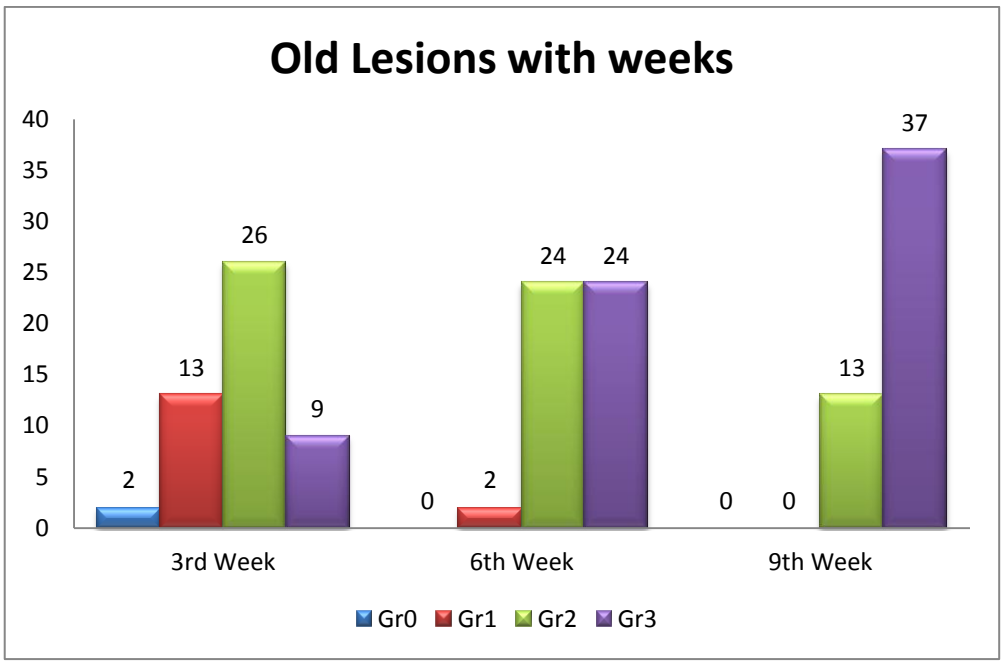
			BA		
			BEFORE	AFTER	Total
DLQISCORE	NO EFFECT	Count	0	18	18
		% within DLQISCORE	0.0%	100.0%	100.0%
		% within BA	0.0%	36.0%	18.0%
	SMALL EFFECT	Count	0	26	26
		% within DLQISCORE	0.0%	100.0%	100.0%
		% within BA	0.0%	52.0%	26.0%
	MODERATE EFFECT	Count	37	6	43
		% within DLQISCORE	86.0%	14.0%	100.0%
		% within BA	74.0%	12.0%	43.0%
	VERY LARGE EFFECT	Count	13	0	13
		% within DLQISCORE	100.0%	0.0%	100.0%
		% within BA	26.0%	0.0%	13.0%
Total		Count	50	50	100
		% within DLQISCORE	50.0%	50.0%	100.0%
		% within BA	100.0%	100.0%	100.0%

CHI-SQUARE TESTS

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	79.349[a]	3	.000
Likelihood Ratio	103.875	3	.000
Linear-by-Linear Association	64.016	1	.000
N of Valid Cases	100		

a.0 cells (.0%) have expected count less than 5. The minimum expected count is 6.50.

NATURE OF LESIONS DURING THERAPY



OLDLESIONS * WEEKS

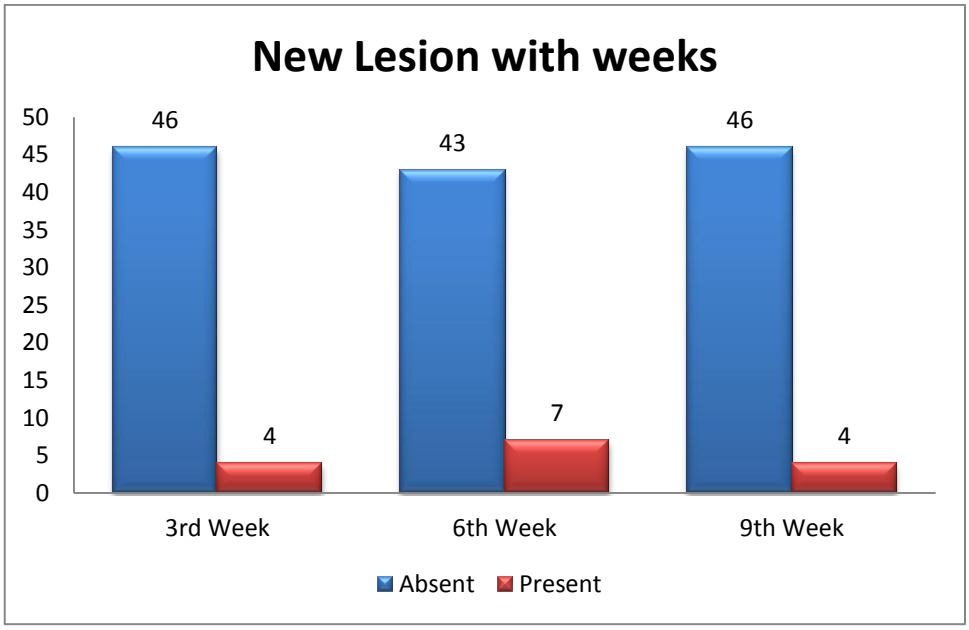
Crosstab

			WEEKS			
			3RD WEEK	6TH WEEK	9TH WEEK	Total
OLDLESIONS	Gr0	Count	2	0	0	2
		% within OLDLESIONS	100.0%	0.0%	0.0%	100.0%
		% within WEEKS	4.0%	0.0%	0.0%	1.3%
	Gr1	Count	13	2	0	15
		% within OLDLESIONS	86.7%	13.3%	0.0%	100.0%
		% within WEEKS	26.0%	4.0%	0.0%	10.0%
	Gr2	Count	26	24	13	63
		% within OLDLESIONS	41.3%	38.1%	20.6%	100.0%
		% within WEEKS	52.0%	48.0%	26.0%	42.0%
	Gr3	Count	9	24	37	70
		% within OLDLESIONS	12.9%	34.3%	52.9%	100.0%
		% within WEEKS	18.0%	48.0%	74.0%	46.7%
Total		Count	50	50	50	150
		% within OLDLESIONS	33.3%	33.3%	33.3%	100.0%
		% within WEEKS	100.0%	100.0%	100.0%	100.0%

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	45.095[a]	6	.000
Likelihood Ratio	48.940	6	.000
N of Valid Cases	150		

a. 3 cells (25.0%) have expected count less than 5. The minimum expected count is .67

NEW LESIONS DURING THERAPY



NEW LESIONS * WEEKS

			WEEKS			
			3RD WEEK	6TH WEEK	9TH WEEK	Total
NEWLESIONS	-	Count	46	43	46	135
		% within NEWLESIONS	34.1%	31.9%	34.1%	100.0%
		% within WEEKS	92.0%	86.0%	92.0%	90.0%
	+	Count	4	7	4	15
		% within NEWLESIONS	26.7%	46.7%	26.7%	100.0%
		% within WEEKS	8.0%	14.0%	8.0%	10.0%
Total		Count	50	50	50	150
		% within NEWLESIONS	33.3%	33.3%	33.3%	100.0%
		% within WEEKS	100.0%	100.0%	100.0%	100.0%

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1.333[a]	2	.513
Likelihood Ratio	1.275	2	.529
N of Valid Cases	150		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected value is 5.00

Frequency Table

ISS

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	3	6	12.0	12.0	12.0
	4	24	48.0	48.0	60.0
	5	20	40.0	40.0	100.0
	Total	50	100.0	100.0	

ISS3

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	2	4.0	4.0	4.0
	2	24	48.0	48.0	52.0
	3	18	36.0	36.0	88.0
	4	6	12.0	12.0	100.0
	Total	50	100.0	100.0	

ISS6

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	16	32.0	32.0	32.0
	1	11	22.0	22.0	54.0
	2	16	32.0	32.0	86.0
	3	6	12.0	12.0	98.0
	4	1	2.0	2.0	100.0
	Total	50	100.0	100.0	

ISS9

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	33	66.0	66.0	66.0
	1	5	10.0	10.0	76.0
	2	10	20.0	20.0	96.0
	3	2	4.0	4.0	100.0
	Total	50	100.0	100.0	

NPar Tests

Wilcoxon Signed Ranks Test

Ranks

		N	Mean Rank	Sum of Ranks
ISS3 - ISS	Negative Ranks	50[a]	25.50	1275.00
	Positive Ranks	0[b]	.00	.00
	Ties	0[c]		
	Total	50		
ISS6 - ISS	Negative Ranks	50[d]	25.50	1275.00
	Positive Ranks	0[e]	.00	.00
	Ties	0[f]		
	Total	50		
ISS9 - ISS	Negative Ranks	50[g]	25.50	1275.00
	Positive Ranks	0[h]	.00	.00
	Ties	0[i]		
	Total	50		
ISS6 - ISS3	Negative Ranks	37[j]	19.00	703.00
	Positive Ranks	0[k]	.00	.00
	Ties	13[l]		
	Total	50		
ISS9 - ISS3	Negative Ranks	47[m]	24.00	1128.00
	Positive Ranks	0[n]	.00	.00
	Ties	3[o]		
	Total	50		
ISS9 - ISS6	Negative Ranks	26[p]	18.54	482.00
	Positive Ranks	7[q]	11.29	79.00
	Ties	17[r]		
	Total	50		

a. ISS3 < ISS
b. ISS3 > ISS
c. ISS3 = ISS
d. ISS6 < ISS
e. ISS6 > ISS
f. ISS6 = ISS
g. ISS9 < ISS
h. ISS9 > ISS
i. ISS9 = ISS
j. ISS6 < ISS3
k. ISS6 > ISS3
l. ISS6 = ISS3
m. ISS9 < ISS3
n. ISS9 > ISS3
o. ISS9 = ISS3
p. ISS9 < ISS6
q. ISS9 > ISS6
r. ISS9 = ISS6

TEST STATISTICS

	Z	Asymp. Sig. (2-tailed)
ISS3 – ISS	-6.327[b]	.000
ISS6 – ISS	-6.217[b]	.000
ISS9 – ISS	-6.246[b]	.000
ISS6 - ISS3	-5.436[b]	.000
ISS9 - ISS3	-6.057[b]	.000
ISS9 - ISS6	-3.703[b]	.000

a. Wilcoxon Signed Ranks Test

b. Based on positive ranks

Based on the "P" value of Itch Severity Score (ISS), Dermatology Life Quality Index (DLQI) and Grading of regression of the old lesions, the study conducted was significant.

DISCUSSION

Lichen planus is one of the common dermatological condition that can affect any age group and it affects both sexes equally[43][57].

Various studies have been done elsewhere assessing the efficacy of low molecular weight heparin in generalized cutaneous lichen planus. Most of these studies used 3 mg of Enoxaparin subcutaneously for a period between 6 to 20weeks. For ease of convenience and follow up in this study, Enoxaparin 4 mg (20mg/0.2ml)[11]was used for 9 weeks.

It is more common in people more than 30 years old, but in our study the common age group affected was between 20 – 40 yrs (78%) that was significantly higher than the study by Sehgal et al[12] (46%) and Kacchawa etal[47](47%).

There was a female preponderance in this study. M : F = 1.38 : 1, which correlated with the study by Lodi et al[49] and Daramola et al[50].

Most of the cases included were with duration between 6 to 9 months, the range is slightly greater than that reported by Sehgal et al[12] and Kacchawa et al[47] study (2 to3 months).

Itching was the major symptom in many cases ranging from ‘very severe itch’ (48%) to ‘worst possible itch’ (40%).

Sehgal et al[12] and Kachawwa et al[47] described moderate to severe itching in 95.91% and 72.8% cases respectively. Fine et al[48] opined that severity of pruritus depends with the extent of involvement of skin lesions. Diabetes mellitus was a significant association in this study (18%).

Hypertension was reported by Naldi et al[45] in 11.5% cases and Kachawwa et al[47] in 2.4% of cases. Boyd et al[46] and Naldi et al[45] reported diabetes mellitus in 1.6% and 4.9%cases respectively.

Oral lesions were noticed in 34.5% and 19.0% of female and male patients respectively. Buccal mucosa was involved in majority of cases (90%) with reticular type in 57%, plaque type in 28.5% and erosive in 14% .Sehgal et al[12] reported oral LP in 12.2% cases with 89% over buccal mucosa, 12.5% on lips and 6.2% on tongue, reticulate type in 89.6% and erosive type in22.9% cases that was higher compared to our study.

Nail changes were significant in 23.8% and 3.4% of male and female patients respectively. Kachawwa et al[47] also reported nail changes in 6.4% cases whereas Sehgal et al[12]reported absence of nail changes.

All the patients included in the study completed their treatment in 9 weeks.

There was a significant reduction in Itch severity score from 68% within week 1 of therapy to 22% in week 2 and another 10% in week 3.

In the study of Hodak *et al*[43], in 1998 done on 10 cases of lichen planus treated with enoxaparin 3 mg did not observe improvement in only 2 cases, with disappearance of itch in 60% in week 1 and 30% in week 2, that correlates with our study.

Onset of regression of cutaneous lesions noticed within 1 to 2 weeks of disappearance of the itch which again correlates with the study by Hodak et al[43]. H. Pacheco[62] in 2001, showed a significant improvement in 5 of 7 patients.

Cutaneous lesions showed dramatic improvement (Grade 3) in 74% and moderate improvement (Grade 2) in 26% of the patients studied, whereas in the study by Wisam Ali Ameen and Zena Saeed Alfadhily[79] reported in the medical journal of babylon showed dramatic reduction in VAS score (86.6%) and all grades of clinical improvement in 80% of the patients.

There was complete disappearance of the itch in 66% of patients with 15 reporting mild to moderate itch at the end of 9 weeks and 5 cases with recurrence of itch during follow up. Hodak et al[43] reported no recurrence of itch during the treatment or follow up except in one patient with itch 5 months later.

There was also a improvement in DLQI in 80% of the cases in this study that is comparable to the study by Fariba Iraji et al[80] that demonstrated 72% complete or partial remission with significant improvement in quality of life.

Also in 1999, M.P. Stefanidou[2]conducted a study on18 patients with lichen planus where complete remission was achieved in 61% of patients, S.Akdeniz et al[61] in 2005 reported 83% remission in a study with 24 patients. Here in this study it is significantly higher (90%).

New lesions were relatively uncommon and seen in 26.7% at the end of 9 weeks of this study. Hodak et al[43] reported no improvement in clinical lesions in 2 out of 10 cases that were studied.

Oral lesions were relatively resistant to treatment possibly due to shorter duration of this study.

There were no adverse effects noticed with Enoxaparin during the study thus highlighting it’s safety for clinical use in lichen planus.

There are also case reports of patients with chronic and refractory lichen planus that responded only to low molecular weight heparin.

CONCLUSION

The study conducted at our institution revealed the following-

- Lichen planus commonly affects younger individuals, most common in the age group between 20 to 40 years.
- There is a significant female preponderance.
- Itching was the major symptom among these patients.
- Diabetes mellitus was a significant association in few patients.
- Clinical improvement noticed in the form of decrease in Itch Severity Score (ISS) within 1 to 3 weeks of commencement of the drug.
- Cutaneous lesions showed regression after 1to 2 weeks of disappearance of itch in 80%-90% of the cases.
- Grade 3 (dramatic response) achieved in 74% and Grade 2 (moderate response) in 26% of cases at the end of 9 weeks.
- There was no evidence of occurrence of any new lesions during the course of treatment in 76% of the cases.
- There was also improvement in DLQI in almost 80% of the patients.

- During the follow up period, 4 patients developed a few papules that later regressed spontaneously.
- There was complete disappearance of itch in 66% of the patients at the end of the study.
- During follow-up, 5 patients noticed a recurrence of mild to moderate itch.
- Lesions healed with post inflammatory hyperpigmentation.
- There is a variable period of remission ranging from 1.5 to 6 months in almost 90% of the treated individuals.
- Oral lesions, palms and soles involvement were resistant to treatment.
- The drug was safer with no significant adverse effects reported during the study period.
- The rapid improvement and sustained remission seen in this study indicate that low molecular weight heparin could be a safe, effective and an alternative monotherapy in the management of generalized cutaneous lichen planus.

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ANNEXURES

ANNEXURE 1

GOVT. STANLEY MEDICAL COLLEGE AND HOSPITAL

DEPARTMENT OF DERMATOLOGY

PROFORMA

NAME: AGE: SEX:

OCCUPATION/INCOME: ADDRESS WITH CONTACT NO:

CHIEF COMPLAINTS:

H/O PRESENT ILLNESS:

PAST HISTORY:

FAMILY HISTORY:

PERSONAL HISTORY:

EXAMINATION:

INVESTIGATIONS:

COMPLETE BLOOD COUNT:

RENAL PROFILE:

PLATELET COUNT:

LIVER PROFILE:

COAGULATION PROFILE (PT, INR, APTT).

HBV, HCV ANTIBOBY TITRE HIV, VDRL

CHEST X-RAY, ECG STOOL OCCULT BLOOD TESTS.

SKIN BIOPSY FOLLOW UP

ANNEXURE 2

CONSENT FORM

Mr,/Mrs,/Miss:

Age:

Address:

Phone:

Name of the Procedure:

I undersigned Mr,/Mrs,/Miss_____ have been explained regarding above said procedure in my regional language. I am fully aware of the possible side effects and risks involved in this procedure. I am also aware that this procedure may not always be successful and no guarantee can be made for successful outcome of the procedure.

I have been informed that this procedure will be performed by

Dr. N. Sudhakar

I have also been explained that during this procedure if any complication arises, I may be given any emergency treatment best suitable without asking my prior permission.

I further state that I have carefully read and understood all the information provided in this form and with full conscious mind I hereby give my consent for the said procedure with its risk involved.

Signature of the patient/ right thumb impression:

Witness:

Name:

Signature: Date:

INSTITUTIONAL ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Efficacy of low-molecular weight heparin in the Management of lichen planus

Principal Investigator : Dr.N.Sudhakar

Designation : PG in MD(Derm)

Department : Department of Dermatology
Government Stanley Medical College,
Chennai-1

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 08.07.2013 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

22/8/13

MEMBER SECRETARY,
IEC, SMC, CHENNAI

MASTER CHART

S. No.	Name	Age (Years)	Sex	Duration	KP	Nail changes	Oral changes	Week 0			Week 3			Week 6			Week 9			DLQI		Remission (months)	Improvement (weeks)	Adverse effects
								ISS	Old lesions	New lesions	ISS	Old lesions	New lesions	ISS	Old lesions	New lesions	ISS	Old lesions	New lesions	Before trt	After trt			
1.	Vijaya	35	F	5mo	-	-	-	5	Gen	+/-	3	Gr3	-	2	Gr3	-	0	Gr3	-	6	2	2	1	-
2.	Rupchandran	22	M	6 mo	+	-	-	5	Gen	+/-	3	Gr1	-	3	Gr2	+	2	Gr2	-	8	4	2.5	3	-
3.	Jamaal	38	M	4mo	-	-	RT	4	Gen	+/-	3	Gr2	-	0	Gr3	-	0	Gr3	-	8	1	6	1	-
4.	Albert	24	M	6mo	-	PT	-	3	Gen	+/-	2	Gr2	-	0	Gr3	-	0	Gr3	-	9	2	6	1	-
5.	Gayathri	25	F	7 mo	+	-	-	5	Gen	+/-	3	Gr2	-	2	Gr2	+	2	Gr2	+	12	7	0	1	-
6.	Nawaz	23	M	6mo	-	-	-	3	Gen	+/-	2	Gr1	-	2	Gr2	-	0	Gr3	-	7	2	3	1	-
7.	Renukadevi	38	F	8 mo	-	-	PL	4	Gen	+/-	2	Gr2	-	2	Gr2	-	0	Gr2	-	10	4	3	1	-
8.	Velankanni	28	F	6mo	-	-	-	3	Gen	+/-	2	Gr3	-	0	Gr3	-	0	Gr3	-	9	1	4	1	-
9.	Balkis	25	F	7mo	-	-	RT	5	Gen	+/-	4	Gr1	+	3	Gr3	-	1	Gr3	-	11	5	2	2	-
10.	Balraj	46	M	5 mo	-	SK	-	4	Gen	+/-	2	Gr2	-	0	Gr2	-	0	Gr3	-	9	2	3	1	-
11.	Selvaraj	44	M	9mo	-	-	-	4	Gen	+/-	2	Gr1	-	2	Gr2	-	0	Gr3	-	8	2	2	1	-
12.	Hemchandra	20	M	7 mo	+	-	-	4	Gen	+/-	3	Gr2	-	1	Gr3	-	0	Gr3	-	9	1	6	1	-
13.	Kousalya	30	F	8mo	-	TL	-	5	Gen	+/-	4	Gr1	-	3	Gr2	-	0	Gr2	-	12	5	5	1	-
14.	Nagesh	45	M	7 mo	+	-	-	5	Gen	+/-	4	Gr0	+	4	Gr1	-	3	Gr2	-	17	6	2	3	-
15.	Nirmala	28	F	8mo	-	-	-	5	Gen	+/-	4	Gr2	-	2	Gr2	-	0	Gr2	-	9	4	2	1	-
16.	Thambiraj	22	M	6 mo	-	TL	-	4	Gen	+/-	3	Gr2	-	2	Gr3	+	0	Gr3	-	9	2	4	1	-
17.	Vanitha	35	F	5mo	-	-	-	5	Gen	+/-	3	Gr1	-	2	Gr2	-	0	Gr2	-	10	5	5	1	-
18.	Vijayalaxmi	37	F	8mo	+	-	PL	4	Gen	+/-	3	Gr3	-	0	Gr3	-	0	Gr3	-	6	1	3	1	-
19.	Srinivasan	37	M	9mo	-	SK	-	5	Gen	+/-	4	Gr0	-	3	Gr1	-	3	Gr2	-	18	8	1.5	2	-
20.	Ravi	25	M	7mo	+	-	-	4	Gen	+/-	2	Gr2	-	1	Gr3	-	0	Gr3	-	7	1	2.5	1	-
21.	Prehalya	21	F	6 mo	-	-	-	3	Gen	+/-	1	Gr3	-	1	Gr3	-	0	Gr3	-	8	1	4	1	-
22.	Arumugam	31	M	7mo	-	-	RT	5	Gen	+/-	3	Gr2	-	3	Gr2	-	2	Gr2	+	11	7	0	2	-
23.	Gomathi	40	F	5mo	-	-	-	5	Gen	+/-	4	Gr2	-	0	Gr2	-	0	Gr3	-	9	4	2.5	1	-
24.	Gowri	27	F	6mo	-	-	-	4	Gen	+/-	2	Gr1	-	1	Gr2	-	0	Gr3	-	8	2	1.5	2	-
25.	Bhagyalaxmi	26	F	5 mo	+	-	-	5	Gen	+/-	3	Gr2	-	2	Gr3	-	0	Gr3	-	10	4	5	1	-

S. No.	Name	Age (Years)	Sex	Duration	KP	Nail changes	Oral changes	Week 0			Week 3			Week 6			Week 9			DLQI		Remission (months)	Improvement (weeks)	Adverse effects
								ISS	Old lesions	New lesions	ISS	Old lesions	New lesions	ISS	Old lesions	New lesions	ISS	Old lesions	New lesions	Before trt	After trt			
26.	Indirani	50	F	6 mo	-	-	-	4	Gen	+/-	2	Gr2	-	2	Gr2	-	0	Gr3	-	9	3	2	1	-
27	Selvarani	21	F	7 mo	-	-	-	5	Gen	+/-	2	Gr1	-	0	Gr2	+	1	Gr3	-	9	4	2.5	3	-
28	Ganesh	42	M	9 mo	-	-	-	4	Gen	+/-	2	Gr3	-	0	Gr3	-	0	Gr3	-	8	1	6	1	-
29.	Marthammal	38	F	8 mo	-	-	ER	4	Gen	+/-	2	Gr2	-	2	Gr2	+	2	Gr2	+	10	7	0	2	-
30.	Shanthi	46	F	6mo	-	-	-	4	Gen	+/-	2	Gr2	-	2	Gr3	-	0	Gr3	-	7	1	2.5	1	-
31.	Vasugi	42	F	5 mo	+	-	-	5	Gen	+/-	3	Gr2	-	2	Gr3	-	2	Gr3	-	9	1	3	2	-
32.	Mani	44	M	7 mo	-	-	RT	4	Gen	+/-	2	Gr3	-	0	Gr3	-	0	Gr3	-	8	1	3	1	-
33.	Senthil	41	M	6 mo	-	TL	-	3	Gen	+/-	2	Gr2	-	0	Gr2	-	0	Gr3	-	9	1	4	1	-
34.	Ramya	38	F	9 mo	+	-	PL	4	Gen	+/-	3	Gr1	-	1	Gr2	-	2	Gr3	-	14	5	2	2	-
35.	Urmila	26	F	6 mo	-	-	RT	4	Gen	+/-	2	Gr2	-	0	Gr3	-	0	Gr3	-	8	1	3	1	-
36.	Mohd. Riyaz	36	M	9 mo	-	-	-	5	Gen	+/-	3	Gr3	+	1	Gr3	-	2	Gr3	-	10	2	6	3	-
37.	Bhavani	23	F	5 mo	-	-	RT	4	Gen	+/-	2	Gr1	-	2	Gr3	-	0	Gr3	-	12	5	6	1	-
38.	Gajalakshmi	37	F	7 mo	-	-	-	4	Gen	+/-	2	Gr2	-	1	Gr3	-	0	Gr3	-	7	1	5	1	-
39.	Venkatesh	49	M	5mo	-	-	-	5	Gen	+/-	3	Gr2	-	1	Gr2	-	2	Gr2	-	11	4	2	3	-
40	Jayalakshmi	20	F	6 mo	-	-	-	4	Gen	+/-	2	Gr2	-	1	Gr3	-	0	Gr3	-	8	1	2	1	-
41.	Devagi	45	F	7 mo	-	-	RT	5	Gen	+/-	2	Gr2	-	0	Gr2	-	1	Gr3	-	11	3	4	2	-
42.	Avinash	21	M	8 mo	-	-	-	3	Gen	+/-	1	Gr3	-	0	Gr3	+	1	Gr3	-	8	2	5	1	-
43.	Abdul	29	M	6mo	-	-	-	4	Gen	+/-	2	Gr2	-	0	Gr3	-	0	Gr3	-	7	1	3	1	-
44.	Kamaladevi	40	F	9 mo	+	-	PL	4	Gen	+/-	3	Gr1	-	1	Gr2	-	1	Gr3	-	9	2	1.5	2	-
45.	Karthika	24	F	8 mo	-	-	-	5	Gen	+/-	3	Gr1	-	2	Gr2	-	0	Gr2	-	11	4	2.5	1	-
46.	Ravikumar	37	M	6 mo	-	-	-	4	Gen	+/-	3	Gr2	-	3	Gr2	+	2	Gr2	+	11	8	0	1	-
47.	Kamatchi	23	F	8 mo	-	-	RT	5	Gen	+/-	2	Gr3	-	0	Gr3	-	0	Gr3	-	7	1	5	2	-
48.	Nagarani	40	F	5mo	-	-	-	4	Gen	+/-	3	Gr2	-	1	Gr2	-	0	Gr3	-	8	1	2.5	1	-
49.	Vijayakumar	40	M	7 mo	-	-	ER	5	Gen	+/-	2	Gr1	-	0	Gr2	-	2	Gr3	-	12	5	1.5	2	-
50.	Suguna	24	F	5 mo	-	-	-	4	Gen	+/-	2	Gr2	+	2	Gr3	-	0	Gr3	-	7	1	2.5	1	-

KEY TO MASTER CHART

SEX

M - Male

F - Female

DURATION:

mo - months

KP – KOEBNERISATION

\+ Present

\- Absent

NAIL CHANGES

TL - Thinning and Longitudinal ridging

SK - Subungual hyperkeratosis

PT - Pterygium

ORAL CHANGES

RT – Reticular type

PL – Plaque type

ER – Erosive type

ISS – ITCH SEVERITY SCORE

Grade 5 - Worst possible itch

Grade 4 - Very severe itch

Grade 3 - Severe itch

Grade 2 - Moderate itch

Grade 1 - Mild itch

Grade 0- No itch.

GRADING OF SKIN LESIONS:

Grade 0 (no response): Same number of lesions.

Grade 1 (mild response): Less than one third of lesions reduction.

Grade 2 (moderate response): More than third and less than two thirds reduction.

Grade 3 (dramatic response): More than two third of lesion reduction.

DLQI – DERMATOLOGY LIFE QUALITY INDEX

0 – 1 = No effect at all on the patient's life

2 – 5 = Small effect on the patient's life

6 – 10 = Moderate effect on the patient's life

11 – 20 = Very large effect on the patient's life

21 – 30 = Extremely large effect on the patient's life.

NEW LESIONS:

+ Present

- Absent

IMPROVEMENT OF LESION IN WEEKS:

Week 1: Regression of skin lesions within a week of disappearance of itch.

Week 2: Regression of skin lesions within two weeks of disappearance of itch.

Week 3: Regression of skin lesions within three weeks of disappearance of itch.

ADVERSE EFFECTS:

No significant adverse effects observed.